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Fertility and fecundity

Adverse childhood experiences, social support, and fecundability in an internet-based prospective cohort study Sharonda M. Lovett* Olivia R. Orta Renée Boynton-Jarrett Yael I. Nillni Amelia K. Wesselink Collette N. Ncube Elizabeth E. Hatch Lauren A. Wise

Childhood adversity is an established health determinant, and two prospective studies report an association between childhood adversity and reduced fecundability (probability of conception per menstrual cycle). Evidence also suggests social support may mitigate the adverse effects of childhood adversity through several pathways. We evaluated the association between childhood adversity and fecundability and whether childhood social support modifies this association. Pregnancy Study Online (PRESTO) is a preconception cohort study of North American women aged 21-45 years. Participants completed bimonthly questionnaires until pregnancy or a censoring event (stopped trying, fertility treatment initiation, loss to follow-up, or 12 months of follow-up), whichever came first. In June 2019, we sent a supplemental questionnaire on life course adversity (SQ) to former and current PRESTO participants; thereafter, women completed the SQ 30 days post-enrollment (n=5,489). The SQ included an adapted Adverse Childhood Experiences (ACE) scale from the Behavioral Risk Factor Surveillance System. Childhood social support was assessed using an adapted Berkman-Syme Social Network Index where we defined a score ≥4 as high vs. low social support. We used proportional probabilities regression to estimate fecundability ratios (FR) and 95% confidence intervals (CIs), adjusted for age, multivitamin use, contraception, and parental education. Overall, 78% experienced ≥1 ACE and 88% reported high social support in childhood. Relative to ACE scores of zero, FRs for ACE scores 1-3 and 4-8 were 0.87 (CI: 0.79-0.95) and 0.82 (CI: 0.74-0.91), respectively. FRs for ACE scores 4-8 relative to ACE scores of zero were 0.84 (CI: 0.75-0.95) among women reporting high social support and 0.67 (CI: 0.45-0.99) among women reporting low social support. Greater childhood adversity was associated with reduced fecundity in adulthood. Associations were stronger among those with low social support in childhood.

Nutrition/obesity

Endotoxin biomarkers are associated with indicators of adiposity and cardiometabolic risk across six years of follow-up in general-risk youth: A prospective study in the EPOCH cohort Wei Perng* Jacob E. Friedman Rachel C. Janssen Deborah H. Glueck Dana Dabelea

Objective: Metabolic endotoxemia may be a shared mechanism underlying childhood obesity and youth-onset metabolic diseases (e.g., type 2 diabetes, non-alcoholic fatty liver disease). This study sought to: (1) examine prospective associations of serum endotoxin biomarkers lipopolysaccharide (LPS), LPS binding protein (LBP), and anti-endotoxin core immunoglobulin G (EndoCab IgG) with adiposity and cardiometabolic risk in youth, and (2) assess the extent to which these associations are independent of exposure to fetal overnutrition.

Design/setting: This prospective study included 393 youth in the EPOCH cohort in Colorado. Participants were recruited 2006-2009 at age 10 y (baseline) and followed for six years (follow-up). We examined associations of endotoxin biomarkers at baseline with indicators of adiposity (BMI z-score, visceral [VAT] and subcutaneous [SAT] adipose tissue depots, skinfold thickness, waist circumference) and cardiometabolic risk (fasting insulin, glucose, adipokines, lipids, blood pressure) across both visits using mixed-effects regression, and with hepatic fat fraction (HFF) at follow-up using linear regression.

Results: Baseline LPS and LBP was positively associated with adiposity across follow-up. Each 1 unit ln-transformed LPS corresponded with 0.23 (95% CI: 0.03, 0.43) units higher BMI z-score, 5.66 (1.99, 9.33) mm^3 VAT, 30.7 (8.0, 53.3) mm^3 SAT, and 8.26 (4.13, 12.40) mm skinfold sum. EndoCab IgG was associated with VAT only (3.03 [0.34, 5.71] mm^3). LPS was associated with higher fasting insulin (1.93 [0.08, 3.70] µU/mL) and leptin (2.28 [0.66, 3.90] ng/mL), and an adverse lipid profile. No association was observed with HFF. Accounting for pubertal status and lifestyle behaviors did not change findings. However, adjustment for pre-pregnancy BMI and gestational diabetes as markers of fetal overnutrition attenuated most associations.

Conclusions: Serum endotoxin may be a marker of pathophysiological processes underlying development of childhood obesity and cardiometabolic conditions and is associated with exposure to fetal overnutrition.

Genetics

CFTR gene variants, air pollution, and childhood asthma in a California Medicaid population Ruwan Thilakaratne* Steve Graham John Moua Caitlin Jones Caroline Collins Jennifer Mann Stanley Sciortino Jacklyn Wong Martin Kharrazi

Carriers of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), the gene responsible for cystic fibrosis (CF), have been found to have an increased risk of asthma, and might benefit from CFTR-related treatments. However, as prior studies have aggregated carriers with a range of CFTR function into a single group, the specific variants that confer this risk are unknown. Additionally, modification of this risk by environmental asthmogens such as air pollution is poorly understood. We conducted a retrospective cohort study of children born in California between July 2007 and December 2013, linking *CFTR* genotype data from the California newborn screening program to (1) Medicaid claims records through March 17, 2020 to identify asthma cases, and (2) fine particulate matter ($PM_{2.5}$) concentrations from CalEnviroScreen version 3.0, a California environmental health screening tool, to estimate early life air pollution exposure. This resulted in 5,746 subjects, including 941 carriers. We fitted log-binomial models to estimate risk ratios adjusted for race/ethnicity and sex. Compared to population controls, carriers had a higher risk of asthma (adjusted risk ratio (aRR)=1.29, 95% confidence interval (CI): 0.98, 1.69). Among those with CF-causing variants on one allele, the presence of additional non-CF-causing variants on the second allele did not further increase asthma risk. Genotypes associated with the greatest asthma risk included F508del on one allele with an intron 10 T7 or (TG)11T5 on the second allele (aRR=1.52, 95% CI: 1.10, 2.12). The associations were slightly elevated among children living in areas at or above *versus* below the current air quality standard for $PM_{2.5}$. These results suggest certain carriers are at increased risk of asthma, and this risk may not be monotonically related to CFTR function. Further research is needed to identify asthma-causing *CFTR* genotypes, as this may open important CFTR-related treatment options for these patients.

Child health and development

Maternal low dose aspirin and self-reported wheezing and asthma in children: Findings from the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial Joseph Stanford* Zachary Shepelak May Shaaban Flory Nkoy Enrique Schisterman Stefanie Hinkle Sunni Mumford Robert Silver Karen Schliep

Historically, exposure to aspirin at therapeutic doses during pregnancy (>300 mg daily) has been associated with a higher risk of asthma in children. In current obstetric practice, lower dose aspirin (LDA, 50–150 mg per day) is used to prevent pregnancy complications, but data on long-term effects of LDA use during pregnancy on offspring's respiratory health are limited. Our objective was to assess whether LDA use at 81mg during pregnancy is associated with wheezing and asthma of offspring up to 14 years after birth. We conducted a follow-up of Utah participants who had a live birth in the EAGeR trial (2007–2011; 256 randomized to LDA treatment and 242 to placebo). Participants were invited to participate in a follow-up study May 2020–July 2021. Consenting women completed an online questionnaire including information on respiratory health of index child. Unadjusted risk differences (RD) and 95% CI were calculated to evaluate effect of LDA vs placebo on outcomes. 70% (n=347, 179 LDA vs. 168 placebo) of women completed the questionnaire. Mean (SD) age of index child at the time of survey was 12.0 years (1.1). 17.5% of respondents reported their child had experienced wheezing at some point in the past, with no difference between LDA vs. placebo, 18% vs. 17%, RD=0.02 (-0.06, 0.10). Among those who reported their child had any wheezing, there was no difference between LDA vs. placebo among women who reported offspring wheezing in last 12 months, 52% vs. 44%, RD=0.07 (-0.18, 0.32); sleep disturbed by wheezing, 27% vs. 29%, RD=-0.01 (-0.24, 0.21); wheezing severely limiting speech, 6% vs. 4%, RD=0.02 (-0.10, 0.15); wheezing during exercise, 45% vs. 43%, RD=0.03 (-0.22, 0.27); experiencing a dry cough apart from a cold/chest infection, 42% vs. 32%, RD=0.10 (-0.14, 0.34); or ever having asthma, 64% vs. 57%, RD=0.06 (-0.18, 0.31). In summary, we found that maternal use of LDA during pregnancy is not associated with wheezing or asthma in offspring up to 14 years after birth.

Child health and development

Motor disorders and health-related quality of life at age five in a European multi-country cohort of children born extremely preterm Adrien Aubert* Raquel Costa Mariane Sentenac Ulrika Ådén Samantha Johnson Marina Cuttini Mairi Männamaa Iemke Sarrechia Arno F. van Heijst Michael Zemlin Véronique Pierrat Jennifer Zeitlin

Background

Motor disorders are a common consequence of extremely preterm birth (EPT; <28 weeks' gestation) and can limit daily activities, schooling and social relationships. Cerebral palsy (CP) affects about 10% of children and non-CP movement difficulties (MD) are highly prevalent, although they have been less studied and tend to be under-diagnosed, especially in the absence of other sensory, cognitive or behavioural difficulties. We investigated the association of CP and non-CP MD with health-related quality of life (HRQoL) among 5-year-old children born EPT.

Methods

We included children followed-up at age 5 from a population-based EPT birth cohort in 2011-2012 in 11 European countries (N=1,021). Children without CP were classified using the Movement Assessment Battery for Children – 2nd edition as having significant MD (≤5th percentile of standardised norms) or being at risk of MD (6th-15th percentile). Parents reported on CP diagnoses and HRQoL using the Pediatric Quality of Life Inventory^{TM}. We compared HRQoL scores between groups and used linear regression to adjust for social characteristics overall and among children without other developmental difficulties.

Results

The prevalence of children born EPT with CP, significant MD and at risk of MD were 10.5%, 25.8% and 21.0%, respectively. They had lower HRQoL total scores [95% confidence intervals] than those without MD: -26.1 [-29.0; -23.2], -9.7 [-11.9; -7.4] and -5.7 [-7.9; -3.5]. Decreases were greater for physical scores: -37.6 [-42.0; -33.3], -12.8 [-16.1; -9.5] and -6.5 [-9.8; -3.3] than psychosocial scores: -20.0 [-23.1; -16.9], -8.1 [-10.4; -5.7] and -5.3 [-7.7; -3.0]. Lower scores associated with MD persisted after adjustment for social circumstances and exclusion of children with other developmental difficulties.

Conclusion

Motor disorders among 5-year-old children born EPT were associated with lower HRQoL, even among children with less severe motor difficulties and without other developmental difficulties.

Environment/climate change

Heat, season, and reproductive success Anne Marie Jukic* Hannah Jahnke D. Robert McConnaughey Clarice Weinberg Donna Baird Allen Wilcox

Climate change brings extreme heat patterns and heat may affect conception and pregnancy loss. We analyzed data from the North Carolina Early Pregnancy Study (EPS), a prospective study of women attempting pregnancy combined with data from the National Weather Service's report of hourly average heat index from surface monitors at the Raleigh-Durham Airport from 1982–86. We estimated average, 1-day peak, and 3-day peak heat index levels during the following critical reproductive windows: spermatogenesis, the menstrual cycle before the index cycle (lag cycle), the follicular and luteal phases of the index cycle, and time near implantation. We used logistic regression to model both the per cycle probability of conception (fecundability) and the risk of early pregnancy loss. We adjusted for age, education, previous window heat index, hours of daylight, income, partner age, and season using the sine and cosine of the menstrual cycle start date and stratified by cool months (October-April), and warm months, (May-September). A 10°F increase in heat index in peak heat index during the lag cycle was associated with higher conception (OR(CI): 2.0 (1.0, 4.0)) in cool months but not in warm months (OR(CI): 1.1 (0.47, 2.42)). A 10°F increase in 3-day peak of heat index during the follicular phase was associated with higher fecundability in warm months (OR(CI): 2.0 (1.0, 3.9)); but not in cool months (OR(CI): 0.94 (0.63, 1.4)). Increasing peak or 3-day peak heat index during the follicular phase were associated with increased early pregnancy loss (OR(CI): 2.3 (1.0, 6.0), 3.3 (1.4, 9.2), respectively) in cool months, not in warm months, OR(CI): 0.26 (0.04, 1.4) and 0.27 (0.03, 1.5). Increasing heat index may be associated with increased conception rates and increased early pregnancy loss.

Men’s health

Acute tear gas exposure symptoms and adverse male reproductive outcomes Damilola Owoade* Emily Reece Madeline Tomlinson Anne Wallis Cynthia Corbitt Ted Smith Aruni Bhatnagar Monica Unseld Kira Taylor

Background: Tear gas exposure often results in acute symptoms, which in turn are possible risk factors for adverse health outcomes, such as male reproductive outcomes. About 30% of couples in the United States have fertility issues, of which 30% is solely due to male factors.

Objective: The aim of the study is to investigate the effects of tear gas, as measured by acute tear gas exposure symptoms, on male reproductive outcomes.

Methods: Data was obtained using an online anonymous questionnaire. Acute tear gas symptoms included eye, lung, skin, and heart effects. The acute tear gas score was defined as the sum of the number of acute health effects (0-14). Male reproductive outcomes that were assessed included erectile dysfunction, ejaculation dysfunction, and trouble conceiving. For modeling purposes, the male reproductive outcome was defined as having at least one of the three reproductive outcomes vs. none. Odds ratios (OR) and 95% confidence intervals (CI) were obtained using logistic regression, controlling for potential confounders.

Results: About 46% of the men (N=92) exposed to tear gas reported at least one reproductive issue. After controlling for age, race, education, and seeking medical care after exposure (yes/no), there was a significant association between acute tear gas exposure score and male reproductive outcomes (OR: 1.48, 95%CI: 1.14, 2.00).

Conclusion: In this study, we observed a higher odds of at least one male reproductive outcome among those with more acute tear gas symptoms, even after controlling for potential confounders. Educating the public on the health impacts of tear gas may help reduce the burden of adverse male reproductive outcomes among protestors.

Fetal loss/stillbirth/infant mortality

Traffic-related air pollution and pregnancy loss in Eastern Massachusetts, USA Michael Leung* Sebastian Rowland Anna M Modest Michele R Hacker Stefania Papatheodorou Joel Schwartz Brent A Coull Ander Wilson Marianthi-Anna Kioumourtzoglou Marc Weisskopf

Background: Prior studies that have examined associations with pregnancy loss have mostly relied on losses identified by medical records (i.e., a subset of all losses). We apply a novel time-series approach that leverages data on live births to infer effects on pregnancy loss. Analyzing live birth-identified conceptions (LBICs) —the difference between the total number of conceptions and those that end in loss for a given time window— can tell us about associations with pregnancy loss (even those undetected). Using this approach, we estimate the association between prenatal nitrogen dioxide (NO_2) —a traffic emissions tracer— and pregnancy loss in a Massachusetts-based cohort. **Methods:** We used data on 21,204 live births from pregnancies conceived in 2003-2015 and had their prenatal care at Beth Israel Deaconess Medical Center in Boston, USA. We used a linear distributed lag model to estimate the association between weekly NO_2 during pregnancy and LBICs adjusted for temperature and time trends. Confidence intervals were obtained through bootstrap. **Results:** The mean number of LBICs per conception week was 30 (standard deviation [SD]: 6.5). Weekly NO_2 concentrations (mean: 23.3 parts per billion [ppb], SD: 6.5 ppb) were below the current USEPA annual standards. Higher prenatal NO_2 in gestational weeks 6-21 was associated with fewer LBICs, and the strongest association was in week 14. A 10-ppb higher NO_2 exposure sustained throughout pregnancy was associated with 11.0 (95% CI: 8.0, 14.1) fewer LBICs. That is, out of 30 LBICs per conception week, 11 would be lost if average NO_2 was 10-ppb higher in every week of pregnancy. **Conclusion:** We show through the analysis of LBICs that higher prenatal NO_2 was associated with pregnancy loss, and that the critical exposure window was in weeks 6-21. The described approach can quantify the change in the number of pregnancy losses per conception week as it is simply the complement of the change in live births from that week’s conceptions.

Fertility and fecundity

The ABC of fertility intentions: a mixed-methods study exploring the spectrum of attitudes towards family building Bola Grace* Jill Shawe Sarah Johnson Nafisat Usman Judith Stephenson

Introduction

Several studies have highlighted poor fertility knowledge across men and women of reproductive age. As the average age of first-time parents continues to rise, there has been a concerted effort to improve fertility awareness. To ensure that these messages are effective and to deploy the best strategies, it is important to understand reproductive health needs. This study therefore aimed to explore the different reproductive intentions to aid tailoring of information to help individuals achieve their family-building desires.

Methods

We conducted a mixed-method study via a UK-wide cross-sectional survey with 1,082 participants and semi-structured interviews of 20 women and 15 men who agreed to follow-up interviews. Interviews lasted an hour on average, data was transcribed and analysed using the thematic framework method. Ethics approval was obtained from University College London Research Ethics Committee.

Results

We identified six key categories of people, grouped alphabetically, in a user-friendly manner to highlight a spectrum of fertility intentions: Avoiders describe those who have no children and do not want children in future; Betweeners describe those who already have child(ren) and want more in future but are not actively trying to conceive (TTC); Completers describe those who have child(ren) but do not want more; Desirers describe those who are actively TTC; Expectants describe those pregnant at the time of the study and Flexers describe those who may or may not already have and are unsure about having child(ren) in the future. Survey analysis showed these proportions: Avoiders,4.7%; Betweeners,11.3%; Completers,13.6%; Desirers,36.9%; Expectants,4.1%; Flexers,28.4% and 2.4% preferring not to answer. A majority of the survey population were pregnant; TTC; or planning to have a child in the future – whether actively, passively or simply open to the idea, with interviews providing deep insights into their decision-making.

Conclusions

We developed a user-friendly, alphabetical categorisation of fertility intentions, which can be used by individuals, healthcare professionals, educators, special interest groups, charities, and policymakers to support individuals and couples in making informed choices to achieve their desired intentions, if and when they choose to start a family.

Gynecological health

Urinary cadmium and endometriosis risk among U.S. women: results from NHANES 1999-2006 Mandy S. Hall* Kristen Upson

Endometriosis, characterized by the presence of endometrial-like glands and stroma outside the uterus, is associated with substantial pain symptoms. Since estrogen is central to endometriosis pathogenesis, cadmium, a toxic metal that exhibits estrogenic properties, may increase disease risk. However, prior studies have reported discrepant results, likely due to the non-case selection approach, small study size, and cadmium measurement. We investigated this association in a nationally representative sample of the US population by conducting a cross-sectional analysis of the National Health and Nutrition Examination Survey 1999-2006 data. In a subset of women ages 20-54 years (unweighted n=1,750), data were available on urinary cadmium concentrations. Urinary cadmium characterizes long-term exposure given the decades-long biologic half-life of cadmium in the kidney. History of endometriosis diagnosis by a healthcare provider was ascertained by self-report. We conducted multivariable logistic regression to estimate the ORs and 95% CIs for the cadmium-endometriosis association, adjusting for age, poverty income ratio, pack-years of cigarette smoking, and parity, and accounting for the complex survey sampling design. To correct for urinary dilution, we standardized urinary cadmium concentrations using urinary creatinine and categorized the standardized concentrations in quartiles. In the study sample, 10% of participants (unweighted n=115) reported a history of endometriosis diagnosis. Our data suggested a positive association between urinary cadmium concentrations and endometriosis (second vs. first quartile: OR 2.27, 95% CI: 1.03, 5.00; third vs. first quartile: OR 1.82, 95% CI: 0.77, 4.32; fourth vs. first quartile: OR 2.33, 95% CI: 1.05, 5.19). These results suggest that long-term exposure to cadmium is associated with increased endometriosis risk. This is concerning given the chronic exposure of the US population to cadmium from contaminated food and cigarette smoke.

Methods

Utility of sibling designs for confounding control when exposure affects fertility Mollie Wood*

Sibling comparison designs allow estimation a causal effect of exposure when randomized studies are not possible, and measurement of relevant confounders is unobtainable. The intuition for the approach is that siblings often share many observed and unobserved variables, such that in some cases, siblings may be considered exchangeable with one another. A common application of the sibling design is to assess the direction and magnitude of confounding in an analysis. If an association is present in the main analysis but absent or substantially attenuated in the sibling sample, researchers often conclude that the observed association was due to unmeasured confounding. The potential for selection bias resulting from conditioning on families with 2 or more siblings has not been evaluated. In this study, we explored scenarios in which exposure causes selection into the sibling sample, either directly (e.g. via assisted reproductive technology) or indirectly (e.g. an effect on outcome which results in reproductive stoppage). Using directed acyclic graphs, we illustrate structural relationships between exposure, conception, pregnancy outcome, and covariates. We used Monte Carlo simulations to evaluate multiple scenarios in which we varied the strength of the true effect, non-shared covariates, and shared covariates. We demonstrate that particularly in the presence of common causes of conception and pregnancy outcome that are not shared by siblings, estimates from sibling analyses will differ substantially from the truth. Further, the direction and magnitude of bias is sufficient to change conclusions drawn from the analysis under realistic scenarios. The sibling comparison design should be used with caution in scenarios where the exposure affects fertility.

Pharmacoepidemiology

Emulating a sequence of target trials to avoid immortal time bias in pregnancy studies – an application to antibiotic initiation and preterm delivery Ellen Caniglia* Rebecca Zash Christina Fennell Modiegi Diseko Gloria Mayondi Jonathan Heintz Mompati Mmalane Joseph Makhema Shahin Lockman Sunni L. Mumford Eleanor J. Murray Sonia Hernandez-Diaz Roger Shapiro

Background: Immortal time bias is introduced when treatment initiation occurs after time zero of follow-up and is common in observational studies of medication use during pregnancy. We describe how emulating a series of hypothetical randomized trials (target trials) avoids immortal time bias and apply the approach to antibiotic initiation and preterm delivery.

Methods: The Tsepamo Study captured birth outcomes at up to 18 delivery sites in Botswana from 2014-2021. To investigate the relationship between antibiotic initiation after 24 weeks gestation and preterm delivery (24-37 weeks gestation) among women presenting for antenatal care <24 weeks gestation we: 1) started follow-up at 24 weeks and defined exposure as antibiotic initiation between 24-37 weeks gestation (susceptible to immortal time bias) and 2) conducted 13 sequential target trials of antibiotic initiation versus no initiation during each week from 24-37 weeks gestation. For each trial, eligible women had not previously initiated antibiotics and remained pregnant at the start of that week. We used log-binomial models to calculate risk ratios (RR) and 95% confidence intervals (CI).

Results: Of 111,403 eligible women, 17,009 (15%) initiated antibiotics between 24-37 weeks gestation. The RR (95% CI) for preterm delivery comparing antibiotic initiation to no initiation between 24-37 weeks was 0.92 (0.89, 0.96). In the series of target trials which address immortal time bias, the RRs (95% CIs) ranged from 1.06 (0.93, 1.22) to 1.28 (1.14, 1.43).

Conclusions: Because the time period between time zero and treatment initiation is “immortal” to the outcome, defining exposure based on treatment initiation after time zero biased the RR for the association between antibiotic initiation and preterm delivery downwards. Conducting a series of target trials can avoid this immortal time bias in pregnancy studies by aligning exposure initiation and start of follow-up.

Pregnancy outcomes

International versus national growth charts for identifying small and large-for-gestational age newborns: a population-based study in 15 European countries Alice Hocquette* Mélanie Durox Rachael Wood Kari Klungsoyr Katarzyna Szamotulska Sylvan Berrut Tonia Rihs Theopisti Kyprianou Luule Sakkeus Aline Lecomte Irisa Zile Sophie Alexander Jeannette Klimont Henrique Barros Miriam Gatt Béatrice Blondel Mika Gissler Jennifer Zeitlin

Background: To inform the on-going debate about the use of universal prescriptive intrauterine growth charts versus national growth charts, we compared perinatal mortality for small and large-for-gestational-age (SGA/LGA) infants according to international and national charts in Europe.

Methods: We classified all singleton births from 33 to 42 weeks of gestation in 2010 and 2014 from 15 countries in the Euro-Peristat network (N=1,475,457) as SGA (birthweight <10^{th} percentile) and LGA (>90^{th} percentile) using the international Intergrowth-21^{st} newborn standards and national charts based on the customised GROW methodology. We computed sex-adjusted relative risks (aRR) for stillbirth, neonatal and extended perinatal mortality by SGA and LGA status using multilevel models.

Findings: SGA and LGA prevalence using national charts were near 10% in all countries (8·5% to 10·6% and 10·3% to 14·8%, respectively) but varied according to international charts with a north to south gradient (3·0% to 10·1% and 8·0% to 24·9%, respectively). Compared with appropriate for gestational age (AGA) infants by both charts, being SGA by both charts increased risks of perinatal mortality by 6·0 (95% confidence interval (CI): 5·4-6·7). Infants reclassified by international charts from SGA to AGA had an aRR of 2·7, (95%CI: 2·5-3·0), while those reclassified from AGA to LGA had an aRR of 0·6 (95%CI: 0·5-0·6). Results were similar for stillbirth and neonatal death.

Interpretation: Using international instead of national charts in Europe could lead to growth restricted infants being reclassified as having normal growth, while infants with low risks of mortality could be reclassified as having excessive growth.

Funding: The Euro-Peristat network receives funding from the European Commission as part of the InfAct (Information for Action) Joint Action (CHAFEA Grant n° 801553). This work also received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking ConcePTION grant n° 821520. Alice HOCQUETTE was supported by a PhD grant from EHESP.

Big Data/Machine Learning/AI

The public health exposome and pregnancy-related mortality in the United States: a high-dimensional computational analysis Emily Harville* Stephen Grady Michael Langston Paul Juarez Dovile Vilda Maeve Wallace

Background: Racial disparities in maternal mortality in the U.S. continue to be stark.

Methods: The 2015-2018, 4-year total population, county-level, pregnancy-related mortality ratio (PRM; deaths per 100,000 live births; National Center for Health Statistics (NCHS), restricted use mortality file) was linked with the Public Health Exposome (PHE). Using data reduction techniques, 1591 variables were extracted from over 62,000 variables for use in this analysis, providing information on the relationships between PRM and the social, health and health care, natural, and built environments. Graph theoretical algorithms and Bayesian analysis were applied to PHE/PRM linked data to identify latent networks.

Results: PHE variables most strongly correlated with total population PRM were years of potential life lost and overall life expectancy. Population-level indicators of PRM were overall poverty, smoking, lack of exercise, heat, and lack of adequate access to food.

Conclusions: In this high-dimensional analysis, overall life expectancy, poverty indicators, and health behaviors were found to be the strongest predictors of pregnancy-related mortality. This provides strong evidence that maternal death is part of a broader constellation of both similar and unique health behaviors, social determinants and environmental exposures as other causes of death.

Mental health

Associations of Toddler Mechanical and Mealtime Distress Feeding Problems with Psychopathology Symptoms Five Years Later Diane Putnick* Erin Bell Akhgar Ghassabian Kristen Polinski Sonia Robinson Rajeshwari Sundaram Edwina Yeung

Background: Feeding problems are common in early childhood and some evidence suggests that feeding problems may be associated with psychopathology, but few prospective studies have examined these associations.

Methods: Mothers of 1,136 children from the Upstate KIDS cohort study provided data. Food refusal (picky eating) and mechanical/distress feeding problems (e.g., difficulty chewing, crying during meals) and developmental delays were assessed at 2.5 years. Child eating behaviors and psychopathology (attention-deficit/hyperactivity (ADHD), oppositional-defiant (OD), conduct disorder (CD), and anxiety/depression) symptoms were assessed at 8 years. Structural equation modeling was used to assess the associations between the frequency of feeding problems at 2.5 years and child psychopathology symptoms at 8 years controlling for developmental delays at 2.5 years, eating behaviors at 8 years, and child and family demographics. Stratification by child sex was examined.

Results: Food refusal (M = 1.46, SD = .51, range = 0-3) and mechanical/distress (M = 1.09, SD = .39, range = 0-3) feeding problems were normally distributed. Mechanical/distress feeding problems at age 2.5 were associated with more ADHD (β = .20, 95%CI = .10, .31), problematic behavior (OD/CD; β = .22, 95%CI = .12, .31), and anxiety/depression (β = .13, 95%CI = .04, .21) symptoms at 8 years. Food refusal feeding problems were not associated with more psychopathology symptoms. Model estimates were similar for boys and girls and for subsets of singletons, children born at term, and children without diagnosed feeding problems.

Conclusions: Much of the research on feeding problems focuses on picky eating. This prospective study suggests that early mechanical and mealtime distress problems may be better indicators of later psychopathology than food refusal. Parents and pediatricians could monitor children with mechanical/distress feeding problems for signs of developing psychopathology.

Child health and development

Chorioamnionitis and risk of long-term neurodevelopmental disorders in offspring; a population-based cohort study in Sweden. Eleni Tsamantioti* Sarka Lisonkova Giulia Muraca Anne Örtqvist Neda Razaz

Introduction: Evidence indicates that maternal infections, in particular chorioamnionitis, might negatively affect the sensitive fetal brain and lead to adverse neurodevelopmental outcomes. In this study we aimed to examine the association between maternal chorioamnionitis and neurodevelopmental disorders (NDDs) in offspring.

Study design: A retrospective population-based cohort study in Sweden, including 3,403,265 singleton live births and stillbirths between 1987 and 2019. Data on maternal characteristics and neurodevelopmental disorders in offspring were obtained by individual record-linkages of Swedish registries. Chorioamnionitis was identified using the Medical Birth Registry. Registered diagnoses of NDDs included epilepsy, Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and intellectual disability (ID). Cox proportional hazards regression was used to estimate the association between chorioamnionitis and each outcome with adjusted hazard ratios(aHR) and 95% confidence intervals (CI). We calculated the proportion of the association mediated through known consequences of chorioamnionitis that are also associated with neurodevelopmental disorders.

Results: A total of 7,896 (0.23%) offspring were exposed to chorioamnionitis during pregnancy. During the study’s follow-up time there were 34,221 cases of epilepsy, 81,156 cases of ASD, 195,034 cases of ADHD and 28,331 cases of ID. After adjusting for potential confounders, compared with offspring not exposed to chorioamnionitis, those exposed were at elevated risks of ASD (aHR 1.37; 95% CI (1.18-1.59), ADHD (aHR, 1.20; 95% CI (1.08-1.34) and ID (aHR, 2.18; 95%CI, 1.77-2.69), while chorioamnionitis was not significantly associated with higher rates of epilepsy. Mediation analysis revealed that these associations were mainly explained through preterm birth.

Conclusion: Chorioamnionitis increases the risks of ASD, ADHD, and intellectual disability in offspring, mainly through preterm birth.

Mental health

Early-life temperament and childhood mental health during COVID-19: Findings from a longitudinal birth cohort in Mexico City Laura McGuinn* Marcela Tamayo-Ortiz Maria Rosa Nadya Rivera Rivera Lourdes Schnaas Erika Osorio Shelley Liu Martha M Tellez-Rojo Rosalind Wright Daniel Klein Robert Wright

Background: The COVID-19 pandemic has disrupted nearly all aspects of life, creating unique stressors and placing vulnerable populations such as children at an increased risk of mental health conditions. The role of early life predictors, including temperament, on childhood mental health symptoms during the pandemic remains largely unknown.

Methods: We used data from 322 mother-child pairs from a prospective birth cohort in Mexico City. Temperament was measured when children were 2 years old using the Carey Toddler Temperament Scale. Temperament profiles were categorized as easy, intermediate, and difficult/ slow-to-warm-up. Depressive and anxiety symptoms were assessed during COVID when children were aged 9-12 years using the Children's Depressive Inventory and the Revised Manifest Anxiety Scale. Linear regression models were used to estimate associations between early life temperament in relation to continuous depressive and anxiety symptom T-scores. We report beta coefficients and 95% confidence intervals (CI). Models were adjusted for child's depressive and anxiety symptoms pre-COVID, child age and sex, and maternal socioeconomic status and age. We assessed whether maternal stress during the pandemic modified associations between toddler temperament and later childhood mental health.

Results: Children classified as having difficult temperaments at age 2 years were more likely to have higher depressive symptoms during the pandemic (β=2.47, 95% CI: 0.09, 4.85). The associations were strongest for children of mothers facing higher negative life events during the pandemic (β=3.11, 95% CI: -0.06, 6.29). No associations were seen with anxiety symptoms in children.

Conclusions: Our findings suggest that early life temperament may be related to higher depressive symptoms in children during the pandemic. Findings may help to identify children and adolescents particularly at risk for elevated mental health symptoms during novel life stressors such as COVID-19.

Child health and development

Pre-pregnancy maternal cardiovascular diseases and risk of offspring's neurodevelopmental disorders: a population-based cohort study M Zakir Hossin* Kyla McKay Lorena Cruz Anna Sandström Neda Razaz

Introduction: Maternal exposure to cardiovascular disease (CVD) during pregnancy is associated with adverse maternal and neonatal health outcomes. However, its association with offspring's long-term neurodevelopmental disorders (NDDs) is not yet known. Therefore, we aimed to investigate the association between mothers' pre-existing CVDs and offspring's NDDs.

Methods: This population-based cohort study included 2.4 million live singleton births recorded in the Swedish Medical Birth Register between 1990 and 2016. Information on maternal pre-pregnancy CVDs was extracted from the National Patient Register, including diagnosis of ischemic heart disease, heart failure, cerebrovascular disease, arrhythmia, cardiomyopathy, and congenital heart disease. Registered diagnoses of offspring NDDs included Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and intellectual disability (ID). Cox proportional hazards models were fitted to estimate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for the associations, adjusting for maternal characteristics including age, parity, education, smoking, psychiatric illness, pre-gestational diabetes and hypertension.

Results: A total of 141 027 individuals received a diagnosis of ADHD, 63 802 of ASD, and 22 385 received a diagnosis of ID. The adjusted analyses showed that offspring of mothers with CVD had 14% higher risk of ADHD (HR 1.14; 95% CI: 1.07-1.22) and 11% higher risk of ASD (HR 1.11; 95% CI: 1.01-1.21), compared with offspring of mothers without CVD. Specifically, maternal heart failure was associated with 2.12-fold increased risk of ASD (95% CI: 1.31-3.41) and maternal cerebrovascular disease was associated with 32% elevated risk of ASD (95% CI: 1.08-1.61) and 17% elevated risk of ADHD (95% CI: 1.01-1.35). No association was found between maternal CVDs and ID.

Conclusion: Maternal CVD before pregnancy may be a risk factor for ADHD and ASD in offspring, with varied risk by CVD subtype.

Fertility and fecundity

Risk of cardiovascular disease in women and men with subfertility: the Trøndelag Health Study Karoline Skåra* Bjørn Olav Åsvold Álvaro Hernáez Abigail Fraser Janet W. Rich-Edwards Leslie V. Farland Øyvind Næss Deborah A. Lawlor Ben Brumpton Maria C. Magnus

Fertility rates are decreasing in many European countries. Subfertility, defined as being unable to conceive after trying for more than twelve month, is estimated to affect between 10 and 15% of couples. However, subfertility remains unexplained in around 25-30% of all cases. Some studies have suggested an association between subfertility and risk various chronic diseases, such as cardiovascular disease (CVD). The aim of the present study was to investigate the association between subfertility and CVD outcomes in both sexes. We studied 31,629 women and 17,630 men participating in The Trøndelag Health Study (HUNT). We assessed the association between self-reported subfertility and CVD outcomes using Cox proportional hazards models adjusted for age, birth year, body-mass index, blood pressure, diabetes mellitus, cholesterol, smoking history, cohabitation, and education. Information on CVD (stroke, coronary heart disease (CHD), myocardial infarction, and angina) was available by linkage to hospital records. A total of 17% of women and 15% of men reported subfertility. In women, subfertility was modestly associated with increased risk of CHD (adjusted hazard ratio [aHR] 1.15; 95% confidence interval [CI]: 1.02, 1.29), angina (aHR 1.22; 95% CI: 1.06, 1.41), stroke (aHR 1.17; 95% CI: 1.01, 1.37) and any CVD (aHR 1.09; 95% CI: 0.99, 1.20) compared to women who were fertile. In men, with the exception of stroke, for which we observed a weak imprecise positive association (aHR 1.11; 95% CI: 0.91, 1.34), associations were weakly inverse (e.g., aHR for CHD: 0.92; 0.81, 1.05), though mostly with no statistical evidence that they differed from equivalent associations in women. We observed modest increased risks of CVD outcomes explored in women and weak inverse associations in men, though with no strong statistical evidence on sex differences. Despite the large sample size, our results indicate the need for larger studies to obtain precise results in both sexes and determine whether there are true sex differences.

Women’s health

Anti-Mullerian Hormone and long-term body composition among women in Project Viva

Ellen Francis* Emily Oken Marie-France Hivert Sheryl Rifas-Shiman Jorge Chavarro Wei Perng

Background: Anti-Mullerian Hormone (AMH), a marker of ovarian reserve, is associated with concurrent body composition. However, data evaluating its longitudinal relationship with anthropometric measures are limited. Here, we examined the longitudinal association of AMH with body composition over ~9 years of follow-up.

Methods: Participants were 697 parous women from the Project Viva cohort without polycystic ovarian syndrome. We measured AMH at ~3 years postpartum (baseline) categorized in quartiles and a clinically relevant cutoff value (≥ vs. < 1ng/ml). Outcomes were weight, body mass index (BMI), and waist circumference (WC) assessed at baseline, 4, and 9 years; % body fat was assessed at 4- and 9-years with bio-impedance. We used linear mixed-effect models including all 3 outcome timepoints and accounting for age at the time of AMH assessment, age at follow-up, race/ethnicity, and education. When the outcome was weight or WC we additionally adjusted for height.

Results: The median (IQR) of AMH was 1.97 ng/ml (0.83, 4.36), 29.1% of women had AMH < 1ng/ml, and the mean (SD) age at AMH measurement was 36.7 years (4.9). There was a significant inverse relationship between AMH at baseline and average weight, BMI, and waist circumference over follow-up. In adjusted models, women with AMH <1 vs. ≥1 ng/ml were 4.04 kg (95% CI 1.39, 6.69) heavier, had a 2.30 cm (95% CI 0.01, 4.59) greater WC, and a 1.40 kg/m^2 (95% CI 0.42, 2.37) greater BMI across the 9 years of follow-up. Findings for weight and BMI were similar when comparing lowest to highest quartiles of AMH levels; however, adjustment for race/ethnicity and education attenuated the trend with BMI. AMH was not associated with percent body fat during the follow-up.

Conclusion: Low AMH status was related to higher weight and WC across 9 years of follow-up. Whether elevated AMH is causally involved in higher adiposity across mid-life or simply a marker of upstream risk factors requires further research.

Fetal loss/stillbirth/infant mortality

History of pregnancy loss and risk of incident cardiovascular disease within 5 years: Findings from the Women's Health Initiative Catherine Wright* Daniel A. Enquobahrie Sarah Prager Ian Painter Charles Kooperberg Robert A. Wild Ki Park Shawnita Sealy-Jefferson Mary A. Kernic

Background Prior findings from the Women's Health Initiative (WHI) and other studies have demonstrated an increased risk of cardiovascular disease (CVD) in women with a history of pregnancy loss. Whether pregnancy loss is also associated with age at CVD onset, which has public health and clinical implications, is unknown. We conducted an age-stratified analysis of pregnancy loss and CVD risk in a cohort of postmenopausal women.

Methods Associations between pregnancy loss history and incident CVD within 5 years of study entry were examined among subjects from the WHI Observational Study (N=73,805). Exposures were history of pregnancy loss (miscarriage/stillbirth), recurrent loss, and history of stillbirth. Outcomes were CVD, coronary heart disease (CHD), congestive heart failure (CHF), and stroke. Logistic regression analyses were used to examine associations between exposures and outcomes in three age strata (50-59, 60-69, 70-79). In subjects aged 50-59 at study entry, Cox proportional hazard regression was used to examine incident CVD prior to age 60.

Results In the total sample, stillbirth was associated with increased risk of all outcomes within 5 years of study entry. In age-stratified analyses, an association between stillbirth and incident CVD was shown in all age groups, with the strongest association seen in women aged 50-59 (odds ratio 1.99 (95% CI 1.16-3.43)); however, no interaction with age was observed. Stillbirth was also associated with CHD risk among women aged 50-59 and 60-69, and with risk of CHF and stroke among women aged 70-79. Among women aged 50-59 with a history of stillbirth, a nonsignificantly elevated hazard ratio was observed for CHF prior to age 60 (HR 2.93 (0.96-6.64)).

Conclusions Stillbirth was associated with risk of cardiovascular outcomes in postmenopausal women, but no association with age at CVD onset was observed. History of pregnancy loss, and of stillbirth in particular, may be a clinically useful marker of CVD risk in women.

Women's health

Pregnancy complications in last pregnancy and mothers' long-term mortality risk: do relations differ from that of first pregnancy? A population-based study Abdu Seid*

Pregnancy complications in last pregnancy and mothers' long-term mortality risk: do relations differ from that of first pregnancy? A population-based study

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Background: Studies have shown that women with pregnancy complications in first pregnancy are at increased risk of later cardiovascular (CVD) morbidity and mortality. However, there is little knowledge about complications in the last pregnancy and later CVD. We therefore studied complications (preeclampsia, preterm, and small for gestational age) in women's last pregnancy and maternal CVD death, after accounting for the women's complete reproduction. **Data and Methods**: In this nationwide population-based cohort study, we used registry-based data from the Medical Birth Registry of Norway (1967-2020) linked to the national Cause of Death Registry. We followed mothers whose first birth was during 1967-2013, from the date of last childbirth until death or December 31st 2020, whichever occurred first. Cox proportional hazards regression was used to analyze risk of CVD death between 40 and 69 years of age, according to pregnancy complications and number of lifetime births, adjusting for maternal age at birth and education, and focusing first and last pregnancy. **Results**: Women with complications in their pregnancy were at higher risk for premature CVD death compared to mothers with two lifetime births and no complications. The higher risk for premature CVD death was particularly evident among women with a complication only in the last than women with a complication in the first pregnancy only.

Conclusions: The risk for premature CVD death was higher among mothers who end their reproduction with a complicated pregnancy than women without complications and women with complications in their first pregnancy.

Pregnancy outcomes

Risk of small for gestational age deliveries among African-born Black women residing in California, 2011-2017 Safyer McKenzie-Sampson* Rebecca Baer Brittany Chambers Laura Jelliffe-Pawlowski Deborah Karasek Scott Oltman Matthew Pantell Larry Rand Elizabeth Rogers Karen Scott Jacqueline Torres Bridgette Blebu

Foreign-born Black women in California have a documented lower risk of small for gestational age deliveries (SGA), compared to US-born Black women. Moreover, past research has found that 82% of all foreign-born Black birthing women in California from 2011-2017 were of African origin. However, we know little about how the risk of SGA varies by country of origin. Thus, additional research is needed to explore heterogeneity in the risk of SGA among African-born Black women. This study compares the risk of SGA among African-born Black women contributing the largest proportion of births to all others in California between 2011- 2017.

Data for all singleton live births to African-born Black women who resided in California between 2011-2017 (n=13,194) were used to fit Poisson regression models, adjusted for known socio-demographic and clinical risk factors. We computed risk ratios (RR) and 95% confidence intervals (CI) for the risk of SGA among Nigerian-born, Ethiopian-born and Somali-born women compared to all other African-born women, as previous work has revealed that more than half of all African-born Black women in California immigrate from these countries.

The majority of the study sample was Nigerian-born (28.4%), Ethiopian-born (22.7%) or Somali-born (9.1%). Somali-born women had a significantly higher risk of SGA (RR 1.27; 95%CI 1.02-1.58), compared with all other African-born women. While Ethiopian-born (RR 0.61; 95%CI 0.51-0.73) and Nigerian-born Black women (RR 0.72; 95%CI 0.61-0.85) had significantly lower risks of SGA, compared to all other African-born women.

In this sample of African-born Black women residing in California, the risk of SGA was significantly higher among Somali-born women, but lower among Ethiopian-born and Nigerian-born women compared to all other African-born Black women. Our research suggests that African-born Black women should not be treated as a monolith in studies of nativity, as it may mask variability in the risk of SGA.

Social determinants of health

Residential mobility and preterm birth among non-Hispanic Black birthing persons Samantha, Collette Gailey, Ncube*, Tim Bruckner Samantha Gailey Collette Ncube Samantah Gailey

Background: Recent research finds that upward residential mobility to less disadvantaged neighborhoods may improve birth outcomes. It remains unclear, however, whether this general finding holds for non-Hispanic (NH) Black birthing persons given their distinct mobility patterns and elevated risks of adverse birth outcomes in the US.

Objective: To test whether strong residential mobility affects the risk of preterm birth (PTB) in sibling pairs delivered by NH Black (N=50,149) and NH white (N= 233,428) birthing persons in California (2005-2015).

Method: We created a longitudinal, sibling-linked dataset and merged residential addresses at each birth to a census-derived index of neighborhood disadvantage. We defined strong mobility as moving from a very high to a very low disadvantage neighborhood, or vice versa. We estimated conditional logistic regression models predicting the odds of preterm birth (PTB; <37 weeks' gestation) in the sibling delivered after moving, controlling for the risk of PTB in the sibling delivered before moving.

Results: Strong upward mobility corresponds with a reduced odds of PTB in NH Black (odds ratio [OR]=0.75, 95% Confidence Interval [CI]: 0.56, 0.99), but not NH white, birthing persons. Likewise, all upward mobility (i.e., any move away from neighborhood disadvantage) varies inversely with PTB only for NH Black birthing persons (OR = 0.92, CI: 0.85, 0.99). Results show no detectable relation between downward mobility and PTB across race/ethnicities.

Discussion: Following residential moves into less disadvantaged neighborhoods, NH Black birthing persons show lower risk of delivering PTB. Policies and programs that enable opportunities for upward mobility among NH Black families in particular may reduce racial disparities in PTB. Additionally, longitudinal study designs using sibling-linked controls have the potential to illuminate relations between mobility and perinatal health previously not identified by cross-sectional studies.

Pregnancy outcomes

Racial Discrimination, Neighborhood Segregation, and Maternal Hypertension among Black Women Brittney Butler*

A growing body of work shows that stressors prior to and during pregnancy impact pregnancy-induced hypertensive disorders (PIHDs) but has centered on financial or work stressors. No study has investigated the association between racial discrimination and PIHDs, a pervasive source of stress for Black women—a population disproportionately burdened by PIHDs. Using a subsample of participants with no report of chronic hypertension (n=1,217) from the Life-course Influences on Fetal Environments Study, a retrospective cohort study of Black women ages 18 to 45, who had a singleton birth in Metro Detroit, we examined (1) the association between stress from racial discrimination and PIHDs and (2) whether the relationship varied by neighborhood privilege, a measure of combined racial and economic segregation. Approximately 9% of the sample (n=104) had a PIHD: gestational hypertension (n=72,6%), preeclampsia (n=53,4%), and eclampsia (n=2,0.2%). Using a mixed-effects logistic model women who report not being bothered (Odds Ratio (OR)= 1.79,95% Confidence Interval (CI)=0.82, 3.89), moderately bothered (OR= 1.69,95% CI=0.98, 2.92), and extremely bothered by racial discrimination (OR= 1.81,95% CI=1.05, 3.12) have higher odds of a PIHD, compared to women who report only being bothered a little. There was suggestive evidence of effect modification. Where the elevated odds for PIHDs among respondents reporting no or moderate bother (vs. low bother), was smaller among respondents in the least privileged neighborhoods relative to most privileged neighborhoods. In contrast, the elevated odds for PIHDs among respondents reporting extreme bother (vs. low bother) was greater among respondents in the most privileged neighborhoods relative to the least privileged neighborhoods. The association between racial discrimination and PIHDs should be explored further using novel measures of racial discrimination to better inform clinical interventions and policy solutions to reduce PIHD incidence.

Disability status

Postpartum Hospital Re-admissions among Massachusetts Women Who Are Deaf or Hard of Hearing: A Retrospective Cohort Study Kim McKee* Ilhom Akobirshoev Michael McKee Frank Li Monika Mitra

Objectives: Deaf or hard of hearing women are at higher risk of adverse pregnancy and birth outcomes compared to other women. However, little is known about postpartum outcomes among Deaf or hard of hearing women. The objective was to compare the risk of postpartum hospitalizations and the leading indications for postpartum admissions for Deaf or hard of hearing compared to other women.

Methods: We analyzed data from the 1998-2017 Massachusetts Pregnancy to Early Life Longitudinal Data System, which encompasses all statewide birth certificates, fetal death reports, delivery, non-delivery-related hospital discharge records for Massachusetts residents. We used Cox proportional hazard models to compare the first hospital admission and ≥2 hospital admissions between Deaf or hard of hearing and other women within 1-42 days, 43-90 days, and 91-365 days after delivery. **Results:** We identified 3,546 singleton deliveries to Deaf or hard of hearing women and 1,381,439 singleton deliveries to other women. Deaf or hard of hearing women had a higher risk for any hospital admissions across all periods (HR=1.84; 95%CI 1.46 – 2.34 within 1-42 days; HR=2.76; 95%CI 1.99 – 3.83 within 43-90 days; and HR=3.10; 95%CI 2.66 – 3.60 91-365 days) after childbirth compared to other women. They had almost seven times higher risk for repeated hospital admissions within 43-90 days (HR=6.84; 95%CI 1.66-28.21) and nearly four times higher the risk within 91-365 days (HR=3.63; 95%CI, 2.00-6.59) after delivery compared to other women. The leading indications for postpartum hospitalizations among Deaf or hard of hearing women included: conditions complicating the puerperium/hemorrhage and soft tissues disorders.

Conclusion: Compared to other women, Deaf or hard of hearing women had significantly higher prevalence re-admission across all postpartum periods and for repeated re-admissions >42 days. Leading postpartum indications were distinct from that of the general population.

Methods

Patterned outcomes, unpatterned counterfactuals, and spurious results: perinatal health outcomes following COVID-19 Claire, Ralph, Joan, Jennifer, Alison Margerison, Catalano, Casey, Zeitlin, Gemmill*, Tim Bruckner Claire Margerison Ralph Catalano Joan Casey Jennifer Zeitlin Alison Gemmill Alison Gemmill

Background: Literature estimating the indirect effects of the COVID-19 pandemic on pregnant people and gestation continues to grow. The predominant methods currently used, however, may produce spurious inferences because the common “stacked calendar” methods do not account for temporal patterning in perinatal outcomes when deriving counterfactual estimates.

Objective: We elaborate on this study design challenge for estimating COVID-19 “effects” on perinatal outcomes and illustrate how use of naïve counterfactuals produces spurious results.

Method: We obtained data on all live births from two countries, for USA (from 2014 to 2020) and France (from 2016 to 2020). In the US, we evaluated potential temporal patterns of five perinatal outcomes: preterm birth (<37 weeks gestational age), extreme preterm birth (<28 weeks gestational age), cesarean delivery, total births, and the sex ratio at birth. We applied interrupted time-series methods to identify patterns. For the French data, we examined weekly incidence of extreme preterm birth and compared inferences drawn about COVID-19 “effects” from two distinct study designs: “stacked calendar” and interrupted time series.

Results: For the US data, we detected strong seasonality in all five perinatal series. All series except for sex ratio contained additional patterning above and beyond a purely seasonal component. For the French data, we observed a reduced odds of extreme preterm during the COVID-19 lockdown period (adjusted Odds Ratio [OR]= 0.84; 95% CI: 0.71 – 0.99) only from the “stacked calendar” design, but not using the more rigorous time-series design (OR = 0.98; 95% CI: 0.82 – 1.17).

Discussion: We recommend that subsequent investigations on COVID-19 and other perturbations on perinatal outcomes use widely available time-series methods to derive counterfactuals that account for this strong temporal patterning. Failure to do so may produce spurious results.

Health equity

Racial/Ethnic Disparities in Severe Maternal Morbidity: An Intersectional Life-course Approach Rachel, Jonathan, Audrey, Elliott, Suzan, Mahasin Berkowitz, Snowden, Lyndon, Main, Carmichael, Mujahid*, Elleni Hailu Rachel Berkowitz Jonathan Snowden Audrey Lyndon Elliott Main Suzan Carmichael Mahasin Mujahid Mahasin Mujahid

The ways in which interacting social inequities across multiple domains may shape racial/ethnic disparities on severe maternal morbidity (SMM) remain undocumented. Evoking Intersectionality theory, we sought to assess SMM risk at the nexus of racial/ethnic marginalization, weathering, and individual/neighborhood socioeconomic disadvantage. We leveraged birth hospitalization records from California across 20 years (1997-2017, N=9,805,760) on all live births delivered ≥20 weeks gestation linked with U.S. Census and American Community Surveys. Maternal education proxied individual socio-economic status (SES) and census-tract level neighborhood disadvantage was measured using the Neighborhood Deprivation Index (NDI). We used logistic regression models with three-way interaction terms and cluster-robust standard errors to estimate adjusted probabilities of SMM per 100 births (P) at the combination of levels of race/ethnicity, age, education, and NDI. Adjusting for hospital-payer information, the highest risk of SMM was observed among Black birthing people aged ≥35 years who either had the lowest SES (P=2.78%, 95% Confidence Interval (CI): 2.58%-2.98%) or resided in the most deprived neighborhoods (P=2.78%, 95% CI: 2.60%-2.97%). Black birthing people conceptualized to be better off due to their social standing (aged 20-34 years, college graduates, and living in least deprived neighborhoods) had comparable, and at times worse risk than White birthing people hypothesized to be worse off (aged ≥35 years, high-school degree or less, and living in the most deprived neighborhoods). Our findings indicate that Black birthing people do not receive the same degree of protection from higher SES, and to a lesser extent, better neighborhood environments against risk of SMM compared to their White peers. This study highlights the need to explicitly address structural racism as the driver of racial/ethnic health inequities and the imperative to incorporate intersectional approaches.

Birth defects

Reported Periconceptional Use of Analgesics and Limb Deficiencies in Offspring: Addressing Potential Recall Bias Nedghie Adrien* Martha Werler Julie Petersen Samantha Parker Matthew Fox

Case-control studies have noted associations between non-steroidal anti-inflammatory drugs (NSAIDs) used in the periconceptional period and increased risk of limb defects in offspring. However, exposure information was collected retrospectively after birth- up to 24 months after delivery- which can result in misclassification due to reporting inaccuracies. We conducted a probabilistic bias analysis to explore the potential effects of differential exposure misclassification (i.e., recall bias) of reported periconceptional NSAIDs use. We compared cases (189 amniotic band syndrome (ABS) and 613 terminal transverse limb defects (TTLD)) to 11,829 controls without congenital anomalies from the US National Birth Defects Prevention Study (1997–2011). We simulated 10,000 datasets to adjust for exposure misclassification, using bias parameters identified from external validation studies of medication use among pregnancies with and without birth defects. We conducted our analyses using symmetric triangular distributions to model the probability density functions for the specificity and sensitivity. Specificity lower and upper limits ranged from 0.81 to 0.94 for controls, and 0.96 to 0.99 for cases. Sensitivity ranged from 0.28 to 0.36 for controls and 0.40 to 0.56 for cases. Correcting for differential misclassification of NSAIDs resulted in similar but less precise ORs than the conventional analysis: ABS bias adjusted OR 1.2 (95% SI 0.5, 3.3) vs conventional unadjusted OR 1.2 (95% CI 0.9, 1.6); and TTLD bias adjusted OR 1.3 (95% SI 0.6, 3.3) vs conventional unadjusted OR 1.3 (95% CI 1.1, 1.5). Even under the assumption of low (<0.5) sensitivity, with cases reporting more accurately than controls, and case-control differences in specificity, findings suggested that differences in the accuracy of recall did not result in evidence of biased ORs. These results provide some reassurance that retrospective data collection to study common medications may not lead to biased results.

Big Data/Machine Learning/AI

An Exploratory Study of Machine Learning-Based Placental Clusters in Relation to Growth and Adverse Neonatal Outcomes Julie Petersen* Samantha Parker Jennifer Hutcheon Kimberly Dukes Katherine Ahrens Martha Werler

Placental abnormalities are hypothesized to be etiologically related to adverse neonatal outcomes, e.g., small-for-gestational age (SGA). In our exploratory study, we aimed to identify clinically relevant groups of placental pathology using hierarchical clustering, an unsupervised machine learning method. Data were from the Safe Passage pregnancy cohort (US and South Africa, 2007-2015). Before 24 weeks' gestation, participants were randomly selected to donate placental tissue for blinded, standardized pathology exam. We used hierarchical clustering to identify 4 placental groups, labeled according to the most predominant feature: maternal vascular malperfusion (n=117), fetal vascular malperfusion (n=222), inflammation (n=444), and normal (n=1222). For validation, we repeated analyses in a split sample; classifications were generally consistent. We described distributions of adverse neonatal outcomes by cluster and used multivariable logistic regression to assess the variability of adverse outcomes explained by combinations of placental clusters and birthweight-for-gestational-age categories. Preterm birth and stillbirth were most common in the maternal vascular malperfusion cluster (27% and 9%) and least common in the normal cluster (12% and 1%). SGA and head circumference $<10^{th}$ percentile were most common in the fetal vascular malperfusion cluster (32% and 18% vs normal 18% and 11%, respectively). The logistic regression models with the placental clusters as the only predictors had good discrimination and adjusted R^2 for stillbirth. Model fit improved for other outcomes with the addition SGA, but was best for all outcomes when the placental clusters and a fuller range of birthweight percentile categories were included. Our study demonstrated hierarchical clustering can identify clinically relevant groups of placental features. Placental data plus the full spectrum of birthweight percentiles—not only SGA—may enhance the etiologic study of adverse neonatal outcomes.

Preterm delivery timing and circumstance and their association with false positive newborn hearing screening results Claudia, Gustavo, Nicholas, Melanie, Nicole Holzman, de los Campos, Drzal, Adkins, Talge*, Mandavni Rathore Claudia Holzman Gustavo de los Campos Nicholas Drzal Melanie Adkins Nicole Talge Nicole Talge

Newborn hearing screening failure helps identify infants with hearing loss, but screening failures also occur among infants without hearing loss. Some speculate these false positive results reflect neurodevelopmental disorder risk. Preterm delivery (PTD), a known neurodevelopmental risk factor, has been associated with false positive results at initial screening. We aim to further characterize this association by stratifying PTD by gestational age and delivery circumstance.

To do this, we analyzed birth certificate and Early Hearing Detection & Intervention data from the Michigan Dept. of Health & Human Services (2007-2015; n=919,363). We restricted our analysis to singleton live births with available hearing screening data and obstetric estimates of gestational age (n=655,079). We used two separate logistic regression models to evaluate the association of PTD defined by gestational age (extreme: $\leq$ 28 weeks; moderate: 29-33 weeks; late: 34-36 weeks) and delivery circumstance (spontaneous, medically indicated) with false positive findings, using full-term birth ($\geq$ 37 weeks) as the referent group.

Approximately 4% infants had false positive findings. All gestational age PTD categories were associated with this phenomenon (extreme: OR=4.2, 95%CI 3.7,4.7; moderate: OR=1.2, 95%CI 1.1, 1.3; late: 1.6, 95%CI 1.5, 1.7). Spontaneous and medically indicated PTD were also associated with false positive findings (OR=1.7, 95% CI 1.6,1.8; OR=1.4, 95% CI 1.3,1.5, respectively); these estimates did not differ from one another. All results persisted following adjustment for socio-demographic, pregnancy, and antepartum factors except for moderate PTD (OR=1.0, 95%CI 0.9, 1.1).

PTD is associated with false positive hearing screening results, though findings may vary more by gestational age than delivery circumstance. Further research is needed to investigate factors underlying these differences and whether they correlate with neurodevelopmental disorder diagnoses.

Child health and development

Bidirectional associations between gut microbiome and 24-hour total sleep time in a racially diverse cohort of US infants Tiange Liu* Curtis Tilves Moira Differding Adam Spira Sara Benjamin-Neelon Noel Mueller

Background: Animal experiments and epidemiological studies in adults suggest a bidirectional association between gut microbiome and sleep. However, little is known about this association in infants. We assessed potential bidirectional, longitudinal associations between gut microbiome and 24-hour total sleep time (TST) during infancy.

Methods: We used data from a sub-sample of infants with available accelerometer and microbiome measurements from the Nurture study (US; 2013-2017). Infants wore accelerometers on the left ankle for 4 continuous days at 3 and 12 months. We derived TST using the Sadeh Infant algorithm and averaged it across days at each timepoint. We collected infant fecal samples concurrently and measured microbiome by 16S rRNA gene sequencing of the V4 region. To explore bidirectional, longitudinal associations of microbial diversity (Shannon Index, weighted UniFrac distance) and microbial composition with TST, we examined: A) microbiome at 3 months in relation to sleep at 3 and 12 months; and B) sleep at 3 months in relation to microbiome at 12 months. We adjusted for delivery mode and breastfeeding status at time of fecal sample collection.

Results: Among the 56 infants, 62.5% were black, 19.6% were white, and 17.9% were other/multiple races. Mean TST was 11.1 hours [standard deviation (SD): 1.1] at 3 months and 10.4 hours (SD: 1.0) at 12 months. After adjustment, at 3 months, 17 and 15 microbial amplicon sequence variants (ASVs) were differentially abundant across TST at 3 months and 12 months, respectively (overlapping ASVs n=4). Further, TST at 3 months was also linked to 10 differentially abundant ASVs at 12 months (overlapping ASVs at both timepoints n=1). All false discovery rate adjusted $P<0.05$. We found no significant associations between microbial diversity and TST.

Conclusion: Gut microbiome composition is associated with 24-hour TST at 3 and 12 months of age (cross-sectionally and prospectively), and associations are likely bidirectional.

Risk factors for cerebral palsy and movement difficulties among children without cerebral palsy at five years of age in a European extremely preterm birth cohort Adrien Aubert* Raquel Costa Véronique Pierrat Samantha Johnson Marina Cuttini Corine Koopman-Esseboom Michael Zemlin Ulrika Ådén Jennifer Zeitlin

Background

Children born extremely preterm (EPT, <28 weeks' gestational age (GA)) have a higher risk of motor impairment than their term-born peers. Cerebral palsy (CP) affects about 10% of children and movement difficulties (MD) are common among children without CP. These conditions have different etiologies and less is known about the clinical risk factors for MD without CP; it is hypothesized that associations with social risk are more pronounced for non-CP MD. This study aimed to compare the perinatal, neonatal and social characteristics of children with CP and with non-CP significant MD.

Methods

We used data on children born EPT and followed-up at 5 years in a European area-based cohort from 11 countries (N=1,021). We included children with a CP diagnosis (n=97) and with non-CP significant MD (Movement Assessment Battery for Children-2nd edition ≤5th percentile; n=224). Children without MD (>15th percentile; n=366) served as a comparison group. Associations with clinical and social risk factors, collected from medical records during the neonatal hospitalization and from parental questionnaires at 5, were assessed with multinomial logistic regression.

Results

Having a young mother, lower maternal education, low GA and male sex were associated with similarly elevated risks of CP and significant MD, when compared to children without MD. Birthweight <3rd percentile was associated with significant MD only, while Apgar score <7 and outborn status were only associated with CP. Severe brain lesions were major risk factors for CP, which was also associated with other severe neonatal morbidities, whereas these were less or not associated with significant MD. Bronchopulmonary dysplasia increased risks for both outcomes by a comparable magnitude.

Conclusion

CP and non-CP MD have different perinatal and neonatal risk factor profiles, with fewer risk associations for non-CP MD, whereas social factors and male sex similarly affected risks of both CP and non-CP MD.

Child health and development

Prenatal Omega-6 Polyunsaturated Fatty Acids And Asthma in Middle Childhood: Effect Modification by Mode of Delivery Marshae Nickelberry* Julie Flom Tebeb Gebretsadik Margaret Adgent Cordelia Elaiho Terry Hartman Alex Mason Rosalind Wright Kecia Carroll

Background: Child asthma is a common chronic respiratory illness with *in utero* origins. Higher prenatal levels of omega-6 (n-6) polyunsaturated fatty acids (PUFAs), inflammatory compounds, may influence predisposition to asthma and modulate immune response. Mode of delivery, an exposure that influences the developing immune system may modify the association between prenatal n-6 PUFAs and child asthma. **Objective:** Determine whether the association between prenatal n-6 PUFAs and asthma at age 8-9 years is modified by mode of delivery (vaginal vs. cesarean delivery (c-section)). **Methods:** Pregnant women from Shelby County, Tennessee were enrolled in the CANDLE cohort between 2006-2011. Prenatal plasma n-6 PUFA status was reported as percent of total fatty acids. Asthma outcomes obtained at 8-9 years included current asthma (yes to ≥2: diagnosis, medication, or wheeze in past 12 months) and strict current asthma (diagnosis and medication and/or wheeze in past 12 months). Multivariable logistic regression analyses modeled associations between prenatal n-6 PUFAs and child asthma (controlling for maternal age, race, education level and parity) stratified by mode of delivery. **Results:** Among 912 participants (65% Black; 34% White), 14% of children had current asthma and 12% had strict current asthma. We observed no association between prenatal n-6 PUFAs and child asthma. In models stratified by mode of delivery, an interquartile range increase in n-6 PUFA was associated with increased relative odds for current (OR=1.88, 95% CI= 1.23,2.90) and strict current asthma (OR=2.16, 95% CI=1.34,3.47) amongst children born via c-section. No association was seen in children born vaginally for current (OR=0.86, 95% CI=0.62,1.21) or strict current asthma.(OR=1.05, 95% CI=0.80,1.40) **Conclusion:** In a diverse prenatal cohort, mode of delivery modified the association between prenatal n-6 PUFAs and child asthma at age 8-9 years.

Child health and development

Extrauterine growth restriction at discharge from the neonatal unit and neurodevelopment at 5 years of age in a European extremely preterm cohort Rolf, Pierre Henri, Mikael, Henrique, Patrick, Arno, Pernille, Marina, Raquel, Michael, Elizabeth S, Jennifer Felix Maier, Jarreau, Norman, Barros, Van Reempts, Van Heijst, Pedersen, Cuttini, Costa, Zemlin, Draper, Zeitlin*, Rym El Rafei Rolf Felix Maier Pierre Henri Jarreau Mikael Norman Henrique Barros Patrick Van Reempts Arno Van Heijst Pernille Pedersen Marina Cuttini Raquel Costa Michael Zemlin Elizabeth S Draper Jennifer Zeitlin Jennifer Zeitlin

Background: Extrauterine growth restriction (EUGR) at neonatal discharge has been associated with neurodevelopmental impairment among children born extremely preterm (EP, <28 weeks' gestational age (GA)), with some studies finding higher risks for boys; however few investigations of this association exist after two years of age. This study aimed to assess associations between EUGR at neonatal discharge and cerebral palsy (CP) and cognitive and motor abilities at age five by sex among EP children.

Methods: Data are from a cohort of 957 EP infants born in 2011-2012 from 11 European countries and followed-up at five years using clinical assessments and parental questionnaires. We used two common definitions of EUGR: <-2 SD decrease in Z-scores between birth and discharge using Fenton's charts (Fenton) and low weight-gain velocity <11.2 grams per kilogram per day (1st quartile) based on Patel's model (Patel). Outcomes included diagnosis of CP (yes/no), intelligence quotient (IQ) assessed with the Wechsler Preschool and Primary Scales of Intelligence (WPPSI) tests and motor function using the Movement Assessment Battery for Children-2nd edition. Logistic and linear models were adjusted for covariables associated with growth and neurodevelopment.

Results: severe EUGR prevalence was 33.9% by Fenton and 26.3% by Patel. Boys with EUGR by Patel had elevated odds of CP (OR: 2.1, 95% CI=0.9-4.7), with no association for girls (OR: 0.6, 95% CI=0.2-2.1, P=0.12 for interaction). Children with EUGR had lower IQ (-3.9 points (95% CI=-7.2; -0.6) by Fenton; -5.0 (95% CI=-8.2; -1. 8) by Patel, with no sex interaction). No association was observed between EUGR and motor performance.

Conclusion: EUGR at discharge from the neonatal hospitalization was common among EPT infants and was associated with a decrease in IQ scores at five years of age and CP risks among boys. Better nutrition and growth in the neonatal unit could be a strategy for improving neurodevelopment after EPT birth.

Child health and development

Early-life Developmental Milestones and Childhood Neurodevelopment in The Adolescent Brain Cognitive Development (ABCD) study Haoran Zhuo* Jingyuan Xiao Wan-ling Tseng Zeyan Liew

Background and Objectives: Infancy developmental milestones may be early markers for long-term neurodevelopment and mental health, but evidence from large and diverse samples is lacking. We investigated whether developmental milestones are associated with childhood neurocognition, behaviors, and mental health in the Adolescent Brain Cognitive Development (ABCD) study.

Methods: We analyzed data of 8,218 singleton-born children enrolled in the ABCD study in 2016-2020. The ABCD includes a geographically and socio-demographically diverse sample of children aged 9-10 from 17 states around the US. Children's ages (month) attaining four developmental milestones (first rollover, unaided sit, unaided walk, and speak first words) were reported by their biological mothers. Linear mixed-effects models estimated associations of these milestones with clinically evaluated neurocognitive function, children-reported behavioral problems and psychotic-like experiences (PLEs), adjusting for maternal social-demographic variables. We additionally compared models with and without adjusting for perinatal risk factors including maternal pre-pregnancy BMI, prenatal care, substance use, pregnancy disorders and birth outcomes that could affect early brain development.

Results: Later attainment of all milestones was associated with poorer neurocognitive abilities in childhood, with first rollover and unaided walk showing the strongest associations. Early or later attainment of unaided sit and speak first words was associated with externalizing problems and PLEs. Effect estimates were moderately attenuated (~5-20%) after adjusting for perinatal risk factors.

Conclusions: Results suggest that specific motor and language milestones during infancy are predictive of childhood neurodevelopment and mental health, and that perinatal risk factors of brain development have contributed to these links. Longitudinal data are needed to rule out influence of potential recall bias of milestones in this dataset.

Breastfeeding initiation and duration: The impact of prenatal alcohol exposure and gestational outcomes Hawa Mariko* Sara Brown Kristina Uban

Benefits of breastfeeding for infants is well established. However, the literature demonstrates a potential paradox where infants born preterm (PTB) or low birthweight (LBW) demonstrate lower likelihoods of being breastfed and, when initiated, shorter durations compared to infants born at term or of normal birthweight (NBW). Moreover, while postpartum alcohol use and lactation are documented, less is understood about prenatal alcohol exposure influencing breastfeeding behavior. Relationships between gestational age at birth, birthweight, infant prenatal alcohol exposure (PAE), and breastfeeding outcomes were investigated among singleton births (n=7,932; ABCD Study). Mixed effects logistic regression models were leveraged to estimate odds ratios (OR) and 95% confidence intervals (CI) of breastfeeding initiation (yes, no) and duration (<6 months, ≥6 months). Models were adjusted for maternal age, number of complications at birth, number of maternal pregnancy medical problems, race/ethnicity, and prenatal tobacco exposure. Findings suggest a reduced likelihood of breastfeeding initiation with earlier gestational ages, and increased likelihood of breastfeeding initiation among infants with PAE. Univariate analyses demonstrated significantly lower odds of ever being breastfed among Late-PTBs [OR=0.68, 95% CI (0.52-0.88)] and LBW [OR=0.61, 95% CI (0.49-0.76)] compared to Full-term births and NBW infants. After adjustment for covariates, a significant 39% lower odds of ever being breastfed was observed among Early-term compared to Fullterm births, while birthweight differences became attenuated. Infants with PAE also significantly demonstrated 64% higher odds of ever being breastfed in univariate analyses and 76% higher odds after adjustment compared to non-PAE infants. There were no significant findings for determining 6-month breastfeeding duration. Current findings between gestational age, birthweight, and PAE with breastfeeding initiation warrant further investigation.

Child health and development

Impact of Ear Infection History and Hearing Impairment on Children's Academic Achievement in Primary School: The U.S. Early Childhood Longitudinal Study–Kindergarten Class of 2010–11 (ECLS–K:2011) Chuan-Ming, Howard J., Le, Christa L., Gregory A., Mabel L. Li, Hoffman, Chen, Themann, Flamme, Rice*, Chuan-Ming Li Chuan-Ming Li Howard J. Hoffman Le Chen Christa L. Themann Gregory A. Flamme Mabel L. Rice Howard Hoffman

Background: Ear infections (EIs) are a common cause of hearing loss in children. The link between these conditions and academic performance is inconclusive in the literature.

Objective: To estimate prevalence of medically-diagnosed EIs, hearing loss, and associations with academic performance.

Methods: ECLS–K:2011 drew a national sample of 18,170 children and followed them from kindergarten to 5th grade. Parent-reported health/demographic information was obtained, including history of medically-diagnosed EIs and perceived hearing trouble (HT). Reading, math, and science achievement were assessed annually. Pure-tone thresholds were obtained on a subsample of ~3,500 in 2nd, 3rd, and 5th grades. Statistical analysis included logistic mixed models, generalized estimating equations, and PATH modeling.

Results: EI prevalence was 58% before age 2, 50% from age 2 to kindergarten entry, 31% in kindergarten, 20% in 1st, 17% in 2nd, 15% in 3rd, and 13% in 4th and 5th grades. By 5th grade, 82% of children had at least one EI and 30% had one or more time periods with 3 or more EIs. Prevalence of reported HT ranged from 2.6% to 3.2% in each time period. Prevalence of measured hearing impairment (HI) was 11.7% in 2nd grade, 7.7% in 3rd, and 6.5% in 5th. After controlling for other risk factors, EIs were significantly associated with increased HT [OR (95% CI): 3.4 (2.7-4.0)] and measured HI [2.2 (1.2-3.1)]. EI history was significantly associated with decreased reading (p=0.0001), math (p=0.002), and science scores (p=0.06). Measured HI was also associated with decreased reading (p=0.001), math (p=0.0003), and science scores (p=0.03). EIs were associated with reading (p=0.007) and math scores (p=0.006) only in the current year, not in subsequent years.

Conclusion: Prevalence of EIs and hearing loss is high in children. EIs and HT/HI are associated with decreased academic achievement. EIs only impacted school performance in the current year. Prior history of frequent EIs is associated with occurrence of subsequent EIs.

Child health and development

Do study features contribute to heterogeneity in results of meta-analyses on cognitive outcomes in children born very preterm?Sabrina, Anna, Valérie, Andrei, Jennifer Twilhaar, Chaimani, Benhammou, Morgan, Zeitlin*, Mariane Sentenac Sabrina Twilhaar Anna Chaimani Valérie Benhammou Andrei Morgan Jennifer Zeitlin Jennifer Zeitlin

Background: Meta-analyses are increasingly used to synthesize the results of the voluminous literature on cognitive outcomes of very preterm (VP) birth. However, these meta-analyses are limited by large heterogeneity in effect sizes, which may be due to variability in study designs and inclusion criteria for VP populations.

Objective: To describe characteristics of study designs and methodology of studies on cognitive VP birth outcomes and investigate their impact on results of meta-analyses.

Methods: Following a systematic literature search, 5 meta-analyses were identified, covering 156 unique studies published before 2018 and reporting results from 103 cohorts. Information on study design, sample characteristics, and relevant results were extracted from included studies. Study design features included study type i.e. population/center-based, sample size, follow-up rates, adjustment for social context, management of severe impairments, test type. We computed standardized mean difference (SMD) for intelligence quotient (IQ) between children born VP and term and used random-effects subgroup meta-analyses and meta-regressions to explore whether study features explained between-study variance in SMDs.

Results: Diversity was found in study design features. Children with severe impairments were excluded in 58 (56%) of the cohorts and 31 (30%) cohorts accounted for potential confounding effect of social context. The least reported study feature was the follow-up rate (missing in 38 cohorts). The largest difference in SMDs was found between studies using full-scale IQ tests (61 cohorts, SMD=-0.89, 95% CI -0.96, -0.82) and short forms (25 cohorts, SMD=-0.68, 95% CI -0.68, -0.57).

Conclusions: Study design and methodology vary greatly across studies investigating cognitive outcomes in children born VP. Recommendations for harmonizing the reporting of design features in primary studies and for including them in meta-analyses would improve the quality of evidence synthesis.

COVID-19 Pandemic

Pandemic worries and stressors in relation to tobacco product use among postpartum women during the COVID-19 pandemic Xuanxuan Zhu* Jihong Liu Peiyin Hung Anthony Alberg Anwar Merchant

Background. Postpartum smoking increases women's health risks and exposes infants to tobacco smoke. Few studies have examined whether pandemic-related worries and stressors have contributed to cigarette smoking and nicotine product use among postpartum women during the COVID-19 pandemic.
Methods. Women throughout the US who gave birth in March 2020 or after completed an online survey between May 21-June 11, 2020 (n=797). Tobacco users were those who reported currently smoking cigarettes, using e-cigarettes, and/or other tobacco/nicotine products. The increased use of tobacco products during the pandemic was also assessed. Pandemic-related worries were assessed by a summary score (range: 0-40) of 10 types of worries that a woman experienced during the pandemic (e.g., worried about giving birth in hospital). Pandemic-related stressors were measured by a sum of 4 stressors (e.g., any household member tested COVID positive) during the pandemic (range: 0-4). Logistic regression models were used to estimate the odds of using tobacco products or increasing their use in relation to pandemic-related worries and stressors.
Results. 24.7% of postpartum women reported using tobacco products after delivery. Among users, 10.8% reported increased use of tobacco products during the pandemic. Pandemic worries were positively associated with higher odds of tobacco use (Adjusted Odds Ratio [AOR]: 1.08, 95% CI: 1.04-1.13) and increased tobacco use during the pandemic (AOR: 1.13; 1.06-1.20). Experiencing one additional pandemic stressor was also associated with increased tobacco use during the pandemic (AOR: 1.80, 95% CI: 1.30-2.51).
Discussion. During the pandemic, tobacco product use was high among postpartum women, particularly among those having more pandemic worries and stressors. Public health programs are much needed to reduce tobacco product use among postpartum women during the pandemic by preventing and reducing pandemic worries and stressors.

COVID-19 Pandemic

Maternal psychosocial stress and perinatal outcomes during versus prior to the COVID-19 pandemic Sarah Comstock* Xiaodan Tang Irene Tung Patrick Tarwater Guojing Wu Cristiane Duarte Akram Alshawabkeh Jessica Arizaga Tracy Bastain Patricia Brennan Carrie Breton Carlos Camargo Camille Cioffi Jose Cordero Dana Dabelea Arielle Deutsch Amy Elliott Anne Dunlop Assiamira Ferrara Margaret Karagas Barry Lester Cindy McEvoy John Meeker Jenae Neiderhiser Julie Herbstman Leonardo Trasande Thomas O'Connor Alison Hipwell Kimberly McKee for the ECHO Program

Many studies investigating the pandemic focus on the impact of COVID infection. We hypothesized that the pandemic may also indirectly affect women and children via the substantial burden of pandemic-related maternal psychosocial stress. Thus, we evaluated the impact of maternal depressive symptoms and perceived stress on birth outcomes among pregnant women enrolled in the Environmental Influences on Child Health Outcomes (ECHO) Program prior to and during the pandemic. We also assessed COVID-specific stressors, including changes in prenatal care, across specific pandemic time periods. We used data collected from 2016 Jan 1-2021 May 31 from a total of 41 cohorts in 23 states and Puerto Rico. Nearly 30% of participants reported mild stress and 10% experienced moderate/severe stress. Furthermore, 15% experienced mild depression and 9% moderate or severe depression. Overall, maternal symptoms of depression and perceived stress during pregnancy were similar in the pre-pandemic and pandemic groups. After propensity matching, generalized estimating equation analyses indicated that the pandemic had a small negative effect on gestational age at delivery (B=-0.33 weeks, SE=0.149), p=0.025), a null association with birth weight (B=-28.14g, SE=49.28, p=0.568; R^2=0.001), and a small positive effect on birth weight for gestational age (B=0.15 z-score units, SE=0.07, p=0.041; R^2<0.001). A majority (72%) of pregnant women reported a negative impact of COVID-19 on their life. The infants of those reporting a negative impact of the pandemic had adjusted birth weights nearly a quarter standard deviation lower than those reporting positive/no impact. Women who gave birth before 2020 Jun 19 were most likely to report being moderately or extremely distressed about changes to prenatal care and birth experiences. In this national cohort study, experiencing the COVID-19 pandemic in pregnancy was associated with small decreases in gestational age at birth and with distress about changes in prenatal care early in the pandemic. Our results demonstrating distinct associations with adjusted birth weight based on reported pandemic experiences suggest future analyses should account for a diversity of positive and negative impacts, and the factors that best differentiate sub-populations should be determined.

COVID-19 Pandemic

Interaction of COVID-19 infection during pregnancy and mother pre-pregnancy obesity status in relation to infant low birth weight Deepika Shrestha* Monica Roundtree Rebecca Winter Larissa Pardo Kossia Dassie Emily Putzer Fern Johnson-Clarke

Background. Low birthweight (LBW, <2500 g) is an important predictor of short- and long-term impact on childhood and adulthood cardio-metabolic health of the infant. In general, high maternal pre-pregnancy (pp)-obesity status is associated with increased birth weight; however, the associations between maternal pp-obesity and LBW remain inconclusive. Investigating the interaction of COVID-19 in pregnant individuals compared with not-infected pregnant individuals and maternal pp-Obesity status with LBW is much needed.

Study Design and Study population: We linked DC Natality vital records data starting from March 1^{t}, 2020 to December 30^{h}, 2021 with DC Health COVID-19 Surveillance system to identify mothers who were infected with COVID-19 during their pregnancy period and/or within 15 days of delivery. COVID-19 positive was determined by PCR laboratory confirmation. Key words such as Mother first and last name, date of birth, address was used for matching the records. Mother pp-obesity status (as underweight, normal, overweight and obese) was calculated using self-reported ppBMI status. Bivariate and multivariate logistic regression was used to assess the relationship between 1. maternal pp-obesity status and risk of having COVID-19+ve, 2. maternal pp-obesity status and LBW, 3. maternal pp-obesity status and LBW stratified by mothers COVID-19 infection during pregnancy. The odds ratio (OR) and 95% CI were calculated adjusting for mother's race/ethnicity, education, plurality, marital status, gestational diabetes and hypertension, pre-pregnancy diabetes and hypertension, and gestational age at delivery.

Results: 715 mothers (3.3 %) were COVID-19 +ve and 10% had LBW out of 21,877 DC births. On full adjusted model, we found mothers who were obese had 28% increased odds of having COVID 19+ve (OR: 1.28, 95% CI: 1.14- 2.17) compared to mothers with normal BMI. Overall Underweight mother had 57% increased odds of having LBW (OR: 1.57, 95% CI: 1.14- 2.17); this relationship strengthened among Blacks and Asians. The odds for having COVID-19 infection during pregnancy were 3.5 times more likely odds for mothers with Underweight BMI (OR: 3.53, 95% CI: (1.15, 10.81) compared to normal BMI in bivariate analyses but remained insignificant on fully adjusted model.

Conclusion: Mothers with underweight BMI and COVID-19 infection during pregnancy showed significant increased odds of having LBW in bivariate analyses.

COVID-19 Pandemic

Postpartum contraceptive provision among rural and urban women before and after the start of the COVID-19 pandemic Catherine Gelsinger* Kristin Palmsten Heather Lipkind Mariah Pfeiffer Christina Ackerman Jennifer Hutcheon Katherine Ahrens

Background: Preliminary findings from select health systems revealed interruptions in reproductive healthcare services due to the COVID-19 pandemic; however, the impact on rural women is not yet understood. The objective of our analysis was to estimates changes in postpartum contraceptive provision at the start of the COVID-19 pandemic by rural residency.

Methods: We used data from the Maine All Payer Claims Database on women who delivered between October 2015 and September 2020 (n=42,226). Using an interrupted time series design, we estimated changes in provision rates of long-acting reversible contraction (LARC), female sterilization, and moderately effective contraception (injectables, pill, patch, ring, and diaphragm) within 3 and 60 days of delivery after the start of the COVID-19 pandemic (March 2020). Negative binomial and Poisson regression models, offset for the number of deliveries, were used to calculate rate ratios (RR) and 95% confidence intervals, overall and by rural residency.

Results: Overall, 3-day provision rates of LARC, female sterilization, and moderately effective were 9.0, 66.4, and 14.6 per 1,000 deliveries; corresponding 60-day provision rates were 153.8, 75.8, and 224.3 per 1,000 deliveries. LARC 3-day provision (RR 1.83; 95% CI 1.71, 1.95), moderately effective 3-day (RR 1.53; 95% CI 1.34, 1.74) and 60-day provision (RR 1.08; 95% CI 1.05, 1.11) increased after March 2020. Sterilization 3-day (RR 0.69; 95% CI 0.62, 0.76) and 60-day provision (RR 0.71; 95% CI 0.65, 0.80) decreased; LARC 60-day provision (RR 0.96; 95% CI 0.94, 0.98) was relatively stable. Findings were generally similar between rural and urban women.

Conclusion: The COVID-19 pandemic increased provision of LARC 3-day and moderately effective contraception, and decreased provision of sterilization for both rural and urban women. Our findings suggest interventions are needed to reduce disruptions in contraceptive services for future healthcare challenges.

COVID-19 Pandemic

Approaches to Mitigating Sexual and Reproductive Health Risks Associated with Intimate Partner Violence Among Adolescents during the COVID-19 Pandemic Jessica LaHote* Maria Olivia Egemba Taahira Thompasionas Nana Serwah Adom Maia Fulton-Black Briana McGhee Vanessa Nigg Nicole Nwaru Yunilda Perez Estelle Raboni

Introduction: In 2019, 6% of adolescents in New York City experienced sexual dating violence. Intimate partner violence (IPV) increased among the general population following the declaration of the COVID-19 pandemic. In April 2020, a peak in COVID-19 case rates coincided with a 30% increase in the number of domestic violence reports filed. Given the overall impact of the pandemic on IPV, the percentage of adolescents experiencing sexual dating violence is expected to have increased since 2019. Maintaining access to sexual and reproductive health (SRH) services throughout the course of the pandemic is crucial to mitigating the SRH risks resulting from sexual violence and ensuring that adolescents can exercise their reproductive rights.

Approaches: New York City Teens Connection (NYCTC), a program of the NYC Department of Health and Mental Hygiene (DOHMH), is committed to ensuring that all New Yorkers can access resources needed to exercise their reproductive autonomy. In response to the COVID-19 pandemic, NYCTC converted its usual in-person clinic tours, where youth learn about the nearby teen-friendly clinics that provide high-quality, free or low-cost SRH services, to an online format that teachers can present as part of a virtual SRH education curriculum. Since March 2020, over 4,200 students have received this presentation. Additionally, NYCTC compiled an informational guide on SRH services provided at clinics around the city during the pandemic and has worked to maintain easy access to condoms stocked at DOHMH buildings around the city. NYCTC has also created and continuously promoted a video campaign on sexual consent; the campaign videos have over 110,000 views to date.

Conclusion: As the COVID-19 pandemic continues, it is crucial not to overlook the health risks posed by IPV. Public health practitioners have a responsibility to address these risks through innovative interventions and adaptations to programs that uphold principles of reproductive justice.

COVID-19 Pandemic

Temporal trends and determinants of COVID-19 vaccination during pregnancy in Ontario, Canada Deshayne Fell* Eszter Török Tavleen Dhinsa Gillian D. Alton Sheryll Dimanlig-Cruz Annette K. Regan Ann E. Sprague Shannon E. MacDonald Sarah A. Buchan Jeffrey C. Kwong Sarah E. Wilson Siri E. Håberg Christopher A. Gravel Kumanan Wilson Sandra Dunn Darine El-Chaâr Jon Barrett Nannette Okun Prakesh S. Shah Mark C. Walker Shelley D. Dougan

Information on COVID-19 vaccine coverage, and its determinants, during pregnancy is limited. This study assessed temporal patterns in COVID-19 vaccine coverage and factors associated with vaccine initiation during pregnancy in Ontario, Canada. We linked population-based prenatal screening records (ongoing pregnancies) and birth records (completed pregnancies) from the provincial birth registry with the COVID-19 vaccination database between Dec 14, 2020 and Nov 30, 2021. Rates of coverage (≥1 dose before or during pregnancy) among all pregnant individuals were computed by month, stratified by maternal age and neighborhood sociodemographic characteristics. Among completed pregnancies between Apr and Nov 2021, we assessed associations between sociodemographic, behavioral, and pregnancy-related factors with COVID-19 vaccine initiation during pregnancy using log binomial regression to estimate adjusted risk ratios (aRR) and 95% confidence intervals (CI). Among 198,915 pregnant individuals, COVID-19 vaccine coverage increased from 0.03% among those pregnant in Dec 2020 to 66.4% among those pregnant in Nov 2021. Gradients in coverage by maternal age and neighborhood income persisted over time. Factors associated with a lower likelihood of COVID-19 vaccine initiation during pregnancy included lower maternal age (<25 vs. 30-34 years aRR: 0.50, 95% CI: 0.47-0.52), smoking during pregnancy (vs. non-smoking aRR: 0.60, 95% CI: 0.57-0.63), rural residence (vs. urban aRR: 0.87, 95% CI: 0.84-0.89), lower neighborhood income (lowest quintile vs. highest aRR: 0.66, 95% CI: 0.64-0.68), and higher material deprivation (highest quintile vs. lowest aRR: 0.68, 95% CI: 0.65-0.71). COVID-19 vaccine coverage during pregnancy in Ontario increased over time, but remained lower than in the general population. Additionally, there was substantial heterogeneity in initiation by sociodemographic, behavioral, and pregnancy-related characteristics in this population.

Disability status

The Relationship Between Disability Status and Homelessness in U.S. Public Schools in 2019-2020 Emily, Paige, Thomas Bock, Brochu, Byrne*, Eric Rubenstein Emily Bock Paige Brochu Thomas Byrne Emily Bock

Background: Youth experiencing homelessness and youth with disabilities experience inequities that lead to negative health outcomes. A large overlap likely exists between the two populations; however, this doubly marginalized sample is poorly documented in education department and epidemiological data.

Objective: To quantify the population of students with a disability experiencing homelessness by school district in the Northeastern US and to compare the occurrence of homelessness by disability status and between states.

Methods: We used publicly available enrollment data from each state's department of education and federal homelessness data. Data were merged by Local Education Agency. The proportion of students with and without disability experiencing homelessness were then calculated along with relative risks and corresponding 95% confidence intervals comparing the risk of homelessness for disabled and abled students at the state level.

Results: In MA, 3.38% and 1.86% of students experienced homelessness with and without disabilities, respectively (relative risk 1.81, 95% CI: 1.78, 1.84). In NY, 2.21% of students with a disability experienced homelessness while 1.65% of students without a disability did (relative risk 1.34, 95% CI: 1.32, 1.36). In RI, 1.92% of students with a disability experienced homelessness and 0.77% of students without a disability experienced homelessness (relative risk 2.49, 95% CI: 2.38, 2.60). In all four states, a higher proportion of students with disabilities experienced homelessness than their abled peers. We will characterize findings at the district and county level and compare between states to estimate the impact of educational policies.

Conclusions: Quantifying this population is an important first step in being able to decide where policies and funding could best be implemented to improve outcomes for these students.

Environment/climate change

Associations of a Metal Mixture with Iron Status in U.S. Adolescents: Evidence from the National Health and Nutrition Examination Survey Samantha Schildroth* Alexa Friedman Julia Anglen Bauer Birgit Claus Henn

Background: Iron (Fe) is a metal needed for normal biologic function. In adolescence, Fe need increases up to 25% to support rapid physical and neurologic maturation. Prior epidemiological evidence suggests that individual metals are associated with Fe status, but no prior study has assessed associations of metal mixtures with Fe status.

Methods: We used cross-sectional data from the National Health and Nutritional Examination Survey (NHANES) for 588 adolescents (ages 12-17 years) to estimate associations of a metal mixture (manganese (Mn), lead (Pb), selenium (Se) and cadmium (Cd)) with Fe status metrics, including ferritin and transferrin receptor (TfR). Bayesian Kernel Machine Regression was used to estimate associations of 1) individual metals, 2) the overall mixture, and 3) interactions between metals, with Fe status, while adjusting for sociodemographic covariates. Beta (β) estimates and 95% credible intervals (CIs) were estimated.

Results: Median blood metal concentrations (µg/L) for Pb, Mn, Se, and Cd were 4.0, 10.8, 187.9, and 0.1, respectively. Mn and Cd were both associated with impaired Fe status, including decreased ferritin (for an increase from 25th to 75th percentiles, Mn: β= -0.45 [95% CI= -0.61, -0.28]; Cd: β= -0.34, [95% CI= -0.50, -0.18]) and increased TfR concentrations (Mn: β= 0.07, 95% CI= [0.03, 0.11]; Cd: β= 0.05, 95% CI= [-0.02, 0.13]), when other metals were held at their 75th percentiles. Suggestive Mn-Cd interactions were found, such that the association of each metal with Fe status was stronger at higher concentrations of the other metal. Concurrently increasing concentrations of all metals were associated with worse Fe status (e.g., decreased ferritin).

Conclusions: Findings suggest that environmental metals, assessed individually and as a mixture, are associated with impaired Fe status. Altered Fe status following metal exposure has significant public health implications for adolescent health.

Environment/climate change

Remotely sensed measures of Hurricane Michael damage and adverse birth outcomes in the Florida panhandle Elaina, Christopher, Leslie, Samendra, Maureen, Emily Gonsoroski, Uejio, Beitsch, Sherchan, Lichtveld, Harville*, Ke Pan Elaina Gonsoroski Christopher Uejio Leslie Beitsch Samendra Sherchan Maureen Lichtveld Emily Harville Emily Harville

Background Studies of effects of hurricanes on birth outcomes often rely on approximate measures of exposure. This study aims to use observed damage from aerial imagery to refine residential building damage estimates, evaluate the population changes post landfall, and assess the associations between the extent of residential building damage and adverse perinatal outcomes.

Method Vital statistics data were used to align maternal geocoded address data to high-resolution imagery (0.5-foot resolution, true color with red, blue, and green bands) aerial photographs. Machine learning (support vector machines) classified residential roof damage across the study area. Perinatal outcomes were compared with the presence or absence of damage to the mother's home. Log-binomial regression models were used to compare the populations living in and outside of high-risk areas, to assess the population changes after Hurricane Michael, and to estimate the associations between damage after Hurricane Michael and adverse birth outcomes. A semi-parametric linear model was used to model time of first prenatal care (PNC) visit and increase in damage.

Result Women with lower education and/or of Black or other non-White race/ethnicity were more likely to live in areas that would see high damage than other groups. Living in the area with relatively high damage increased the risk of having intermediate or inadequate PNC (adjusted Risk Ratio=1.21, 95% CI: 1.03, 1.43), but not other adverse perinatal outcomes.

Conclusion Aerially observed damage data enable us to evaluate the impact of natural disasters on perinatal outcomes based on residential building damage immediately surrounding a household. The association between the extent of damage and adverse perinatal outcomes should be further investigated in future studies.

Environment/climate change

Preterm birth following the 1995 Chicago Heat Wave: an integrated synthetic control and time series approach Tim Bruckner* Heather McBrien Alison Gemmill Ralph Catalano Joan Casey

Background: The 1995 Chicago Heat Wave produced the city's second hottest July on record and accounted for 739 heat-related deaths. Low-income urban residents with limited access to air conditioning were disproportionately affected. Previous work finds elevated risk of preterm birth (i.e., delivery at <37 weeks) among gestations exposed to extreme heat but has not converged on a specific critical window for heat exposure.

Objective: To use the Chicago Heat Wave as a natural experiment to evaluate racial disparities (non-Hispanic Black versus non-Hispanic white) in the relation between heat and preterm birth.

Method: We obtained incidence of preterm birth to low-income residents of Chicago over 84 months (Jan 1990 to Dec 1996). We applied ARIMA interrupted time series methods to identify and remove autocorrelation in preterm birth. We integrated a synthetic control method into the time-series approach by specifying a composite comparison (control) population outside of the mid-western US that did not experience the heat wave but that had similar pre-heat wave trends in preterm birth. We examined males and females separately.

Results: The risk of preterm birth among females born to low-income birthing persons rose to the highest level in the entire time period three to five months after the heat wave, for both non-Hispanic Black (risk difference at 3 months=.059, 95% CI: .017—.10, a 27% increase above the mean) and non-Hispanic white infants (risk difference at 5 months=.071, 95% CI: .022—.12, a 64% increase above the mean). We, by contrast, observed no detectable change in preterm among male births following the heat wave.

Discussion: The Chicago Heat Wave during the second trimester preceded an increased risk of preterm birth among females born to low-income Black and white birthing persons. The specificity of the relation to low-income birthing persons suggests the need for targeted interventions such as financial assistance to use air conditioning.

Fertility and fecundity

Interpregnancy intervals of Black native-born and foreign-born women in the US: A cross-sectional study Comfort Olorunsaiye* Larissa Brunner Huber Edward Wolff Lauren Fisher

Background: Short interpregnancy interval (IPI) is associated with adverse pregnancy and birth outcomes. Black US women experience higher rates of short IPI. The evidence on IPI in Black immigrants in the US is not well documented. Hence, the purpose of this study was to assess the prevalence of short IPI and related factors among Black US-born and foreign-born women.

Methods: We conducted an online, cross-sectional survey of women born abroad or in the US (n=418) in September 2021. Eligibility criteria included: living in the US, aged 18-44 years, identified as Black, and proficient in English. The exposure variable was nativity (US-born or foreign-born). The outcome variable was the interval between the birth of the most recent child and the preceding one (<6, 6-17, 18-35, ≥36 months). Multivariate ordinal logistic regression, adjusted for potential confounders, was used to assess the nativity-IPI association. Study procedures were approved by our local IRB.

Results: There were 98 (23%) foreign-born and 320 (77%) US-born women and 196 non-first births in the sample. While foreign-born and US-born women had a similar prevalence of IPI <6 months (21% vs. 17%), US-born women had higher rates of IPI ≥36 months (44% vs. 34% foreign-born, p=0.04). After adjustment for age, parity, marital status, education, income, contraceptive attitude, ethnicity, access to health care, and postpartum care, foreign-born women had statistically significantly decreased odds (odds ratio=0.79, 95% confidence interval=0.60-0.99) of being in the higher categories of IPI (i.e., 6-17, 18-23, ≥36 months), compared to <6 months.

Conclusion: Foreign birth was statistically significantly associated with IPI <6 months among Black women in the US. Further research to understand the predictors of short IPI in foreign-born Black women would help tailor contraceptive counseling and preconception care to optimize IPI in this population.

Fertility and fecundity

A Prospective Cohort Study of Thyroid Disorders and Fecundability Holly Crowe* Elizabeth Pearce Elizabeth Hatch Lauren Wise Amelia Wesselink

Thyroid disorders have been associated with menstrual irregularities and subfertility, although thyroid treatments can mitigate these risks. We analyzed data from a preconception cohort of pregnancy planners in the United States and Canada. From 2013-2021, we followed 12,432 female pregnancy planners who had been trying to conceive for ≤6 cycles at entry. Participants completed a baseline questionnaire and bi-monthly follow-up questionnaires for up to 12 months or until pregnancy. On baseline questionnaires, participants reported thyroid disorder diagnosis and medications used to treat thyroid disorders. We used multivariable-adjusted proportional probabilities regression models to estimate fecundability ratios (FR) and 95% CIs, comparing those with and without thyroid disorders. We adjusted for demographic/lifestyle factors and medical/reproductive history. Overall, 1,064 participants (9%) reported a previous diagnosis of thyroid disorder, of whom 879 (83%) reported a diagnosis of hypothyroidism, Hashimoto’s disease, or use of thyroid hormone replacement, indicating likely hypothyroidism. The remaining participants reported hyperthyroidism, Grave’s disease, or medication indicating hyperthyroidism (2%), a diagnosis of thyroid autoimmunity (2%), or a diagnosis of thyroid nodules or cancer (3%). Ten percent of individuals with a thyroid disorder did not report a specific diagnosis or thyroid medication use. Individuals with hypothyroidism had slightly reduced fecundability compared to those without a thyroid disorder (FR=0.85, 95% CI: 0.78-0.93). The FRs for diagnosis of hyperthyroid, thyroid autoimmunity, or thyroid nodules/cancer were 1.26 (0.85-1.86), 1.12 (0.71-1.75), and 0.82 (0.53-1.20), respectively. The FR for individuals who did not report medication use or a specific diagnosis was 0.81 (0.62-1.05). While our findings show that hypothyroidism is associated with slightly reduced fecundability, we did not have lab results to confirm participant thyroid status.

Fetal loss/stillbirth/infant mortality

A prospective cohort study evaluating periconceptional exposure to seasonal inactivated influenza vaccines and risk of miscarriage Annette Regan* Amelia Wesselink Tanran Wang Elizabeth Hatch Kenneth Rothman Olivia Orta David Savitz Jennifer Yland Lauren Wise

Background: Although pregnant individuals are a priority group for inactivated influenza vaccination (IIV), <40% of individuals receive vaccination during pregnancy. Safety concerns are a major contributor to vaccine refusal. While clinical trial and observational data have provided reassurance about the safety of IIV during second and third trimesters, effects of periconceptional IIV exposure on early pregnancy outcomes, such as miscarriage, have not been well studied.

Methods: We analyzed data from PRESTO (2013-2021), a preconception cohort study of female pregnancy planners in the US and Canada. Participants completed a baseline questionnaire, bimonthly follow-up questionnaires until pregnancy, and pregnancy questionnaires at ~8 weeks and ~32 weeks of gestation. In a subset of couples, male partners provided vaccine data. We used Cox proportional hazard models to estimate the hazard ratio (HR) for the association between IIV and miscarriage, with gestational weeks as the time scale. Models included IIV as a time-varying exposure, with fine-stratification weights inversely proportional to the probability of vaccination to control confounding by seasonality and maternal factors.

Results: Of the 7159 pregnancies, 58.2% of female partners reported IIV: 6.2% during early pregnancy, 12.3% <3 months before pregnancy, and 39.8% ≥3 months before pregnancy. Risk of miscarriage was not appreciably associated with IIV before conception (HR 0.96; 95% CI 0.78, 1.16) or during pregnancy (HR 1.09, 95% CI 0.88, 1.34). Among the 2002 couples with male partner data, 9.3% reported IIV <3 months before pregnancy. We observed little association between male partner vaccination and miscarriage (HR 0.90; 95% CI 0.58, 1.39).

Discussion: Neither female partner vaccination before or during pregnancy nor male partner vaccination before pregnancy was materially associated with miscarriage risk. These findings provide additional reassurance about vaccine safety for pregnant individuals.

Fetal loss/stillbirth/infant mortality

The Causes of Infant Deaths in Dhi Qar, Iraq in 2019 Hashim Talib Hashim* Mustafa Ahmed Ramadhan

Background and objectives:

The high percentage of newborn deaths in Iraq generally and in Dhi Qar particularly can be elucidated to the deterioration of the healthcare services and the socioeconomic status of the population. The paucity in available data related to infant fatality causes in Dhi Qar, Iraq impedes the efforts for addressing this gap. In this paper, we aim to study the leading causes of all infant deaths recorded in the year 2019 in Dhi Qar according to the central statistics office of the Ministry of Health in Iraq and the Directorate of Health in Dhi Qar.

Methodology:

This is a cross-sectional study involving 1307 infant mortality case in Dhi Qar in 2019 out of 7632 registered deaths of all ages in the state. Inclusion criteria included all those reported dead under the age of 1-year-old in Dhi Qar between the 1st of January and the 31st of December in 2019.

Results:

Infant deaths account for 17.12%, 1307 deaths from a total of 7632 recorded deaths. Infant mortality rate (IMR) in 2019 in Dhi Qar was found to be 23.34 per 1,000 live births, with a total resident live birth count of 56,000.

Out of the 1307 deaths, 166 case were reported dead at an age of less than a day, 781 case of days and 360 case of months.

The most common causes of death were contributed to perinatal period conditions (64,5%) and congenital malformations (11%).

Conclusion

The high infant mortality rate and percentage of infant deaths in Iraq generally and in Dhi Qar in particular could be explained by the deterioration of the health services and the socioeconomic status of the population. The mortality rate of infants among all deaths in 2019 is 17.12% (1307 deaths from 7632 deaths), which is 1712 per 10000 deaths. The most common cause of death was the conditions originated from perinatal period with a rate of 64,5% followed by the congenital malformations with a rate of 11%. There is a statistically significant difference between the cause of death and the age group of the infants, and between the cause of death and the month of death with the majority of deaths have occurred during March, July and December.

Fetal loss/stillbirth/infant mortality

Failure of heuristic diagnosis: Gestational diabetes is not a disease Sid John* KS Joseph

Background: Although diseases are typically defined as somatic anomalies, they are sometimes diagnosed heuristically based on anomalous states that increase the risk of complications, e.g., hypertension. However, such heuristic formulations require the anomalous state and the associated complications to follow specific epidemiologic patterns.

Objective: To examine the use of current (NICE and IADPSG) criteria for diagnosing gestational diabetes mellitus (GDM).

Methods: We examined the distribution of blood glucose among pregnant women, and the distribution and rates of complications such as large-for-gestational age (LGA) and shoulder dystocia (SD) by blood glucose level. This was contrasted with the distribution of blood pressure among adults, and the distribution and rates of cerebrovascular (CVD) and cardiovascular disease (CHD) by blood pressure level.

Results: Rates of GDM-associated complications (LGA and SD) increased linearly with increasing blood glucose, whereas rates of hypertension-associated complications (CVD and CHD) increased exponentially with increasing blood pressure (J-shaped curve). There was a large overlap in the blood glucose distributions of pregnant women and women with GDM associated complications, while adult blood pressure distributions were left-shifted compared with those of CVD and CHD cases. 5% and 15% of LGA cases and 4% and 17% of SD cases occurred among women with a diagnostic fasting plasma glucose by NICE (≥5.6 mmol/l) and IADPSG criteria (≥5.1 mmol/l), respectively. In contrast, 65% of CVD deaths and 63% of CHD deaths occurred among adults with systolic/diastolic pressure ≥140/90 mm Hg.

Interpretation: Blood glucose patterns mean that GDM diagnosis will fail to accurately identify women with GDM complications, irrespective of the blood glucose criteria used. Blood glucose is preferably viewed as a determinant for adverse perinatal outcomes, and hyperglycemia is preferably treated as a risk factor managed through a graded approach.

Fetal loss/stillbirth/infant mortality

Antenatal corticosteroids for preventing respiratory morbidity and mortality in twins: a regression discontinuity study Peter Socha* Jennifer Hutcheon Erin Strumpf Sam Harper

Background: Antenatal corticosteroids prevent morbidity and mortality in singletons, but their effectiveness in twins is less clear. In 2020, the American College of Obstetricians and Gynecologists called for “further research…[on] outcomes for multifetal gestation.” We aimed to determine if twins with higher (vs lower) rates of exposure to antenatal corticosteroids had lower respiratory morbidity and mortality.

Methods: We used medical records in a perinatal data registry, for all liveborn twins whose parent was admitted for delivery at 31+0 through 36+6 weeks’ gestation, 2008-2018, in British Columbia, Canada. Our primary outcome was a neonatal diagnosis of respiratory distress or in-hospital mortality; our secondary outcome was neonatal ventilation or in-hospital mortality. During our study period, guidelines recommended antenatal corticosteroids for all pregnancies with imminent preterm birth before 34+0 weeks. We used a regression discontinuity design to compare twins born from pregnancies admitted directly on either side of this 34-week cut-point. We used generalizing estimating equations to account for clustering within twin pairs, and bootstrapped 95% confidence intervals (CIs).

Results: In our cohort of 5,120 liveborn twins, 45% of pregnancies admitted for delivery at <34+0 weeks were administered antenatal corticosteroids, compared with 4.6% admitted at ≥34+0 weeks. Twins whose parent was admitted for delivery just before 34+0 weeks had lower risk of neonatal respiratory distress or mortality (risk difference [RD] = -8.6 per 100 livebirths, 95% CI = -14.4 to -3.4; risk ratio [RR] = 0.78, 95% CI = 0.63 to 0.90), but similar risk of neonatal ventilation or mortality (RD = 0.32 per 100 livebirths, 95% CI = -2.2 to 2.3; RR = 1.06, 95% CI = 0.66 to 1.64).

Conclusion: Our results suggest that current antenatal corticosteroid treatment practices reduce neonatal respiratory distress or mortality in twins. We found no evidence of an effect on ventilation or mortality.

Genetics

Prenatal and childhood lead exposure associations with epigenetic age in adolescence

Olivia Halabicky* Mara Tellez Rojo Jaclyn Goodrich Dana Dolinoy Adriana Mercado-García Howard Hu Karen Peterson

Early life lead exposure alters child development and may induce dysfunction of physiological stress response pathways in puberty. In turn, alterations in functionality of stress pathways may accelerate biological age, which further increases the risk of future disease. This study examined the influence of lead exposure on adolescent biological age measured via epigenetic age. 246 mother-child pairs from the Early Life Exposures in Mexico to ENvironmental Toxicants cohort were included. Maternal bone lead levels (patella) were measured one month postpartum and children's blood lead levels were measured at 3, 6, and 12 months and in adolescence. Epigenetic clocks (Horvath and GrimAge) were estimated from Infinium EPIC data from blood samples collected during adolescence and then regressed on chronological age. The residuals of those models were used as the outcomes of interest. Time specific lead measures were regressed on Horvath and GrimAge residuals in models stratified by sex and adjusted for batch, cell type, chronological age, and BMI. Average age was 12.93 years (range 10-16) and 51.22% were female. For males, blood lead at 12 months was associated with a 0.24 yr higher GrimAge (95%CI 0.09, 0.39) and 0.25 yr higher Horvath's age (95%CI 0.06, 0.43). Adolescent blood lead was associated with a 0.24 yr higher Horvath's age (95%CI 0.01, 0.46) while blood lead at 6 months was associated with a 0.29 lower age (95%CI -0.57, -0.01). For females, there were no significant associations for GrimAge. Blood lead at 6 months was associated with a 0.15 yr lower Horvath's age (95%CI -0.26, -0.05) while adolescent blood lead was associated with a 0.21 yr higher age (95%CI 0.02, 0.41). There were no significant associations for maternal bone lead. Early childhood and adolescent lead exposure may alter the rate of epigenetic aging approximated in adolescence. These findings may suggest dysfunction of stress pathways and hold implications for increased risk of future disease.

Genetics

Maternal pre-pregnancy obesity and gestational diabetes are associated with epigenetic gestational aging in the placenta Katelyn Huff* Kyle Roell Catherine Bulka Kristen Boyle Carrie Breton Amber Burt Dana Dabelea Linda Kahn Margaret Karagas Christine Ladd-Acosta Carmen Marsit Sierra Niemiec Heather Volk T. Michael O'Shea Rebecca Fry

BACKGROUND: Pregnancy conditions like maternal pre-pregnancy obesity and gestational diabetes (GDM) have been linked with the development of placenta, a critical organ required for maternal-fetal interface during gestation, and can lead to adverse health outcomes in both mother and fetus. However, the molecular signatures associated with these conditions are not fully understood. Epigenetic clocks, which are based upon DNA methylation of age-related CpGs, are thought to better reflect biological age compared to chronological age and have been used in different tissues as potential biomarkers.

HYPOTHESIS: Altered placental epigenetic gestational aging is associated with pre-pregnancy obesity and GDM.

METHODS: We leveraged data from three diverse cohorts in the Environmental influences on Child Health Outcomes (ECHO) program (overall N=830). Using linear mixed modeling, we investigated associations between maternal pre-pregnancy obesity and GDM and estimated placental epigenetic gestational age acceleration (eGAA) while adjusting for the appropriate covariates. Similarly, we examined associations between these two conditions and methylation of each CpG site within the robust placental clock (558 CpGs).

RESULTS: Significant associations were not observed between pre-pregnancy obesity and GDM and eGAA. Interestingly, pre-pregnancy obesity was associated with methylation levels at 28 placental clock CpGs ($q<0.1$). These sites were annotated to 17 unique genes that enrich processes like circadian entrainment and cellular response to glucagon stimulus (*GNAS, GNG2*). Additionally, GDM was associated with methylation levels at 22 CpGs that mapped to 14 genes related to apoptosis (*TNFRSF10B, TRADD*) and neurological development (*CACNA1G, ATXN1*).

CONCLUSION: Overall, findings suggest that maternal pre-pregnancy obesity and GDM are associated with CpG methylation of the placental epigenetic clock, revealing potential markers vital for healthy pregnancy and fetal development.

Global health

Impact evaluation of healthcare and community worker trainings on maternal health in Tanzania Erin Hetherington* Sam Harper Rebecca Davidson Charles Festo Nadia Lampkin Sally Mtenga Clarissa Teixeria Ilona Vincent Arijit Nandi

Background: From 2018 to 2019, a multi-component intervention to improve maternal and newborn health was delivered in the Tabora region of Tanzania, by Tanzanian and Canadian collaborators. Intervention components included training healthcare and community workers, infrastructure upgrades to health facilities and improvements to regional planning and management. The study aim was to examine the impact of trainings on three key outcomes: skilled birth attendance, antenatal care and respectful maternity care.

Methods: Trainings were delivered sequentially in 8 districts (2 districts at a time), resulting in 4 treatment groups. A series of cross-sectional surveys were administered to a random sample of households in all districts at baseline and after each wave of training. Risk differences were estimated using a difference in difference approach comparing outcomes in treated districts to not yet treated districts. The overall Average Treatment Effect on the Treated (ATT), and group/time dynamic effects were aggregated using estimators for multiple groups in multiple time periods.

Results: Respondents reported 3,895 deliveries and 3,492 pregnancies over the course of the intervention and up to 2 years prior. The overall ATT for women receiving 4 or more antenatal care visits was -0.02 (95%CI -0.22, 0.18); for delivery with a skilled birth attendant 0.13 (95%CI 0.00, 0.25); and for disrespectful treatment at delivery 0.03 (95%CI -0.06, 0.13). Results of the dynamic treatment estimates suggest that skilled birth attendance began to increase 4 months after the end of training in each district.

Discussion: We found stronger evidence of impact on skilled birth attendance than other outcomes, though all estimates were imprecise. Practical considerations, including the non-sequential delivery of other parts of the intervention (facility upgrades, ambulance purchase and community meetings), made estimating the overall impact of the intervention challenging.

Gynecological health

Tear Gas Exposure During the 2020 and 2021 Protests and Female Reproductive Health

Emily Reece* Monica Unseld Madeline Tomlinson Aastha Kakar Anne Wallis Cynthia Corbitt Ted Smith Aruni Bhatnagar Kira Taylor

Background

During the racial justice protests of 2020-2021, lacrimator agents, also known as “tear gas”, were deployed against protestors. Effects on the eyes, skin, and respiratory system are well-documented; however, effects on the female reproductive system are not.

Objective

The objective is to determine whether acute symptoms of tear gas exposure, and/or seeking medical care, are associated with menstrual cycle outcomes.

Methods

Individuals who believed they were exposed to tear gas were recruited using an online questionnaire. Demographic, acute exposure symptom, medical care, and menstrual outcome data were collected using RedCap. Acute exposure symptoms of the eye, lung, skin, and heart were assessed. Menstrual cycle outcomes were cycle length, bleed length and intensity, and period pain. Composite acute and menstrual scores were the total number of symptoms. Correlation and linear regression were used to assess the relationship between acute and menstrual scores. Chi-square tests and t-tests examined associations between the seeking medical treatment for tear gas exposure and both acute scores and menstrual scores.

Results

81 women under 46 years of age contributed data on acute symptoms of tear gas exposure and menstrual cycle outcomes. Acute and menstrual scores were correlated (rho=0.34, P=0.0004). Mean menstrual scores were lower among women who sought medical care for tear gas exposure (mean=1.0 versus 2.6, t-test P=0.014). Mean acute scores were not significantly different based on whether medical care was sought (t-test P=0.48). After adjusting for confounders, acute scores (beta=1.17, 95% confidence interval [CI]=-0.20, 2.54) and medical care (beta=1.35, 95% CI=0.22, 2.93) were not associated with menstrual scores.

Conclusions

Before adjusting for confounders, acute tear gas symptoms and not seeking medical care were associated with menstrual cycle abnormalities. Confounding may account for the association between acute symptoms and menstrual outcomes.

Gynecological health

Sleep health in adulthood and incidence of uterine leiomyomata in the Study of Environment, Lifestyle and Fibroids Chad M. Coleman* Traci N. Bethea Amelia K. Wesselink Quaker Harmon Ganesa Wegienka Donna D. Baird Lauren A. Wise

Disparities in sleep health by race and gender are well-documented, with Black women more likely to report poor sleep. Black women are also more likely to develop uterine leiomyomata (UL), or benign fibroid tumors of the uterus, than White women. Poor sleep health could influence UL risk through stress and endocrine biologic pathways; however, there have been no epidemiologic studies of this association. We examined the association between self-reported sleep health in adulthood and UL incidence in the Study of Environment, Lifestyle and Fibroids, a prospective cohort study of 1,693 Black women. Eligible participants were aged 23-35 years, resided in the Detroit, MI region, had no history of UL, and were recruited from 2010-2012. Participants reported their duration of sleep, frequency of sleep troubles, and sleep quality on self-administered questionnaires at baseline. UL incidence was ascertained using standardized ultrasounds at baseline and every 20 months through 80 months. We used Cox proportional hazards regression models to estimate adjusted incidence rate ratios (aIRR) and 95% CI for the association between baseline sleep health and UL risk. Among 1,246 participants without prevalent UL and with at least one post-baseline visit, 62% reported not feeling well-rested ≥4 days/week, 58% slept <7 hours/night on a typical workday, and 30% had trouble falling asleep or going back to sleep ≥5 nights/month. Preliminary findings indicate little association between sleep health and UL incidence. The aIRR for not feeling well-rested ≥4 days/week compared with <3 days/week was 0.99 (95% CI: 0.81-1.23), for sleeping <7 vs. ≥7 hours/night on a typical workday was 0.90 (95% CI: 0.73-1.10) and for sleep troubles 5-14 and ≥15 vs. 0 nights/month were 0.93 (95% CI: 0.69-1.26) and 0.89 (95% CI: 0.60-1.32), respectively. We will next perform latent class analysis to examine changes in sleep patterns during 80 months of follow-up with UL incidence.

Health equity

Acculturation proxies and progression to type 2 diabetes after gestational diabetes in a multiethnic population-based retrospective cohort Teresa Janevic* Katharine McCarthy Shelley Liu Joseph Kennedy Hui Tai Chan Luciana Vieira Victoria Mayer Gretchen Van Wye Mary Huynh

Gestational diabetes (GDM) is a common complication of pregnancy for which immigrant women are at increased risk relative to US-born women. Over half of women with GDM will be diagnosed with type 2 diabetes (T2DM) in their lifetime, but it is unknown if region of origin or proxies for acculturation are associated with longitudinal T2DM risk. Our objective was to measure associations between region of origin, years in the US, and paternal nativity with 8-year cumulative risk of T2DM. We used data from the NYC APPLE Cohort, a retrospective cohort of linked 2009-2011 birth certificate and hospital discharge data, and 2009-2018 HbA1C test data. We ascertained GDM with no history of elevated HbA1c to comprise the baseline cohort (n=21,695). We classified women with 2 or more HbA1c tests >6.5% from 12 weeks to 8 years postpartum with T2DM. We used Cox proportional hazards models to estimate associations between acculturation proxies and 8-year cumulative incidence of T2DM. Covariates included sociodemographic and clinical factors at baseline. Models were generalized to accommodate non-proportional hazards by allowing interaction with time. Covariate-adjusted hazard ratios (aHR) for T2DM comparing region of origin to all US-born women were elevated for South Asian women (aHR=1.7, 95% Confidence Interval(CI)=(1.7, 1.4,2.1), Sub-Saharan African women (aHR=1.6, 95%CI=1.6, 1.2, 2.1), and Latin American women (1.4, 95%CI=1.2, 1.6). Compared to women living in the US for 10 or more years, 0-4 years was associated with a borderline increased incidence of T2DM (aHR=1.2, 95%CI=1.0, 1.5); 5-9 years was not (aHR=1.0, 95%CI=0.8, 1.2). Immigrant women whose husband was also foreign born had an increased hazard of T2DM relative to US-born women of 1.3(95%CI=1.1, 1.5). T2DM risk after GDM varies by region of origin. Paternal nativity is associated with T2DM after GDM, but longer time in the US is not, suggesting structural inequities as an explanation for observed findings.

Health equity

Black-White disparity in severe cardiovascular maternal morbidity: a systematic review and meta-analysis Ugochinyere Vivian Ukah* Xinting Li Shu Qin Wei Jessica Healy-Profitós Natalie Dayan Nathalie Auger

Introduction: Racial disparities exist in adverse pregnancy complications but no study had quantified Black-White disparities in the occurrence of severe cardiovascular maternal morbidity. Our objective was to systematically review and synthesize existing evidence on Black-White disparities in the prevalence of severe cardiovascular maternal morbidity.

Methodology: MEDLINE, EMBASE, and CINAHL databases were searched until July 31, 2021 for studies comparing the risk of severe cardiovascular maternal morbidity between Black and White women. Severe cardiovascular maternal morbidity included stroke, acute myocardial infarction, and peripartum cardiomyopathy, occurring during pregnancy, delivery, or postpartum. Relevant information including adjusted and unadjusted effect estimates were extracted and the quality of included studies was assessed using the Newcastle-Ottawa scale. Random-effects models were used to estimate the pooled association between Black and White race and severe cardiovascular maternal morbidity.

Results: Eighteen eligible studies, which included a total of 7,656,876 Black women and 26,412,600 White women, were included in our systematic review and meta-analysis. Black women had an increased risk of any severe cardiovascular maternal morbidity (adjusted odds ratio, 1.90; 95% confidence interval, 1.54-2.33), compared with White women. Black women were also at increased risks of stroke (adjusted odds ratio, 2.13; 95% confidence interval, 1.39-3.26), acute myocardial infarction (adjusted odds ratio, 1.38; 95% confidence interval, 1.14-1.68), and peripartum cardiomyopathy (adjusted odds ratio, 1.71; 95% confidence interval, 1.51-1.94).

Conclusion: The risk of severe cardiovascular maternal morbidity is significantly higher in Black women than in White women, despite adjusting for confounders. Identifying effective ways to reduce Black-White inequality in serious cardiovascular maternal outcomes should be a priority for public health.

Infectious disease

Geographic Proximity to Care is Not Associated with Pediatric Sepsis Outcomes Morgan Swanson* James Torner Ryan Carnahan Knute Carter Kang Zhao Nicholas Mohr

Objective

Pediatric sepsis is a serious, critical illness where time to care is important. Many children do not have ready geographic access to pediatric emergency and hospital care. We hypothesized closer proximity to pediatric sepsis care was associated with better clinical outcomes among pediatric sepsis patients.

Study Design

A retrospective cohort of pediatric sepsis patients was built from three states' administrative claims data. Geographic proximity was defined as driving distance in miles from the centroid of the zip code area of residence to the nearest hospital with a pediatric intensive care unit (PICU). The primary outcome was 28-day hospital-free days, which is a composite outcome of mortality, hospital length-of-stay, and readmission. Negative binomial and logistic regression estimated the effect of geographic access on sepsis outcomes after adjusting for subject and illness characteristics.

Results

Pediatric sepsis subjects (n = 3,671) resided a median 5.7 miles from the closest hospital and 17.7 miles from the closest hospital with a PICU. Subjects were a median age of 4 years with 1.6% mortality. Driving distance was not associated with 28-day hospital-free days (closest quartile [<6.2 miles] median: 23 days (IQR: 13 to 25) vs. farthest quartile [>50.9 miles] median: 23 days (IQR: 12 to 25), p= 0.724) and remained not associated after adjustment (farthest vs. shortest adjusted quartile incidence rate ratio (aIRR): 1.03, 95%CI: 0.95 to 1.13]). Proximity to care was associated with an increased odds of transfer (adjusted odds ratio = 3.26 [95%CI: 2.33 to 4.57]).

Conclusions

Shorter driving distance to a pediatric sepsis hospital was not associated with improved clinical outcomes for pediatric sepsis patients. Pediatric sepsis patients who lived farther from a pediatric sepsis hospital did have increased inter-hospital transfer. This suggests local emergency care with current transfer practices provides quality care for pediatric sepsis patients.

Mental health

Violence in childhood and self-reported symptoms of psychological distress among adolescents and young adults: Evidence from the Côte d'Ivoire 2018 Violence Against Children and Youth Survey (VACS) Otobo Ujah* John Ferron

Evidence regarding variations in psychological distress in adolescence based on number, types and combinations of violence experienced in childhood is limited. The objective was to determine whether types and patterns of lifetime violence differ with respect to a set of psychological distress symptoms among adolescents and young adults.

Males and females 15-24 years old participating in the Côte d'Ivoire 2018 Violence Against Children and Youth Survey (VACS) were selected for analysis. Multivariate Analysis of Variance (MANOVA) was used to test whether no experience of violence, emotional violence only, physical violence only, sexual violence only, both emotional and physical violence, both emotional and sexual violence, both physical and sexual violence and, a combination of emotional, physical and sexual violence differed with respect to nervousness, hopelessness, restlessness, depressed, effort and worthlessness based on Kessler's Psychological Distress Scale (K6). Post-hoc univariate *F*-tests and multiple pairwise comparisons provided information on the extent to which specific factors contributed the overall differences.

MANOVA revealed significant differences in means between groups based on the linear combination of psychological distress factors [Wilk's $\Lambda = 0.82$, $F(42,8910\ .6) = 9.31$, $p < 0.0001$, partial $\eta^2 = 0.03$]. *Post-hoc* univariate *F* tests with Tukey test performed showed feeling nervous [$F(7,1904) = 15.97$, $p < 0.0001$, $\eta^2 = 0.06$]; Hopeless [$F(7,1904) = 26.46$, $p < 0.0001$, $\eta^2 = 0.09$], Restless [$F(7,1904) = 16.86$, $p < 0.0001$, $\eta^2 = 0.06$]; Worthless [$F(7,1904) = 25.05$, $p < 0.0001$, $\eta^2 = 0.08$]; Depressed [$F(7,1904) = 17.31$, $p < 0.0001$, $\eta^2 = 0.06$]; and, everything was an effort [$F(7,1904) = 18.56$, $p < 0.0001$, $\eta^2 = 0.06$].

Exposure to multiple types of violence in childhood is associated with severe psychological distress. Interventions should focus both on addressing specific and multiple forms of violence as well as, specific psychological distress symptoms.

Mental health

Characterization of maternal psychosocial stress during pregnancy: The Health Start Study
Satvinder K Dhaliwal* Dana Dabelea Angela Lee-Winn Deborah H. Glueck Greta Wilkening Wei Perng

Objective: Despite the multifaceted nature of stressful experiences and their manifestations, most studies on this topic have used single questionnaire-based assessments of psychosocial status during pregnancy. Here, we sought to capture multidimensional maternal psychosocial stress using responses from the Edinburgh Postnatal Depression Scale (EPDS) and Cohen's Perceived Stress Scale (PSS) administered during pregnancy, and identify perinatal correlates of the stress domains.

Methods: Using data from 1,079 pregnant women, we implemented principal components analysis on EPDS and PSS responses and retained factors based on the Scree plot and Eigenvalues>1. We then used linear regression to identify perinatal correlates of each domain.

Results: We identified three stress domains: "Feeling Overwhelmed", "Anhedonia", and "Lack of Control" that accounted for 10.6% of variance in questionnaire responses. In multivariable analyses, household income ≤$70,000 (β=0.21 [95% CI: 0.05, 0.39]), primiparity (0.36 [0.02, 0.71]), inadequate (0.21 [0.04, 0.39]) or excessive gestational weight gain (0.27 [0.11, 0.42]), and Healthy Eating Index [HEI] score ≤57 (0.14 [0.00, 0.28]) were associated with Feeling Overwhelmed. Older age (0.02 [0.00, 0.03] per 1-year), Hispanic ethnicity (0.19 [0.00, 0.38]), and HEI score ≤57 (0.15 [0.02, 0.28]) were associated with Anhedonia. Non-Hispanic Black race/ethnicity (0.37 [0.10, 0.63]), not having graduated college (0.16 [-0.02, 0.35]), having a partner born outside the US (0.17 [-0.02, 0.37]), household size ≥5 persons (0.21 [-0.02, 0.37]), receiving public assistance (0.18 [-0.02, 0.37]), and prenatal smoking (0.32 [0.05, 0.59]) were associated with Lack of Control.

Conclusions: Three domains of maternal psychosocial stress during pregnancy were differentially related to sociodemographic, biological, and health behavioral characteristics during the perinatal period that may be targets for interventions to ameliorate stress in pregnant women.

Mental health

A systematic review and meta-analysis of chemical exposures and attention-deficit/hyperactivity disorder Lina Dimitrov* Jennifer Kaminski Joseph Holbrook Rebecca Bitsko Brenna O'Masta Brion Maher Audrey Cerles Margaret Rush

Exposure to certain chemicals prenatally and in childhood can impact development and may increase risk for attention-deficit/hyperactivity disorder (ADHD). Leveraging a larger set of literature searches conducted to synthesize results from longitudinal studies of potentially modifiable risk factors for childhood ADHD, we present meta-analytic results from 66 studies that examined the associations between early chemical exposures and later ADHD diagnosis or symptoms. Studies were eligible for inclusion if the chemical exposure occurred at least 6 months prior to measurement of ADHD diagnosis or symptomatology. Included papers were published between 1975 and 2019 on exposure to anesthetics (n=5), cadmium (n=3), hexachlorobenzene (n=4), lead (n=22), mercury (n=12), organophosphates (n=7), and polychlorinated biphenyls (n=13). Analyses are presented for each chemical exposure by type of measure of association reported (categorical vs. continuous), type of ADHD measurement (overall measures of ADHD, ADHD symptoms only, ADHD diagnosis only, inattention only, hyperactivity/impulsivity only), and timing of exposure (prenatal vs. childhood vs. cumulative), whenever at least 3 relevant effect sizes were available. Childhood lead exposure was positively associated with ADHD diagnosis and symptoms in all analyses; the strongest association was for hyperactivity/impulsivity. Other statistically significant associations were limited to organophosphates (r=0.11, 95% confidence interval (CI):0.03–0.19 for continuous ADHD outcomes overall) and both prenatal and childhood mercury exposure (r=0.02, 95% CI:0.00–0.04 for continuous ADHD outcomes overall for either exposure window). Our findings provide further support for negative impacts of prenatal and/or childhood exposure to these chemicals and raise the possibility that primary prevention and targeted screening could prevent and mitigate ADHD symptomatology.

Methods

Seeing the invisible: A novel study design in reproductive epidemiology Marc Weisskopf* Michael Leung Sebastian Rowland Raanan Raz Brent Coull Ander Wilson Marianthi-Anna Kioumourtzoglou

When all events of an outcome cannot be counted, it may be impossible to identify risk factors associated with the outcome due to small numbers, or bias may be introduced if the events missed are non-random. An example is pregnancy loss because many of these events never come to medical attention, and some may not even be recognized by the mother. This greatly limits the research that can be done into risk factors for pregnancy loss. The few studies that have examined pregnancy loss as an outcome have relied on either a) medically-identified losses, which as a subset of all pregnancy losses is limited and could introduce unknown biases, or b) enrolling and tracking women intensively around conception (i.e., a preconception cohort), which are generally small and may not be representative.

We present a new study design to analyze exposure-pregnancy loss associations that considers all pregnancy losses, even those that go unrecognized by the medical community and even the mother. This approach relies on live birth records, which are generally much more widely available. This novel approach involves resorting live births by their estimated conception date, and then takes advantage of the fact that the total number of conceptions (TC) in a given period of time is the sum of live births that result from those conceptions (live birth-identified conceptions; LBIC) and those that are lost (pregnancy losses; PL). Put in simple mathematical terms, for a given period, e.g., week, TC = LBIC + PL.

Thus, for any risk factor that does not affect total conceptions, e.g. post-conception exposures, associations with total pregnancy loss can be inferred from associations with LBIC, which are identifiable.

Here we describe this novel, inferred-effects approach, its implementation, and assumptions required for causal inference. This new approach could be a powerful method to study effects on events that have to date been hidden to epidemiologists.

Molecular

Placental cell type DNA methylation reference panel for epidemiological studies Kyle Campbell* Justin Colacino Muraly Puttabyatappa Joseph Ciarelli Steven Domino Dana Dolinoy Rita Loch-Caruso Vasantha Padmanabhan Kelly Bakulski

DNA methylation perturbations in placental tissue are linked to adverse perinatal outcomes. To distinguish mechanistic DNA methylation changes from cell composition differences, robust placental cell type-specific DNA methylation profiles are needed. From 18 uncomplicated, Cesarean-section term placentas, we isolated DNA and measured methylation via the IlluminaEPIC microarray from cell type-specific fractions of cytotrophoblasts (n=14), fibroblasts (n=11), Hofbauer cells (n=9), and syncytiotrophoblasts (n=8), and/or unsorted whole tissue samples (n=17). We subsampled four placentas by quadrant for 34 additional samples. All samples (n=93) passed quality control metrics. We interpreted all tests at false discovery rate adjusted p-value<0.05. We excluded 44,590 genotype-specific, sex-specific, cross-reactive, or low-quality probes. We fit linear models (n=821,328 sites) adjusted for individual to control for unmeasured confounding with empirical Bayes standard error moderation. To identify cell type-specific differentially methylated sites, we compared methylation M-values to values in one cell type against the average across other cell types with an absolute beta-value difference threshold of 10%. DNA methylation signatures distinguished cytotrophoblasts (214,496 sites), Hofbauer cells (216,990 sites), syncytiotrophoblasts (17,260 sites), and fibroblasts (7,220 sites). Differentially methylated sites were annotated to genes enriched for cell type differentiation and placental cell type-specific functions such as epithelial cell development among cytotrophoblasts ($p\text{-value}_{adj}<0.001$), phagocytosis among Hofbauer macrophages ($p\text{-value}_{adj}<0.001$), and regulation of ERK1 and ERK2 cascade among syncytiotrophoblasts ($p\text{-value}_{adj}=0.007$). These cell type DNA methylation references can be used to robustly estimate cell composition from placental DNA methylation data for application in epidemiological scale studies to reveal biological mechanisms and improve casual inference.

Nutrition/obesity

Maternal weight trajectories and eating behaviors in the Study of Latinos Family Lifestyles Outcome Research (SOL-FLOR) Christina Cordero* Daniela Sotres-Alvarez Anna Maria Siega-Riz Alan Delamater Marc Gellman Carmen Isasi Linda Gallo Linda Van Horn Madison LeCroy Amanda McClain Martha Daviglus Maria Llabre

Food addiction and reward-related eating are known risk factors for obesity. Whether weight changes in the reproductive years affect maternal eating behaviors is unknown. We aim to identify weight trajectory classes in a diverse group of Hispanic/Latina women and examine the association with eating behaviors. The Study of Latinos Family Lifestyles Outcome Research (SOL-FLOR; 2019-2022) is enrolling women from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) who became pregnant after the baseline visit (2008-2011) and their offspring (N=278 dyads as of 1/4/22). Among women eligible for SOL-FLOR (n=548), we identified weight trajectories using a latent class growth model of body mass index from up to 4 weights, self-reported for age 21, 1 year prior to baseline, baseline, and at a 6-year follow-up. Two weight trajectories were identified, Trajectory 1 (74%) started with lower BMI and had a slower rate of weight gain and Trajectory 2 (26%) started with higher BMI and had a higher rate of weight gain. The 13-item Reward-based Eating Drive scale was administered to women in SOL-FLOR, z-scores for each item were calculated and then averaged. Food addiction was measured through the modified Yale Food Addiction Scale 2.0; 7 items were summed and ≥3 contribute to a diagnosis of food addiction. Linear and logistic regression models tested for the association between maternal weight trajectory and food addiction and reward-related eating behaviors, adjusted for education, income, Hispanic/Latina background, and nativity/years in the US. Compared to Trajectory 1, Trajectory 2 was associated with ≥3 food addiction symptoms (12.2%; OR=3.28 (95% CI 1.41, 7.65)). No significant associations were observed with reward-related eating (Trajectory 1 vs. 2 b=0.08 (95% CI -0.10, 0.26)). Hispanic/Latina women with a higher weight trajectory were more likely to report symptoms of food addiction. Screening for food addiction in women with higher weight gain may be beneficial.

Nutrition/obesity

The association between maternal diet quality and pregnancy and subacute postpartum outcomes among Latinas Megan Harvey* Sofija Zagarins Katherine Tucker Bess Marcus Milagros Rosal JoAnn Manson Lisa Chasan-Taber

Maternal diet quality has been inversely associated with adverse pregnancy and birth outcomes, although findings are inconsistent and few studies have examined the impact on subacute postpartum outcomes. Furthermore, the majority of did not use dietary quality indexes designed for pregnancy and did not focus on Latinas, a group with poorer diet quality and higher rates of adverse maternal outcomes, relative to non-Latina White women. Therefore, we evaluated the association between the Alternate Healthy Eating Index for Pregnancy (AHEI-P) and pregnancy, birth and subacute postpartum outcomes among 168 predominantly Puerto Rican participants in Estudio PARTO, a randomized trial of a lifestyle intervention in Western Massachusetts (2013-2017). Diet was measured at a mean of 28.1 (SD=6.6) weeks gestation by trained bicultural/bilingual personnel via three 24-hour recalls. Associations were modeled with multivariable linear and logistic regressions, adjusting for age, pre-pregnancy body mass index, physical activity level, caloric intake, and intervention group. Higher scores on the AHEI-P (indicating better diet quality) were not associated with total gestational weight gain (β=-0.08, p=0.30), hypertension (OR=0.99 95% CI=0.95-1.03) or fasting glucose during pregnancy (β=0.04, p=0.65). Women with higher scores on the AHEI-P experienced a slightly longer second stage of labor (β=0.23, p=0.048), but AHEI-P scores were not associated with other birth outcomes, including gestational age at delivery, infant birth weight, number of days spent in the hospital, length of first or third stage of labor, or APGAR scores. AHEI-P scores were also not associated with postpartum body mass index (β=-0.17, p=0.08) or fasting glucose tolerance (β=-0.07, p=0.72).Findings suggest that current measures of maternal diet quality may be of limited value among Puerto Ricans in the United States and highlight the need for better tools to identify the nutrient profile among Latinas in the United States to best predict favorable birth outcomes.

Nutrition/obesity

Obesity in Children with Amblyopia Carolyn Drews-Botsch* Kyle Machicado Scott Lambert Ali Weinstein

Purpose: Children with amblyopia, and the resultant loss of stereopsis, may have fine and gross motor deficits. In other contexts, such deficits have been associated with a higher risk of obesity. However, the risk of obesity in individuals with amblyopia is unknown.

Methods: These analyses use data from the 1999 – 2008 National Health and Nutrition Examination Survey (NHANES). We focus on the 8295 children between the ages of 12 and 18 who participated in the visual examination component of NHANES and had a best corrected visual acuity in the better eye of at least 20/40. Amblyopia was defined as at least a two-line intraocular difference in acuity. In separate analyses, obesity was defined as a body mass index (BMI) or a body fat percentage (BFP) greater or equal to the 95^{th} percentile for age and gender. BFP was measured using a dual-energy X-ray absorptiometry (DEXA). Cardiovascular fitness level (CFL) was assessed using a submaximal exercise test. We calculated odds ratios to examine the relative prevalence odds of obesity in children with and without amblyopia.

Results: The prevalence of amblyopia was 4.3%. The prevalence of high BMI was higher in children with amblyopia than those without (30.3% versus 21.4%; OR =1.56; 95% CI 1.24-1.98). Children with amblyopia were also somewhat more likely to have a high BFP (15.3% versus 13.2%; OR = 1.15 95% CI 0.77,1.70) and have low CFL (OR = 1.15; 95% CI 0.83,1.57) but these measures were available for only about half of the population.

Conclusions: Our findings suggest that adolescents with amblyopia may be more likely to be obese and sedentary. Given the range of morbidities associated with childhood obesity, targeted interventions promoting physical activity among children with amblyopia could be important to minimize the potential for future weight-related health issues.

Nutrition/obesity

Dietary Quality Indices in Early Pregnancy and Gestational Weight Gain Rate among a Prospective Multi-Racial/Ethnic Cohort Emily Liu* Yeyi Zhu Assiamira Ferrara Monique Hedderson

Meeting the Institute of Medicine (IOM) gestational weight gain (GWG) guidelines is associated with a reduced risk of adverse perinatal outcomes. Overall diet quality comprehensively assesses dietary components and accounts for interactions between them. While GWG is influenced by maternal diet, its association with overall diet quality — measured by various indices — is not well-defined.

We examined multiple diet quality indices in relation to GWG in a prospective multi-racial/ethnic cohort of 2,914 pregnant women from the Pregnancy Environment and Lifestyle Study (2014–2017). We calculated the Healthy Eating Index 2010 (HEI-2010), alternate Healthy Eating Index-Pregnancy, alternate Mediterranean Diet, and Dietary Approaches to Stop Hypertension using a Block Food Frequency Questionnaire administered in the first trimester, with higher scores indicating better diet quality. Subsequent GWG was determined as weight change between the dietary assessments and delivery dates. Rate of GWG was categorized according to IOM guidelines into inadequate (below guidelines), adequate, and excessive (above guidelines). Multinomial logistic regression assessed the risk of inadequate and excessive GWG in association with each dietary index, adjusting for total energy intake, race/ethnicity, age, parity, household income, maternal education, and pre-pregnancy BMI.

Overall, 860 (29.5%) of pregnancies had adequate, 1,640 (56.3%) had excessive, and 414 (14.2%) had inadequate GWG. Adjusted model results showed increased odds of excessive GWG among the two lowest quartiles compared to the highest quartile of the HEI-2010: Odds Ratio [95% Confidence Interval] Quartile 1 vs. 4 = 1.26 [0.99-1.6]; Quartile 2 vs. 4: 1.37 [1.07-1.74]. The other indices were not associated with excessive GWG. We found null results across all diet indices and inadequate GWG. Adhering to the 2010 Dietary Guidelines for Americans (HEI-2010) during pregnancy may lower the risk of excessive GWG.

Nutrition/obesity

The association between measures of acculturation and established diet quality indices in Hispanic women Sofija Zagarins* Megan Harvey Katherine Tucker Bess Marcus Milagros Rosal JoAnn Manson Lisa Chasan-Taber

Prior research indicates that maternal diet quality impacts pregnancy and birth outcomes. Puerto Rican populations living in the continental US have lower diet quality as compared to those living in Puerto Rico, although research examining the association between acculturation and diet quality in pregnancy in this population is sparse. Therefore, we evaluated this association using baseline data from 169 Hispanic (predominantly Puerto Rican) participants enrolled in Estudio PARTO, a randomized controlled trial conducted in Western Massachusetts (2013-17). Acculturation was assessed via Psychological Acculturation Scale (PAS), language preference, and birthplace. 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, and Healthy Plant-Based Diet Index, and adjusted for age, pre-pregnancy BMI, activity level, and energy intake in multivariable models. Mean PAS score was 2.46 ± 0.67, and 23.7% of women reported Spanish language preference. Mean diet scores were 54.9 ± 14.6 (HEI-2015), 36.5±11.6 (AHEI-2010), 24.4±5.5 (aMED), 51.8±7.7 (HPDI). In unadjusted models, each one-unit lower PAS score was associated with a 3.2-unit higher HEI-2015 (SE=4.3; P=0.06) and 2.6-unit higher AHEI-2010 (SE=1.3; P=0.05), although associations were attenuated in multivariable models. Spanish language preference (indicating lower acculturation) was associated with a 5.6-unit higher HEI-2015 (SE=2.7, P=0.04) and 4.2-unit higher AHEI-10 (SE=2.0, P=0.04) in adjusted models. No significant associations were seen with aMED or HPDI. Lower psychological acculturation and Spanish language preference were associated with higher maternal diet quality in Puerto Rican women. Public health interventions aimed at improving pregnancy outcomes in this population should be tailored to acculturation level.

Obstetric health

A prediction model of postpartum hospital use incorporating social determinants of health
Teresa Janevic* Kimberly Glazer Natalia Ergorova Jennifer Zeitlin Elizabeth Howell

Racial inequities in maternal mortality are largest in the postpartum period. Postpartum hospital use is a marker of poor maternal health, with similar Black vs White disparities present. Our objective was to develop a risk prediction model of postpartum hospital use (emergency department visit and/or readmission), and to evaluate if inclusion of individual- and area-level social determinants of health (SDH) improved model prediction. We used birth data linked with inpatient and outpatient hospital claims data. We included deliveries to individuals residing in the New York City metropolitan area between January 1, 2016-November 30, 2018 and followed patients until December 31, 2018 (n=317,677) to ascertain 30-day hospital use. Candidate variables included sociodemographics, comorbidities, obstetric complications, and severe maternal morbidity. Individual-level SDH included psychosocial factors, maternal education and intimate partner violence (IPV). Area-level SDH were publicly available indices of the built/natural (BNI) and social/economic (SEI) environment. We randomly selected a 70% training sample and 30% internal validation sample. We used logistic regression with backwards selection to build the prediction model, with and without SDH indices. We evaluated model performance using the area under the receiver operating characteristic curve (AUC). The overall incidence of postpartum hospital use was 5.7%. Prediction of postpartum use was fair (AUC=0.671). Covariates selected in the final model included both individual-level and area-level SDH (e.g. adjusted odds ratio(aOR) for IPV=1.7, 95%confidence interval(CI) 1.2-2.4; aOR for very high vs. very low SEI=0.7, 95%CI=0.6-0.7). However, SDH variables only marginally improved the prediction of postpartum hospital use. Results were similar in the internal validation model. Findings highlight associations between SDH and postpartum health, but further research is needed to optimize their use in risk prediction.

Obstetric health

Fibroids, neonatal anthropometry, and preterm birth in singleton pregnancies: NICHD Fetal Growth Studies Susanna Mitro* Rajeshwari Sundaram Zhen Chen Shyamal Peddada Germaine Buck Louis Jagteshwar Grewal Anthony Sciscione Jessica Gleason Karin Fuchs Mary D'Alton Cuilin Zhang Katherine Grantz

Background: Leiomyomata (fibroids) are common in pregnancy. However, findings on the association between fibroids and birthweight are inconsistent. Lack of consensus could partly be due to prior studies not accounting for delivery timing. We investigated the relationship of fibroids, preterm birth, and neonatal anthropometry.

Methods: Pregnant women (n=2,578) had up to 6 sonograms from weeks 10-41. Sonographers recorded fibroid number and volume of the 3 largest fibroids. Women were compared by the presence of any fibroid, fibroid number, and total volume categorized as <1cm (small), 1-<3cm (medium), or ≥3cm (large) diameter at first visualization. Neonatal anthropometry was measured by trained personnel. Linear and logistic regression assessed associations between fibroids, neonatal anthropometry, and pregnancy outcomes. Causal mediation analysis evaluated preterm birth as a mediator.

Results: Fibroid prevalence was 9.5% (n=245) in the cohort. Presence of fibroids was associated with 1.73-2.65 times higher odds of preterm delivery and 2.42-4.37 times higher odds of premature rupture of membranes (varying by fibroid number and volume) compared to the absence of fibroids. Presence of fibroids was not associated with birthweight, but neonates from pregnancies with single fibroids had on average 0.3 (95% confidence interval (CI): 0.0, 0.5) cm larger head circumferences; those with multiple fibroids had on average 0.3 (95%CI: 0.0, 0.6) cm larger arm circumferences; and those with small fibroids had on average 0.7 (95%CI: 0.3, 1.2) cm larger head circumferences, 0.4 (95%CI: 0.0, 0.8) cm larger arm circumferences, and 0.7 (0.1, 1.3) cm larger thigh circumferences compared to neonates from pregnancies without fibroids. Mediation analysis indicated that variation in risk of preterm birth did not explain anthropometry results.

Conclusions: Fibroids were associated with both higher odds of preterm birth and slightly larger neonatal size. Investigation of mechanisms is warranted.

Obstetric health

Prenatal Exposure to Ambient Particle Radioactivity and Fetal Growth in Eastern Massachusetts Veronica A. Wang* Michael Leung Longxiang Li Anna M. Modest Michele R. Hacker Joel Schwartz Brent Coull Petros Koutrakis Stefania Papatheodorou

Background: Particle radioactivity (PR) is the radioactive component of particulate matter (PM) that mainly originates from the natural decay of PM-attached radon and has been previously associated with elevated glucose levels during pregnancy.

Method: We included 9,409 singleton pregnancies that had routine obstetric ultrasounds and delivered at Beth Israel Deaconess Medical Center in 2011-2016. Particle gross β-activity (mBq/m^3) representing PR exposure was estimated from an ensemble model and was assigned based on residential zip-code. We considered two exposure windows: first 16 weeks of pregnancy and conception until fetal growth measurement (cumulative PR). Standardized (z-score) biparietal diameter (BPD), head circumference (HC), femur length (FL), and abdominal circumference (AC) were examined on anatomic scans (<24 weeks' gestation) and growth scans (≥24 weeks' gestation), and weight was measured at birth. We used linear mixed models to examine the association of PR with fetal growth measurements and adjusted for maternal risk factors, meteorologic variables, and long-term trends. As a sensitivity analysis, we adjusted for PM ≤2.5 $\mu g/m^3$ ($PM_{2.5}$).

Results: An interquartile range (IQR) increase in cumulative PR was associated with reduced BPD (-0.06 [95% CI: -0.12, -0.01]) and FL (-0.06 [95% CI: -0.12, -0.01]) on anatomic scans and birth weight (-0.05 [95% CI: -0.11, -0.001]). While the association with AC was positive in early growth scans, it decreased with gestational age and was negative after week 35. First 16 weeks of gestation was not a critical window. Estimates were similar after controlling for $PM_{2.5}$.

Conclusion: Prenatal PR was associated with fetal growth, where the direction of the association depended on the fetal growth measure and the gestational age at measurement. Our findings are consistent with patterns previously observed among pregnancies complicated with gestational diabetes and bring awareness to a novel environmental exposure.

Obstetric health

Rural-urban residence and sequelae of hypertensive disorders of pregnancy in the first year postpartum, 2013 – 2019 Mariah Pfeiffer* Catherine Gelsinger Kristin Palmsten Heather Lipkind Christina Ackerman Katherine Ahrens

Background:

Hypertensive disorders of pregnancy (HDP) are one of the leading causes of maternal morbidity and mortality in the US. Rural women have higher prevalence of pre-pregnancy hypertension and increased risk for severe maternal morbidity and mortality compared to urban women.

Objective:

To estimate the association between rural residence and sequelae of HDP in the first year postpartum.

Methods:

We used the Maine All Payer Claims Database to identify women with HDP who delivered during 2013-2019 (n=5748). We estimated the risk of having at least one Emergency Room and/or Inpatient visit related to hypertension in the first year postpartum and receipt of postpartum antihypertensive medications from 4 days to 1 year postpartum, separately. We excluded women with chronic hypertension or pre-pregnancy cardiac conditions. Cox proportional hazards modeling was used to estimate rural-urban hazard ratios (HR) and 95% confidence intervals (95% CI), adjusting for HDP severity, age, public insurance, nulliparity, and co-morbidities. Observations were censored upon loss of health insurance, start of next pregnancy, or at 12 months, whichever came first.

Results:

Rates of HDP increased from 6.9% to 11.0% of all deliveries over the study period. 65% of women with HDP were rural residents. Risk of at least one acute care visit in the first year postpartum was not different between rural vs. urban women (5.4% vs. 4.8%; adjusted HR 1.09; 95% CI 0.85,1.40). Similarly, receipt of a prescription for antihypertensive medication was not different (13.1% vs. 14.0%; adjusted HR 0.94; 95% CI 0.81, 1.09).

Conclusions:

Though acute care visits and antihypertensive medication in the first year postpartum are common among women with HDP, rural and urban women do not differ. Further research is needed to determine whether early prescribing of antihypertensive medications, cardiac evaluations, and enhanced postpartum follow-up are effective for risk reduction in both rural and urban women.

Obstetric health

Adverse Childhood Experiences, Domestic Violence and racial disparities in early prenatal care in North Dakota (ND PRAMS 2017-2019) Andrew Williams* Lexie Schmidt MichaeLynn Kanichy Grace Njau Matthew Schmidt Anastasia Stepanov

Background. In North Dakota(ND), American Indian(AI) women have higher prevalence of adverse childhood experiences(ACE), higher exposure to domestic violence(DV), and higher risk of late prenatal care than other racial groups. Evidence regarding ACE, DV and prenatal care is mixed. In the context of ACE, we explored whether DV accounts for racial disparities in prenatal care in ND.

Data. Data for 2141 women were from 2017-2019 ND Pregnancy Risk Assessment Monitoring System. First prenatal care visit after week 13 was “late prenatal care.” DV was measured for 12 months preconception via self report(yes/no) of violence from husband/partner, family member, someone outside of family, or ex-husband/partner. An “Any DV” variable was created if women reported “yes” to any DV. Women reported(yes/no) to 10 ACE and ≥4ACEs was “High.” Logistic regression(adjusted for maternal demographic, medical, and behavioral factors) estimated odds ratios and 95% confidence intervals for late prenatal care among AI and Other race women compared to White women, stratified by high/low ACE. In separate models, we included DV to assess if DV accounted for racial disparities.

Results. Odds of late prenatal care were similar for AI women in High ACE (1.98 95%CI:1.09-3.61) and Low ACE (2.57 95%CI:1.67-3.97) groups; the effect of DV differed between groups. Including husband/partner violence reduced odds of late prenatal care for AI women with Low ACE by 6 percent (2.41 95%CI: 1.55-3.74), yet increased odds of late prenatal care for AI women with High ACE by 5 percent (2.09 95%CI: 1.16-3.80). Of note, in High ACE group, DV estimates suggest reduced odds of late prenatal care, yet the opposite was observed in Low ACE group.

Discussion. DV does not explain racial disparities in early prenatal care. Women with High ACE may be more likely to seek early prenatal care when exposed to DV than women with Low ACE. Resiliency in the face of DV among women seeking prenatal care should be further examined.

Obstetric health

Postpartum Emergency Care Visits among North Carolina Medicaid Recipients Clara Busse* Catherine Vladutiu Divya Mallampati Milton Molina M Kathryn Menard

Medicaid recipients frequently use emergency care, but little is known about their patterns of emergency care use in the postpartum period. We sought to describe the rate and timing of emergency care visits up to 8 weeks (56 days) after live birth among Medicaid recipients in North Carolina. We constructed a retrospective cohort by linking the Medicaid hospital claims and live birth records of 380,307 Medicaid recipients who delivered a live-born infant in North Carolina between January 1, 2013 and November 4, 2019. We excluded those missing data on Medicaid member months and those without Medicaid coverage for at least 8 weeks postpartum. Emergency care visits were defined as encounters in the Emergency Department or obstetric triage unit. A total of 336,885 postpartum people were included in this analysis. In this cohort, 45,159 postpartum people (13.4%) had at least one emergency care visit within 8 weeks of live birth (range= 0 to 19 visits per person). There were 58,213 emergency care visits with an overall rate of 17.3 visits/100 people. Postpartum people with the highest rates of emergency care visits completed less than a high school education (22.9 visits/100 people), were ≤19 years old (19.9 visits/100), were non-Hispanic Black (18.4 visits/100), and had a rural residence (18.3 visits/100). The rate of emergency care visits peaked in weeks 2 and 3-4 postpartum: 1.3 visits/100 people (postpartum week 1), 4.5 visits/100 (week 2), 4.5 visits/100 (weeks 3 and 4 combined), 3.6 visits/100 (weeks 5 and 6 combined), and 3.4 visits/100 (weeks 7 and 8 combined). Approximately one in eight postpartum Medicaid recipients in this North Carolina cohort used emergency care within 8 weeks after live birth, and the patterns of use varied meaningfully by sociodemographic characteristics. This information should be used to inform interventions aimed at improving access and continuity of care during the postpartum period.

Obstetric health

Maternal Prenatal Diurnal Cortisol Patterns Associated with Impaired Glucose Tolerance in Pregnancy Hannah Murphy* Amber Kautz Ying Meng Emily Barrett Richard Miller Tom O'Connor

The hypothalamic-pituitary-adrenal (HPA) axis regulates the release of glucocorticoids that play crucial roles in stress physiology and glucose metabolism. Diurnal cortisol is an important end-product and natural target for human research. Excess blood glucose levels and resulting insulin resistance, a precursor to Type 2 diabetes, has been negatively associated with HPA axis activity in non-diabetic/non-pregnant populations. However, among diabetic populations, a paradoxical effect of higher HPA axis activity in conjunction with higher glucose levels has been noted. We leverage data from a prospective longitudinal study that characterizes maternal prenatal diurnal cortisol at multiple points across gestation to test the hypothesis that flatter diurnal slopes are associated with higher glucose levels, moderated by obesity, in participants with normal fasting glucose following a challenge test in pregnancy.

Understanding Pregnancy Signals and Infant Development (UPSIDE) is a longitudinal pregnancy cohort study in Rochester, NY with 326 mothers recruited in their first trimester. Glucose levels were obtained following a glucose challenge test, which sensitively detects clinically relevant metabolic alterations. 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 using a high-sensitivity enzyme immunoassay (Salimetrics). Cortisol parameters were derived from the diurnal pattern to include an early morning level and diurnal slope.

Using a linear mixed effects model to account for the longitudinal, repeated measures and inherent nested structure of our dataset, we examined the diurnal cortisol pattern of participants with normal blood sugar levels (≤140 mg/dL; n=169) and those with high blood sugar levels (>140 mg/dL; n=40), adjusting for BMI. Within the normal range, higher glucose scores were associated with more negative diurnal slopes (estimate=-.002 SE .001; p=.015). In contrast, high range blood sugar levels were associated with more positive, flatter diurnal slopes (estimate=.007 SE .004; p=.056). We intend to expand these analyses to include biomarkers of obesity, such as leptin, and clinically relevant diet measures.

Obstetric health

Pregnancy-associated and pregnancy-related mortality in the United States military, 2003–2014 Celeste Romano* Clinton Hall Anna Bukowinski Gia Gumbs Ava Marie Conlin

Objective: To assess trends and variation in pregnancy-associated and pregnancy-related mortality in the US military, a population with comprehensive health coverage and stable employment.

Study Design: Live births to active duty Service members were captured in Department of Defense (DoD) Birth and Infant Health Research program data, 2003–2014. Pregnancy-associated deaths (deaths temporally related to pregnancy from any cause) were identified through one year after pregnancy end date using National Death Index Plus (NDI+) data from the DoD Suicide Data Repository. Pregnancy-associated deaths were classified as pregnancy-related (causally related to pregnancy) based on cause of death (including suicide and unintentional overdose), administrative medical encounter data, and chart review. Mortality ratios (deaths per 100,000 live births) were reported overall and biennially; the relative contribution of each cause of death to all pregnancy-associated deaths was reported overall and by age and race/ethnicity.

Results: A total of 179,252 live births occurred to active duty Service members, 2003–2014. Pregnancy-associated and pregnancy-related mortality ratios were 41.3 (95% confidence interval [CI]: 32.4–51.8) and 18.4 (95% CI: 12.7–25.9), respectively. Deaths from suicide and unintentional overdose comprised a larger proportion of pregnancy-associated and pregnancy-related deaths over time and accounted for 17.6% of all pregnancy-associated deaths. Whereas deaths from suicide and unintentional overdose constituted a larger share of pregnancy-associated deaths among those who were 18–29 years and non-Hispanic White, deaths from other pregnancy-related causes accounted for a greater share among individuals ≥30 and non-Hispanic Black.

Conclusion: Pregnancy-associated and pregnancy-related mortality ratios and causes varied over time and by age and race/ethnicity. Suicide and overdose are major recent causes of pregnancy-related mortality among active duty Service members.

Obstetric health

Associations of maternal paraben levels with gestational weight gain through late pregnancy Diana Pacyga* Joseph Braun Susan Schantz Rita Strakovsky

Background/Aims: Parabens are endocrine/metabolic disrupting chemicals and exposure is ubiquitous in pregnant women, but their impact on gestational weight gain (GWG) is unclear. We evaluated associations of maternal parabens with GWG and considered differences by pre-pregnancy BMI (ppBMI).

Methods: Pregnant women from Illinois (n=459) reported their weight pre-pregnancy and at their final obstetric visit before delivery (median 38 weeks gestation). We calculated ppBMI- and gestational age-specific GWG z-scores (GWGz) using a reference population. We quantified ethyl, methyl, and propyl parabens in pools of five first-morning urines collected from 8-40 weeks gestation. We categorized ppBMI (kg/m^2) as under-/normal weight (<25.0), overweight (25.0-29.9), and obese (≥30.0). Using linear regression, we assessed associations of parabens with GWGz accounting for race/ethnicity, education, income, smoking, diet, and ppBMI. We fit models with paraben levels as continuous (ln-transformed) or in quartiles (Q). We included paraben*ppBMI interactions to explore differences by ppBMI.

Results: These mostly non-Hispanic white, college-educated women gained 14.9 kg on average through late gestation and ~50% had a normal ppBMI. We observed strongest associations of methyl paraben with GWGz, where each 2-fold increase in methyl paraben was associated with -0.05 (95%CI: -0.10, 0.00) lower GWGz. Associations were prominent at higher Qs compared to Q1 (Q2 β: -0.20, 95%CI: -0.47, 0.08; Q3 β: -0.28, 95%CI: -0.55, 0.00; Q4 β: -0.27, 95%CI: -0.55, 0.01; P_{trend} = 0.27). Associations were prominent in women with under-/normal ppBMI (Δ: -0.07 for 2-fold methyl paraben increase; 95%CI: -0.14, -0.01; $P_{\text{interaction}}$ = 0.31), modest in women with obesity (β: -0.06, 95%CI: -0.16, 0.05), but minimal in women with overweight (β: 0.03, 95%CI: -0.08, 0.14).

Conclusions: Higher methyl paraben levels were associated with reduced GWG. Because optimal GWG is critical, these findings should be corroborated.

Obstetric health

Outcome-based cesarean delivery rate targets by Robson group: population-based analysis of deliveries from Canada and Sweden Giulia Muraca* KS Joseph Neda Razaz Sarka Lisonkova Linnea Ladfors Olof Stephansson

Objective: To estimate the relationships between cesarean delivery rates and rates of severe maternal and perinatal morbidity and mortality within each Robson group.

Methods: We carried out a population-based, cohort study of deliveries in British Columbia, Canada and Sweden (2004-2016), with institution-year serving as the unit of analysis. The main independent variable was the cesarean delivery (CD) rate and the outcomes were severe maternal morbidity (SMM) and severe perinatal morbidity/mortality (SPMM). Associations between the CD rate and rates of SMM/SPMM were quantified using ecological Poisson regression, while controlling for confounders. These associations were tested for non-linearity using the likelihood ratio test (LRT), comparing the model with only the linear term to the model with the linear and the cubic spline terms.

Results: 2,226,584 deliveries were included among 1,372 institution-year units. The overall mean CD rate was 21.8% and the SMM and SPMM rates were 11.0 and 9.1 per 1,000. In Robson Group 1 (nulliparas with a singleton, term, cephalic fetus with spontaneous labor) the average CD rate was 13.3% and the SMM and SPMM rates were 11.9 and 7.1 per 1,000, respectively. A non-linear relationship was observed between the CD rate and SMM (LRT $p<0.0001$). The predicted probability of SMM in Group 1 declined as the CD rate increased from 10% to 20%, after which the SMM rate was unchanged. Group 5 (multiparas, singleton, term, cephalic with a previous CD) had a mean CD rate of 61.0% and SMM and SPMM rates of 12.7 and 13.5 per 1,000, respectively. An inverse, linear relationship was observed between the CD rate and both the SMM (ARR=0.988, 95% CI 0.984-0.994) and SPMM rates (ARR=0.992, 95% CI 0.985-0.999), with morbidity rates decreasing as CD rates increased.

Conclusion: Outcome-based CD rate targets vary among subpopulations of pregnant individuals. Lower CD rates are not universally associated with better maternal/perinatal outcomes.

Occupational

Maternal exposure to occupational noise during pregnancy: prevalence and selected pregnancy outcomes, National Birth Defects Prevention Study, 1997-2011 Kristen Van Buren* Carissa Rocheleau Wayne Sanderson Leslie MacDonald Elizabeth Masterson Elizabeth Ailes I-Chen Chen Eirini Nestoridi

Introduction: Noise-induced oxidative stress may be a risk factor for adverse birth outcomes and select disorders during pregnancy. Associations between expert-rated occupational exposure to noise were investigated for adverse health outcomes, including preterm birth, small-for-gestational age infants, gestational diabetes mellitus and gestational hypertension (with or without preeclampsia).

Methods: Our population-based sample included >7,000 mother/infant pairs who were controls (without birth defects) enrolled in the National Birth Defects Prevention Study from 10 sites in the United States from 1997-2011. Estimates of maternal occupational exposure to noise occurring anytime from one month prior to conception through the end of pregnancy were determined by expert rater based on standard occupational and industry codes. Unconditional multiple logistic regression was used to estimate associations between occupational maternal noise exposure and each adverse health outcome.

Results: Preliminary, adjusted results showed a statistically significant association between estimated occupational noise exposure of 76-85 decibels among expectant workers and live-born infants characterized as small-for-gestational age. No significant associations were observed for the outcomes preterm birth, maternal hypertension, or maternal gestational diabetes. Significant differences were also observed between categorical levels of occupational noise exposure and maternal race/ethnicity, nativity, and education.

Discussion: Findings suggest that moderate levels of occupational noise exposure (76-85 decibels), below the threshold known to induce hearing loss and require hazard controls, may have an adverse impact on normal fetal growth. Observed differences in exposure to elevated noise levels, such as those by race/ethnicity, highlight the need to consider disparities in occupational environmental conditions as potential reproductive risk factors among expectant worker populations.

Omics

DNA methylation age at birth and childhood: Performance of epigenetic clocks and predictors of epigenetic age acceleration in the Project Viva cohort Anne K. Bozack* Sheryl L. Rifas-Shiman Diane R. Gold Wei Perng Marie-France Hivert Andres Cardenas

Background: Epigenetic clocks based on DNA methylation (DNAm) predict chronological age and estimate biological aging. We evaluated correlations between chronological and epigenetic age at birth and childhood, and investigated factors associated with epigenetic age acceleration (EAA).

Methods: In the Project Viva cohort, we measured DNAm in cord blood (N=485, 31-43 wks gestation), early (N=120, 3-5 yrs), and mid-childhood blood (N=460, 6-10 yrs) with the Illumina 450K BeadChip. We calculated epigenetic gestational age (Bohlin and Knight clocks) and epigenetic age (Horvath, Hannum, PhenoAge, Skin and Blood, and GrimAge clocks). We calculated correlations and median absolute error between chronological and epigenetic age, and evaluated associations of infant sex, maternal characteristics, and epigenetic age at birth with childhood EAA using linear models.

Results: Chronological age was correlated with all measures of childhood epigenetic age (p<0.01). The highest correlations observed for the Horvath (early childhood r=0.54, mid-childhood r=0.45) and Skin and Blood clocks (early childhood r=0.65, mid-childhood r=0.59). Females had higher Knight gestational EAA [B (95% CI)=3.11 (0.07, 0.55) days] but lower mid-childhood Horvath EAA [B (95% CI)=-0.63 (-0.95, -0.32) yrs]. Epigenetic clocks appeared to start recording biological age prior to birth; adjusting for gestational age decreased the median absolute error between childhood chronological and epigenetic age. Horvath EAA at birth was positively correlated with Horvath EAA in early- (r=0.42) and mid-childhood (r=0.19; p<0.01). In addition, for each one-yr increase in Horvath age at birth, childhood EAA increased by approximately 2 yrs.

Conclusions: Epigenetic clocks can reasonably predict chronological age in childhood. Intrinsic EAA, which is independent of age-related immune changes, may be influenced by sex and epigenetic age at birth. Our results suggest that biological aging might be partially programmed *in utero*.

Other

Validity of administrative chorioamnionitis diagnoses at two U.S. Naval Hospitals, 2013-2018 Sandra, Kathy, Celeste, Anna, Gia, Ava Marie Magallon, Snell, Romano, Bukowinski, Gumbs, Conlin*, Clinton Hall Sandra Magallon Kathy Snell Celeste Romano Anna Bukowinski Gia Gumbs Ava Marie Conlin Sandra Magallon

Background: Chorioamnionitis, or intra-amniotic infection, can occur during pregnancy and is characterized by acute inflammation of the membranes and chorion of the placenta, but clinical presentation is heterogenous. Chorioamnionitis affects 1-5% of births, with estimates varying by diagnostic criteria used. Little is known about the validity of administrative chorioamnionitis diagnoses, though International Classification of Diseases (ICD) diagnosis codes are often used to define chorioamnionitis in observational research, particularly studies of vaccine safety in pregnancy.

Methods: Using medical encounter data from a cohort of births among active duty military service members at two southern California U.S. Naval Hospitals from 2013 to 2018, we identified (suspected) chorioamnionitis case status by the presence or absence of ICD-9/10 codes 658.4x/O41.12x on maternal delivery records. We selected a complete sample of cases and a random sample of non-cases for chart review, and systematically abstracted clinical parameters from the delivery episode to inform a gold standard case definition developed by the Brighton Collaboration. We calculated positive predictive values (PPV) and weighted sensitivity and specificity, with 95% confidence intervals (CI), to determine the validity of administrative chorioamnionitis diagnoses in our cohort.

Results: We selected 1868 deliveries (467 cases; 1401 non-cases) for chart review and used 1857 (99.4%) for analysis. The PPV for administrative chorioamnionitis diagnoses was 0.17 (95% CI: 0.14-0.21); weighted sensitivity and specificity were 0.85 (95% CI: 0.78-0.92) and 0.94 (95% CI: 0.94-0.95), respectively.

Conclusion: Administrative chorioamnionitis diagnoses poorly predict true case status, but have high sensitivity and specificity. Observational research studies using ICD codes to define chorioamnionitis could produce valid risk estimates in the setting of nondifferential misclassification by exposure status.

Policy

Federal legislation to reduce racial/ethnic inequities in access to worker policies that promote maternal and child health Candice Johnson* Penelope Howards Helen Chin

Background. Three bills currently under consideration by Congress—the Build Back Better Act, the Healthy Families Act, and the Pregnant Workers' Fairness Act—would provide workers nationwide with access to paid parental leave, paid sick time, and reasonable accommodations during pregnancy. These policies promote maternal and child health, particularly among low-wage workers whose jobs are unlikely to offer these benefits in the absence of a mandate. Without federal legislation, some states have enacted their own version of these policies. We quantified current racial/ethnic inequities in workers' access to these state-level benefits that are caused by this patchwork of policies and that could be reduced by federal legislation.

Methods. Using demographic data from 96,468 participants in the 2016–2019 American Community Survey, we estimated the proportion of recently pregnant workers in each racial/ethnic group who lived in a state with these policies. We used six broad racial/ethnic groups (Latina; non-Latina American Indian/Alaska Native [AIAN], Asian or Pacific Islander, Black, Multiracial, White) and further disaggregated groups when sample sizes allowed.

Results. Among the six broad racial/ethnic groups, Asian or Pacific Islander (50%) workers were the most likely to live in a state that offered all three of paid parental leave, paid sick time, and reasonable accommodations during pregnancy, followed by Latina (41%), Multiracial (31%), White (23%), Black (16%), and AIAN (13%) workers. After disaggregating racial/ethnic groups, Chinese and Dominican workers were the most likely to live in a state with all three policies (65% each) and Cuban workers were the least likely (9%).

Conclusions. Federal legislation granting nationwide access to paid parental leave, paid sick leave, and reasonable accommodations during pregnancy could reduce existing racial/ethnic inequities in coverage.

Pregnancy outcomes

A prospective study of migraine and spontaneous abortion, stillbirth, and ectopic pregnancy Alexandra Purdue-Smithe* Leslie Farland Jennifer Stuart Jae Hee Kang Andrea Harriott Kathryn Rexrode Janet Rich-Edwards

Migraine is a neurovascular disorder most prevalent among women 18-45 years of age (~25%). Among those with migraine, 30% experience aura, transient neurological symptoms that precede headache onset. Women with migraine, particularly those with aura phenotype, have elevated inflammatory cytokines, endothelial dysfunction, and platelet activation, which may confer greater risks of adverse pregnancy outcomes. However, prospective studies of migraine and spontaneous abortion, stillbirth, and ectopic pregnancy are lacking. We therefore estimated associations of self-reported physician-diagnosed migraine occurring before pregnancy (14%) and aura phenotype with spontaneous abortion (losses <20 weeks' gestation), stillbirth (losses ≥20 weeks' gestation), and ectopic pregnancy among incident pregnancies in the prospective Nurses' Health Study 2 (1989-2009; n=40,339). Relative risks (RR) and 95% confidence intervals (CI) were estimated using log-binomial regression that accounted for multiple pregnancies per participant. In models adjusted for age, adiposity, chronic hypertension, and other health and behavioral factors, pre-pregnancy migraine was modestly associated with overall risk of spontaneous abortion (RR=1.08; 95% CI=1.02-1.15). This association was more prominent for losses occurring during 12-19 weeks' gestation (RR=1.15; 95% CI=1.01-1.32) than earlier losses (<8 weeks RR=1.04; 95% CI=0.92-1.17; 8-11 weeks RR=1.06; 95% CI=0.95-1.18). The overall risk of spontaneous abortion appeared slightly stronger for migraine with aura (RR=1.12; 95%CI=1.03-1.22) than without aura (RR=1.04; 95% CI=0.96-1.13), compared to no migraine. Migraine was not statistically significantly associated with stillbirth (RR=1.14; 95% CI=0.86-1.52) or ectopic pregnancy (RR=1.31; 95% CI=0.97-1.76), though power for these analyses was limited. Overall, our findings suggest that migraine history is associated with a modestly higher risk of spontaneous abortion, especially later in gestation.

Pregnancy outcomes

The association between fetal sex and preeclampsia in a diverse cohort of nulliparous women Brandie DePaoli Taylor* Camillia Comeaux Ashley Hill Akaninyene Noah Maria Perez-Patron Abbey Berenson

Women with male fetuses have higher risk of pregnancy loss, preterm birth, and infant mortality. Differences in placental adaptations to maternal stressors may explain these epidemiologic findings. Interestingly, prior studies conducted in primarily non-Hispanic White and Asian populations suggest that female fetal sex is associated with preterm preeclampsia. Others have suggested that associations may vary by race and ethnicity. Our analysis included 12,689 singleton nulliparous pregnancies from an administrative database that recruits women from three urban hospitals. Women in this study are primarily on Medicaid/Chip (55.2%), are of Hispanic ethnicity (48.2%) and are married (68.2%). Outcomes included mild preeclampsia or preeclampsia with a term delivery >37 weeks, preeclampsia with severe features, and preeclampsia with preterm delivery (<37 weeks). Log-binomial regression was used to calculate relative risk (RRs) and 95% confidence intervals (CIs). Multivariable models adjusted for maternal age, race/ethnicity, marital status, and aspirin use. Relative excess risk due to interaction determined if there was an interaction between race/ethnicity and preeclampsia subtypes. Multiple imputations were used for missing data. Nulliparous women with a male fetus had higher risk of HELLP/eclampsia (RR_{adj}. 2.0, 95% CI 1.0-4.4) and preeclampsia with severe features (RR_{adj}. 1.2, 95% CI 1.0-1.4) compared to women with a female fetus. Male:female ratios displayed a male excess for all other preeclampsia subtypes (range 1.04-1.11). There was a significant interaction between Hispanic ethnicity and fetal sex (RERI 0.80, 0.10-1.51) for preterm preeclampsia and preeclampsia with severe features (RERI 0.90, 0.24-1.6) but not HELLP/eclampsia. In contrast to other investigations, our study found that male fetal sex was associated with severe forms of preeclampsia. This association was modified by Hispanic ethnicity. Population structure may influence the relationship between fetal sex and preeclampsia, possibly due to different underlying maternal stressors.

Pregnancy outcomes

Hypothetical interventions on anemia to reduce HIV disparities in adverse birth outcomes

Ellen Caniglia* Rebecca Zash Modiegi Diseko Gloria Mayondi Mompati Mmalane Joseph Makhema Angela Bengtson Shahin Lockman Roger Shapiro Sonja A. Swanson

Background: Women living with HIV (WLHIV) have a higher risk of adverse birth outcomes than HIV-negative women, even in the modern era of antiretroviral therapy. A higher risk of anemia in WLHIV could partially explain this persistent disparity. We evaluated whether hypothetical interventions on anemia could reduce these disparities.

Methods: The Tsepamo Study measured birth outcomes at up to 18 delivery sites in Botswana from 2014-2021. We evaluated 5 hypothetical interventions on anemia among women presenting to antenatal care <24 weeks gestation: 1) eliminate all maternal anemia by 24 weeks; 2) initiate all women on multiple micronutrient supplementation (MMS) by 24 weeks; 3) initiate all women on iron and folic acid supplementation (IFAS) or MMS by 24 weeks; 4) initiate all women on MMS plus Vitamin C by 24 weeks; and 5) a joint intervention including 1 and 2. Any adverse birth outcome comprised stillbirth, preterm delivery, small-for-gestational-age, or neonatal death. We estimated the counterfactual disparity measure (CDM) under each intervention using inverse probability weighted marginal structural models. We compared the CDM with the observed disparity measure (ODM) under no intervention by calculating the proportion explained (PE).

Results: Of 137,499 eligible women (22% WLHIV), risk of anemia was 13.9% in HIV-negative women and 25.4% in WLHIV. The observed risk of any adverse birth outcome was 26.0% in HIV-negative women and 34.5% in WLHIV (ODM, 8.5% [95% CI, 7.9%-9.1%]). The risk of any adverse birth outcome was smaller under each intervention in both groups. CDMs (95% CIs) ranged from 6.6% (4.8%-8.4%) for the joint intervention eliminate anemia and initiate all women on MMS to 8.4% (7.7%-9.1%) for eliminate anemia only, corresponding to modest PEs (0.8% to 21.9%).

Conclusions: Preventing maternal anemia and expanding MMS access may decrease the risk of adverse birth outcomes overall and modestly reduce HIV disparities in adverse birth outcomes.

Pregnancy outcomes

Prenatal weight change trajectories among twin gestations Amy Nichols* Sina Haeri Anthony Rudine Natalie Burns Paul Rathouz Monique Hedderson Saralyn Foster Rachel Rickman Elizabeth Widen

Despite an increase in twin pregnancies in recent decades, the Institute of Medicine twin gestational weight gain (GWG) recommendations remain provisional and provide no guidance for timing or pattern of weight change. We sought to characterize GWG trajectory patterns and examine associations with birth outcomes.

Prenatal and delivery records were examined for 320 women who delivered twins at a maternal-fetal medicine practice in Austin, TX 2011-2019. We modeled GWG for those with at least 1 measured weight in the first trimester and a minimum of 3 prenatal weights. Trajectories were modeled to 32wk (mean delivery 33.7±3.3wk) using flexible latent class mixed models with low-rank thin plate splines. Associations between trajectory classes and neonatal outcomes were analyzed using linear or Poisson regression.

GWG at delivery was 15.4±6.3kg for underweight BMI, 15.4±5.8kg for normal weight, 14.7±6.9kg for overweight, and 12.5±6.6kg for obesity. Three GWG trajectory classes were identified: low (1), moderate (2), or high gain (3). Those in Class 1 (24.7%) maintained weight to 15wk, then gained an estimated 6.6kg at delivery. Class 2 (60.9%) exhibited steady gain with 13.5kg predicted gain, and Class 3 (14.4%) showed rapid gain with a predicted 21.4kg gain. Compared to Class 3, Class 1 pregnancies were associated with lower continuous size for gestational age z-score (CSGAZ; b=-0.50, 95%CI -0.81,-0.19), and reduced risk for large for gestational age (LGA) infants (IRR=0.19, 95%CI 0.05,0.65) and preterm birth <32wk (IRR=0.54, 95%CI 0.32,0.93). Class 2 pregnancies were associated with decreased CSGAZ (b=-0.28, 95%CI -0.55, -0.01) and LGA risk (IRR=0.40, 95%CI 0.20,0.80).

GWG followed a low (1), moderate (2), or high (3) weight gain trajectory; both low and moderate patterns were associated with lower CSGAZ and reduced risk for LGA and preterm birth. The optimal pattern of maternal weight change that balances risk for mothers and infants requires further investigation

Pregnancy outcomes

Maternal body mass index and unexpected complications among low-risk, term newborns
Kimberly Glazer* Teresa Janevic Natalia Egorova Jennifer Zeitlin Elizabeth Howell

Maternal obesity increases risks of congenital anomalies, growth restriction, placental insufficiency, and preterm delivery, but the contribution of body mass index (BMI) to neonatal complications in routine births is not well understood. Our objective was to examine associations between maternal BMI and morbidity among low-risk newborns. **Methods:** We studied 2016-2018 linked birth certificate and maternal-infant discharge data. We restricted to low-risk newborns (term, singleton, non-anomalous, birthweight≥2,500 grams, without fetal or placental conditions, n=254,255) and classified morbidity according to the Joint Commission "unexpected newborn complications" (UNC) measure. Pre-pregnancy BMI (kg/m^2) was ascertained via birth certificate self-reported height and weight. We compared UNC among births to women with underweight (BMI<18.5), overweight (25≤BMI<30), class I-II obesity (30≤BMI<40), and class III obesity (BMI≥40) versus normal weight (18.5≤BMI<25) using logistic regression, and adjusted incrementally for maternal sociodemographic and medical characteristics. **Results:** Roughly 25% of births were among women with overweight and 15% with obesity. UNC incidence increased with increasing BMI (underweight: 29/1000 births; normal weight: 32/1000, overweight: 40/1000, class I-II obesity: 47/1,000, class III: 60/1000). Adjusted for socio-demographics and parity, UNC was higher among births to women with overweight (adjusted odds ratio [aOR] 1.2, 95% confidence interval [CI] 1.1-1.3) and obesity (1.4 [1.3-1.5] class I-II; 1.8 [1.6-2.0] class III) compared to normal weight. Further adjustment for comorbidities (e.g. diabetes, hypertension) slightly attenuated but did not eliminate associations. **Conclusions:** Maternal BMI was associated with complications among a low-risk subset of term infants with adequate growth. Understanding the pathobiology of obesity in pregnancy and care practices on delivery units may help to address potentially preventable newborn morbidity.

Pregnancy outcomes

Birthweight in second singleton babies following a first twin versus singleton pregnancy
Prativa Basnet* Rolv Skjaerven Nils-Halvden Morken Linn Marie Sørbye Janne Mannseth Liv Kvalvik

Introduction: Birthweight is an important indicator of short and long-term outcome of pregnancy for both the infant and the mother. Previous studies have found that second born babies are on average heavier than first born babies, indicating an independent effect of parity on birthweight. Existing data is mostly based on singleton pregnancies and does not consider higher order pregnancies.

Aims: To determine the parity effect of plurality on birthweight in second born singleton babies after first twin versus singleton birth.

Methods: This was a population-based cohort study with data from the Medical Birth Registry of Norway (1967-2020). The study population included 862 729 first singleton and 5 017 first twin pregnancies followed by a second singleton pregnancy. Birthweight (grams) for second singletons were evaluated by means and ANOVA using STATA. The values were adjusted for maternal age at first pregnancy, year of first pregnancy and maternal education.

Results: Second singleton babies were heavier after a first twin than after a first singleton. This was evident across all gestational ages (GA) in first pregnancy. For GA 34-36 and 37-39 weeks in first twin and singleton, mean birthweight of second babies were 3613 vs 3358 and 3712 vs 3528 grams, respectively. Birthweight in the second singleton declined when the interpregnancy interval was > three years in women with first singleton pregnancy. A similar decline was not observed after a first twin pregnancy. Women with a first twin pregnancy had a lower peak in interpregnancy interval around three years compared to women with first singleton.

Conclusion: Women with first born twins have higher birthweight in a second singleton birth than women with a first-born singleton. Interpregnancy interval differs between women with twins and singletons. Birthweight in a second singleton did not decline after long intervals following a twin pregnancy.

Pregnancy outcomes

Racial and socioeconomic disparities in the association between adverse childhood experiences and preterm delivery Yasamean Zamani-Hank* Ahnalee Brincks Nicole Talge Claire Margerison

Life stressors, including adverse childhood experiences (ACEs), may contribute to persistent racial and socioeconomic disparities in preterm delivery (PTD). Few studies have assessed the influence of ACEs on PTD within race & socioeconomic status (SES) subgroups in diverse, national samples. We examined impacts of ACEs on PTD within race & SES subgroups among 2,929 women in The National Longitudinal Study of Adolescent to Adult Health (1994-2018). Data on 11 ACEs (sexual, physical, and emotional abuse; family member suicide attempt or death, neglect, household substance abuse risk, foster care placement, foster care abuse, maternal or paternal death, and maternal incarceration), PTD, and race was collected via self-report. A composite childhood SES construct included parental occupation and education, family income, and public assistance receipt. We utilized 1) chi-square tests to assess differences in ACE levels (low, moderate, high) by race (White, Black, Hispanic, Asian, Pacific Islander, American Indian/Alaska Native, Other) & SES (low, middle, high) and 2) logistic regression to assess relations between all 11 ACEs & PTD overall and within race & SES subgroups. We found no differences in ACEs by race (X^2=14.2, F=1.2, p=0.3) or SES (X^2=5.2, F=1.3, p =0.3). Among Black women, sexual abuse (Odds Ratio OR 3.9, 95% CI 1.2,12.3) and physical abuse (OR 2.4, 95% CI 1.1,5.6) were associated with higher odds of PTD. However, emotional abuse (OR 0.4, 95% CI 0.2,0.8) and family member suicide attempt or death (OR 0.1, 95% CI 0.0,0.5) were associated with lower odds of PTD among Black women. Among women with low SES, household substance abuse risk was associated with higher odds of PTD (OR 2.5, 95% CI 1.1,5.8), while physical abuse was associated with higher odds of PTD among women with middle SES (OR 2.3, 95% CI 1.3,4.1). Our findings suggest the relationship between ACEs and PTD operates differently within race and SES subgroups rather than equally for all women.

Pregnancy outcomes

Does Length of Stay Influence Association between Foreign-born Status and Gestational Diabetes? Akaninyene Noah* Brandie Taylor Ashley Hill Maria Perez-Patron

The healthy migrant hypothesis posits that foreign-born (FB) women experience better birth outcomes than their native-born counterparts, although this effect appears to wane with increased length of stay in the US, prior to delivery. Gestational diabetes (GDM) is a notable exception to this hypothesis, as prior studies show FB women have a higher risk, especially Asian women. Our study aimed to examine the association between FB status and GDM across different race/ethnic groups and the influence of length of stay in the US. We obtained data on 43,777 singleton pregnancies from a perinatal database, which recruits women from Houston, TX hospitals. A modified Poisson regression model was used to calculate the relative risk (RR) and 95% confidence intervals (CI) for the association between FB status and GDM within the entire cohort and stratified by race/ethnicity. We further compared FB women by time spent in the US (0 – 5)/ (5+ years) to US-born women. Models were adjusted for age, insurance method, BMI, and chronic health conditions. Multiple imputation was used for missing data. FB status was associated with an increased risk of GDM (RR_{adj}. 1.65, 95%CI 1.53 – 1.79) this trend was consistent, across all race/ethnicity groups. Compared to US-born women, we observed higher risk of GDM as length of stay in the US increased where more recent migrants (0 – 5 years) had slightly lower risk of GDM ($RR_{adj.}$ 1.17, 95%CI 1.05 – 1.31), than women who have lived in the US 5 + years ($RR_{adj.}$ 1.79, 95%CI 1.64 – 1.95). This trend was also consistent across all race/ethnicity groups. The risk of GDM among FB women appears to increase with longer time spent in US. Future studies should examine the acculturative factors that appear to be driving this risk.

Pregnancy outcomes

Latent class analysis to identify social and clinical risk clusters for preeclampsia subtypes by race/ethnicity Camillia Comeaux* Ashley Hill Akaninyene Noah Maria Perez-Patron Levent Dumenci Brandie DePaoli Taylor

Nulliparous women have an increased risk of preeclampsia (PE), but individual clinical factors are poor predictors of severe disease. We used a latent class analysis (LCA) to identify heterogeneity in social and health risk factors associated with PE by race/ethnicity among 9,809 nulliparous women with singleton pregnancies from a perinatal database. Exploratory LCA identified a three-class solution for Hispanic women, NH-White women, and NH-Black women. Indicators included maternal age, sociodemographic factors, foreign-born status (FBS), pregnancy intendedness, body mass index, mental health, chronic health conditions, substance use, and sexually transmitted infections (STI). Structural equation modeling identified predictors of PE with and without a preterm delivery (<37 weeks) using a multinomial logistic link function and multiple imputation for missing data. Odds ratios (OR) and 95% confidence intervals (CIs) are presented. Reference classes had the highest probability of membership. In NH-Whites and Hispanics, this included older, educated, married women with planned pregnancies. The reference class for Black women consisted of younger, US-born women, with unplanned pregnancies, mental health conditions, and STIs. In NH-Whites, Class 2 was associated with preterm PE (OR 4.9, 95%CI 2.1-11.2). In Hispanics, Class 1 (OR 2.1, 95%CI 1.1-3.7) and Class 2 (OR 2.1, 95%CI 1.1-3.9) were associated with preterm PE. Effect estimates were similar for term PE. In Black women, Class 1 reduced odds of preterm PE (OR 0.4, 95%CI 0.2-1.0). Classes that included young, US-born, single women, with lower socioeconomic status, unplanned pregnancies, mental health conditions, and STIs had higher odds of preterm PE. In Hispanic women, a mostly FBS cluster, with lower socioeconomic status but better health indicators also had increased odds of PE subtypes. Different PE risk patterns by race/ethnicity, suggests that prevention strategies must consider varying needs of pregnant women.

Pregnancy outcomes

How well do neonatal growth charts predict adverse neonatal outcomes? K.S. Joseph* Sid John John Fahey Shiliang Liu Michael Kramer

Background Despite the creation of new neonatal growth standards, no chart for growth assessment has been proven superior. We evaluated the performance of outcome-based population-based centiles and centiles from the Intergrowth and WHO growth charts for identifying infants at risk for adverse neonatal outcomes.

Methods We included singleton live births at 37-41 weeks' gestation in the United States, 2003-2019. Birth weight-specific neonatal morbidity/mortality (NMM), which included 5-min Apgar score <4, seizures, ventilation and neonatal death, was modeled by gestational week using penalized B-splines. Birth weights at which NMM odds were minimized, and increased by 10%, 50% and 100% relative to the minimum were estimated. Population, Intergrowth and WHO centiles corresponding to the birth weight at which NMM odds were minimized/increased were identified, and the predictive performance of these birth weight/centile cut-offs was compared.

Results The study included 40,196,326 live births and 1,001,738 NMM cases. Among singleton girls at 39 weeks, NMM odds were lowest at 2949 g (Population, Intergrowth and WHO centiles 18, 26 and 23) and 10% higher at 2722 g (Population, Intergrowth and WHO centiles 6, 11 and 8). Birth weight/centile cut-offs performed poorly as predictors of NMM, regardless of chart. The birth weight cut-off of 2722 g for singleton girls at 39 weeks yielded a sensitivity of 8.3% and specificity of 94.0%. The pretest probability of NMM was 20.3 per 1,000 live births and increased to 27.8 per 1,000 given a positive test, while the pretest probability of not having NMM was 979.7 per 1,000 and barely changed to 980.1 per 1,000 given a negative test.

Conclusions All growth charts perform poorly as predictors of adverse neonatal outcomes in term infants. Birth weight for gestational age (as a continuous centile) is strongly associated with adverse neonatal outcomes in populations but works poorly when used as the sole predictor at the individual level.

Pregnancy outcomes

Physical Activity during Pregnancy and Markers of Placenta Vasculature Amber, Robert, Jessica, Diana, Richard, Ruchit, Theresa, Carolyn, Susan, Thomas, Emily Kautz, Block, Brunner, Fernandez, Miller, Shah, Girardi, Salafia, Groth, O'Connor, Barrett*, Nicole Mayo Amber Kautz Robert Block Jessica Brunner Diana Fernandez Richard Miller Ruchit Shah Theresa Girardi Carolyn Salafia Susan Groth Thomas O'Connor Emily Barrett Amber Kautz

Background: Physical activity (PA) in pregnancy is beneficial for mother and baby, however little is known about the underlying mechanisms. The placenta is the maternal-fetal interface for nutrient, gas and waste exchange, yet limited research has examined the impact of PA on the placenta. To date, studies have had small sample sizes and crude placental measures. Here, we examined PA during pregnancy in relation to placental morphology and chorionic vascularization in a large observational cohort.

Methods: The Pregnancy Physical Activity Questionnaire (PPAQ) was used to characterize PA among pregnant women in the Understanding Pregnancy Signals and Infant Development (UPSIDE) cohort (n=199). At birth, placentae were collected and imaging was conducted. Using multivariable linear regression, we examined the mean total PA (Total METs) and moderate to vigorous PA (MVPA METs) across pregnancy in relation to a set of novel, specialized markers of placental vascular health.

Results: In fully adjusted models, Total and MVPA METs were inversely associated with distance from the ends of arteries to the perimeter of the placenta (smaller distance indicates better chorionic surface vasculature "fit"; Total: -0.27 [-0.57, 0.03]; MVPA: -0.45 [-0.84, -0.06]). PA was positively associated with the total length of the placental arterial "tree" (longer length indicates more extensive vascularization), though associations were attenuated in fully adjusted models. PA was not associated with placental weight or fetoplacental weight ratio.

Conclusion: Our results suggest that prenatal PA is associated with greater placental vascular function. Although there was no evidence of gross differences in the placenta, when we examined specialized vascular markers, we observed evidence that PA may enhance vascularization, which has implications for fetal growth and development. More research is needed to examine placental health markers in relation to maternal postnatal and child health.

Pregnancy outcomes

Variability in risk factors and outcomes related to maternal and infant health among Asian, Native Hawaiian, and Pacific Islander Individuals giving birth in California Shalmali Bane* Barbara Abrams Mahasin Mujahid Chen Ma Aileen Xu Latha Palaniappan Suzan Carmichael

Despite Asian, Native Hawaiian, and Pacific Islander (ANHPI) populations being the fastest growing racial/ethnic group in the US, they are understudied, underrepresented, and underfunded in research. Existing research often aggregates these populations, thus obscuring diversity and disparities among ANHPI sub-groups. Our goal was to examine variability in risk factors and outcomes related to maternal and infant health among disaggregated subgroups of ANHPI populations.
We used linked live birth and fetal death certificate and maternal hospital discharge data from California (2007-2017), for the following subgroups: Cambodian, Chinese, Filipino, Guamanian, Hawaiian, Hmong, Indian, Japanese, Korean, Laotian, Samoan, Thai, Vietnamese, Other-Asian, Other-PI.
For assessed risk factors, there was high variability ranging from a 2-fold difference between the lowest and highest groups for English as the principal language spoken (Chinese: 54.2% to Hawaiian: 99.8%) to 54-fold for smoking during pregnancy (Hawaiian: 5.9% to Indian: 0.1%). For perinatal outcomes, variability ranged from 2-fold for severe maternal morbidity (Korean: 1.1% to Samoan:1.9%) to 5-fold for high birthweight (Vietnamese: 3.1% Vietnamese to Samoan: 17.2%). Within sub-groups, the number of variables ranked highest or lowest risk varied considerably (i.e., no single sub-group was consistently high or low risk across all variables).

There is substantial variability in risk factors and perinatal health outcomes across ANHPI subgroups, and for high- or low-risk status across these variables within subgroups. Future work on this topic should consider disaggregated subgroups.

Pregnancy outcomes

Investigating the impact of patient-centered medical homes on racial disparities in severe maternal morbidities using Medical Expenditure Panel Survey Data Curisa Tucker* Nathaniel Bell Cynthia L. Corbett Audrey Lyndon Tisha M. Felder

Purpose: The primary purpose of this study was to examine the association between participation in care consistent with a patient-centered medical home (PCMH) on severe maternal morbidity (SMM) outcomes and the association between PCMH status among racial groups on the prevalence of SMM.

Methods: We conducted a longitudinal analysis of pooled Medical Expenditures Panel Survey data of respondents for the years 2007-2016 merging self-reported primary care experiences with clinical care outcomes. We estimated odds ratios of SMM and calculated Generalized Estimation Equation models.

Main Findings: A total of N=2801 respondents who gave birth during the study period were identified, representing 5,362,782 U.S. lives. Among all respondents, 76% were never in a PCMH, 18% were sometimes in a PCMH, and 7% were always in a PCMH. An SMM was experienced by 2% of respondents which did not differ significantly (p=0.11) by PCMH status. We found marginal statistical significance between respondents who were always in a PCMH versus never (p=0.05). There was no overall interaction effect between race and PCMH status on the SMM outcome (p = 0.80).

Conclusions: Few respondents (7%) were always enrolled in care consistent with a PCMH. There is an implication that the PCMH model may produce fewer SMM outcomes. The trend of decreased SMM outcomes for respondents in a PCMH indicates that more research is needed to investigate this model and its impact on SMM outcomes, as well as race as an effect modifier.

Pregnancy outcomes

Relation Between Poor Maternal Cardiovascular Health Scores During Pregnancy and Adverse Pregnancy Outcomes Andrea Kozai* Melissa Jones Michele Levine Kara Whitaker Bethany Barone Gibbs

Introduction

Adverse pregnancy outcomes (APOs), including hypertensive disorders of pregnancy, gestational diabetes, growth restriction, and preterm birth, are related to negative health consequences for mother and child. Lifestyle cardiovascular health (LCVH) components, such as those in the Life's Simple 7 CVH score, may predict risk of APOs, although its utility is not well-established in pregnancy. Thus, we examined the association between LCVH scores during pregnancy and APOs.

Methods

Pregnant participants (N=114, 31±4.7 years) enrolled in a cohort study prior to 14 weeks gestation. Five lifestyle components of Life's Simple 7 were adapted for pregnancy. Diet quality (Diet History Questionnaire), self-reported smoking, and physical activity (PA) (GT3X accelerometer) were measured each trimester. Pre-pregnancy body mass index (ppBMI), gestational weight gain (GWG), and APOs were abstracted from medical records. Components were averaged across gestation, scored as ideal (2), intermediate (1), or poor (0), and summed for an overall LCVH score (range 0-10). Odds ratios (OR) were calculated using logistic regression and adjusted for maternal demographics.

Results

Mean±SD LCVH score was 5.6±1.69 (range 2-10). APOs occurred in 29 participants (25%). Ideal scores were uncommon for GWG (11%) and diet (8%), but at least half scored ideal on ppBMI (50%), PA (76%), and smoking (79%). Mean LCVH score was nonsignificantly higher (more favorable) in those with no APO compared to those with at least 1 APO (5.8±1.71 vs. 5.2±1.59, p=0.12). Adjusted odds of APO were 23% lower with each 1-point increase in LCVH score, though this clinically meaningful reduction was not statistically significant (aOR=0.77, 95% CI 0.58, 1.01, p=0.056).

Conclusion

LCVH are intervention targets in pregnancy and this metric provides a useful composite to assess APO risk. Future research should examine associations in larger samples with greater power and consider trimester-specific associations with APO risk.

Pregnancy outcomes

A mediation analysis of maternal smoking and infant birth weight on the US-Mexico border
Chino Ogbutor* Stephanie Mishaw Zuber Mulla

Published data on the indirect effect of maternal smoking on birth weight as mediated by gestational age in Hispanic populations are lacking. Our goal was to conduct a mediation analysis in which maternal smoking during pregnancy was the causal antecedent variable, gestational age was the mediator, and the outcome was birth weight using data from El Paso County, Texas. El Paso County is located on the US-Mexico border. A mediation analysis was conducted using year 2010 birth certificate data. The SAS macro PROCESS 3.5.3 was used to estimate the direct and indirect effects of active maternal smoking (by trimester) on birth weight in the setting of linear regression. The single mediator was gestational age in weeks. A direct or indirect effect was deemed to be present if the 95% confidence limits (CL) excluded 0. Analyses were adjusted for multiple variables including maternal pre-pregnancy body mass index. The indirect effect was reported along with a 95% bootstrap CL based on 12,000 bootstrap samples. 16,654 singleton births were included in the cohort. The majority of the mothers were White Hispanic (87.2%). The mean (standard deviation) birth weight was 3198.6 grams (517.2). Mean gestational age was 38.4 weeks. A direct effect of maternal smoking during each trimester on birth weight was detected. In the third trimester, for every one-unit increase in the mean number of cigarettes smoked per day, there was a decrease in birth weight of 14.8 grams (95% CL: -25.0, -4.6). An indirect effect of maternal smoking was not detected in any of the trimesters. In the third trimester the indirect effect of the mean number of cigarettes smoked per day was -4.2 (95% bootstrap CL: -10.6, 2.0). In our large, predominantly Hispanic cohort, it appears that gestational age is not a mediator of the effect of maternal smoking on birth weight. Future studies in our population should explore other possible mediators of the association between maternal smoking and birth weight.

Pregnancy outcomes

Risk of severe postpartum hemorrhage according to the sum of birthweights in twin pregnancies Lola Loussert* Thomas Schmitz Diane Korb Aurélien Seco Elie Azria Loïc Sentilhes François Goffinet Catherine Deneux-Tharaux

Background

Twin pregnancies have a five-fold increased risk of severe postpartum hemorrhage (PPH) compared with singleton pregnancies. This study aimed to characterize the strength and pattern of association between birthweights and severe PPH in twin pregnancies.

Methods

This was a secondary analysis of the JUMODA cohort, a national, prospective, population-based study of twin deliveries, in 2014-2015 in France. We excluded women with fetal death or medical termination of either twin, with antepartum hemorrhage, placenta previa, placenta abruptio and with missing birthweight. The primary outcome was severe PPH. The exposure was the sum of the birthweights of the two twins (SBW). To assess the association between SBW and severe PPH, we used multilevel multivariable modified Poisson regression modeling. Analyses were conducted on the overall population and by planned and actual mode of delivery. Three sensitivity analyses were performed, assessing the association between SBW and a) most severe PPH, b) PPH caused by uterine atony or genital tract laceration, and c) PPH from 32 weeks.

Results

Among the 8373 women included, 76.1% had a SBW above 4000 grams, considered the high-risk threshold in singleton pregnancies. Severe PPH occurred in 4.5% (95% confidence interval (CI) 4.1-5.0), from 2.1% for SBW less than 3000g up to 8.8% for SBW greater than 6500g. In the multivariable analysis, the association between SBW and severe PPH was linear with an adjusted relative risk of severe PPH for each 500 grams increase in SBW of 1.36, 95% CI 1.24–1.49. In subgroup and sensitivity analyses, results were similar.

Conclusion

In twin pregnancies, the risk of severe PPH gradually increased with the SBW. By improving the identification of high-risk women, this result may help to promote optimal PPH management. This study highlights the importance of considering both maternal and neonatal risks when assessing a twin pregnancy, in order to provide the most appropriate peripartum care.

Social determinants of health

Impact of access to rideshare on satisfaction, healthcare utilization, and preterm delivery among pregnant women with Medicaid coverage: a randomized controlled trial Courtney Lynch* Sara Conroy Kenneth Jackson Rachel Smith Erinn Hade

Lack of access to reliable transportation is a barrier to receipt of prenatal care. We aimed to assess the impact of modernization of non-emergency medical transportation (NEMT) services on patient satisfaction, prenatal care utilization, and preterm delivery. We conducted a randomized controlled pilot trial in an urban community with high rates of infant mortality. From May 31, 2019 to June 30, 2020, we enrolled 143 pregnant individuals. Eligibility criteria included: pregnant and <32 weeks of gestation, age 18 years or older, enrolled in one of two participating Medicaid Managed Care Organizations (MCO), lives in the county with no plans to move, and can communicate in English. Women were randomly assigned to usual NEMT services from their MCO or enhanced smart transportation (EST) services (i.e., on demand transportation with access to a mobile application and rides to the grocery store, food bank or pharmacy). The primary outcome was satisfaction with transportation services. Secondary outcomes included prenatal care utilization and preterm delivery <37 weeks of gestation. We also examined the number of trips taken by participants in each randomized group.
Among the 4,120 women screened, 143 (3.5%) were eligible and enrolled. Women in the EST group took more medical-related trips than those in the usual care group, with a median number of 8 versus 1 respectively. Some evidence of increased traveler satisfaction was observed in the intervention group compared to usual transportation, with 90 percent and 79 percent respectively reporting being satisfied or very satisfied [risk difference = 11.5 percent (95 percent confidence interval (CI): -1.3, 24.3), p-value=0.08]. There were no meaningful differences in prenatal care utilization or preterm delivery between groups. EST increases use of NEMT and may increase traveler satisfaction. It remains unclear whether provision of EST increases prenatal care utilization or decreases preterm delivery.

Social determinants of health

Food insecurity during pregnancy: data from the National Children's Study Rachel M. Smith* Sarah E. Anderson Eben Kenah Mark A. Klebanoff Courtney D. Lynch

Background: Over 38 million people in the United States are living in food insecure households, but little is known about the prevalence of food insecurity (FI) during pregnancy.

Methods: Using data from the National Children's Study–Initial Vanguard Study (NCS-IVS), conducted in 2009-2010, we examined the characteristics of pregnant women (n=770) who reported past year FI. Most women entered the study during the first (79.1%) versus the third trimester, and FI and covariate data were collected at enrollment. FI was assessed using the 6-item USDA Food Security Short Form during the first study visit, which occurred during the first or third trimester, with individuals with a score of 0-1 being considered FI.

Results: Of the 770 pregnant women in NCS-IVS, 12.6% reported FI. FI prevalence varied by demographic characteristics. More Hispanic and Non-Hispanic Black/African American women were FI than Non-Hispanic white women (33.9% and 14.6% vs. 6.7%, respectively). The youngest (age 15-24) and oldest (age).

Discussion: Those who are underserved and those of racial and ethnic minority carry a larger burden of prenatal FI, however, the prevalence and risk factors might differ given COVID-19.

Social determinants of health

Eviction as a social determinant of pregnancy health: County-level eviction rates and adverse birth outcomes in the U.S. Emily Harville* Maeve Wallace Katherine Theall

Access to housing is an important manifestation of structural racism and discrimination, and birth outcomes show wide health disparities, but few studies have examined eviction and birth outcomes. This multilevel study merged data from the Eviction Lab on 2015 eviction judgments and records with the National Center for Health Statistics natality dataset. The analytic sample included 2950965 births across 5924 counties in 45 states. Outcomes of interest were low birthweight (<2,500g; LBW) and preterm birth (<37 weeks gestation; PTB). We fit generalized estimating equations to account for clustering within county and a logistic distribution to estimate the odds ratio of LBW or PTB associated with the county-level eviction rate, with control for individual and county-level characteristics. Results were calculated separately for non-Hispanic white, non-Hispanic Black, and Hispanic mothers. After adjustment for covariates, living in the counties in the highest quartile of eviction was associated with a 12-13% increased odds of LBW. The magnitude of association with PTB was not as large. Non-Hispanic Black women were more likely to live in counties in the highest quartile of eviction rate (43%, vs. 23% for white women and 23% for Hispanic women) or filing rate (44%, vs. 23% for white and 18% for Hispanic). The association between eviction rate and LBW/PTB was strongest for Black women, while there was essentially no association among Hispanic women. Housing instability may be a key social determinant of poor birth outcomes and should be considered in state and local maternal and child health policy and programming.

Social determinants of health

Assessing the Impact of Neighborhood Deprivation on Birth Defects among North Carolina singleton live births from 2011-2015 Kristen Cowan* Monica Jimenez Thomas Luben Kristen Rappazzo

One in 33 babies born in North Carolina (NC) are diagnosed with any birth defect. Little has been done to examine the association between community-level risk factors and birth defects. The objective of this study was to estimate the association of census-tract level neighborhood deprivation and prevalence of birth defects. Data from 2011-2015 from the NC Birth Defects Monitoring Program, the State Center for Health Statistics, and the Census were combined. The Neighborhood Deprivation Index (NDI) was created using principal component analysis with census variables representing income/poverty, education, employment, housing, and occupation; we dichotomized NDI into high and low deprivation areas. Linear binomial regression was used to estimate the prevalence differences (PD) of birth defect diagnoses in the first year of life stratified by with and without early prenatal care (within first 5 months) adjusting for maternal age and education level at delivery, race/ethnicity. Among the final sample of 566,799 births, 17,691 infants (3.1%) were diagnosed with at least one birth defect in the first year of life. The adjusted prevalence of birth defects among those with early prenatal care was 35.57 per 10,000 higher for those in high deprivation neighborhoods compared to those in low deprivation neighborhoods (PD=35.57, 95% CI: (25.26, 45.88)). The adjusted prevalence of birth defects among those without early prenatal care was 2.27 per 10,000 lower for those in high deprivation neighborhoods compared to those in low deprivation neighborhoods (PD=-2.27, 95% CI: (-39.84, 35.81)). Among those with early prenatal care, high levels of neighborhood deprivation had a significant impact on birth defect prevalence. These findings can be used to inform more specific research into other environmental- or neighborhood-level exposures that should be investigated in relation to birth defects, along with research into specific birth defects and groupings.

Social determinants of health

Neighborhood fatal police violence and severe maternal morbidity in California Curisa, Corinne, Jennifer, Patrick, Suzan, Mahasin Tucker, Riddell, Ahern, Bradshaw, Carmichael, Mujahid*, Elleni Hailu Curisa Tucker Corinne Riddell Jennifer Ahern Patrick Bradshaw Suzan Carmichael Mahasin Mujahid Mahasin Mujahid

Police violence is a pervasive public health issue that may have implications for adverse pregnancy outcomes such as severe maternal morbidity (SMM). We aimed to assess how the occurrence of fatal police violence (FPV) in one's neighborhood before/during pregnancy may influence SMM risk, and its racial/ethnic disparities. Hospital discharge records from California were linked with the Fatal Encounters database between the years 2000-2017 (N=3,027,537). We identified 2,800 neighborhoods (i.e. census tracts) with at least one incident of FPV during the study period. We used neighborhood fixed effects models adjusting for individual sociodemographic characteristics to estimate odds of SMM associated with experiencing FPV in the neighborhood anytime within the 24 months before childbirth. We also considered more granular exposure time-windows (within 18, 12, and 9 months before childbirth) and examined differential associations based on frequency of such events (1-2 vs ≥3) and by using race/ethnicity stratified models. Birthing people who experienced at least one FPV in their neighborhood within 24 months before their child's birth had 9% higher odds of experiencing SMM compared to their counterparts (95% Confidence Interval (CI): 6%-12%). Among birthing people experiencing ≥3 FPV in the neighborhood, the occurrence of any such event within 24, 18, 12, or 9 months of giving birth was associated with 24% (95% CI: 8%-31%), 20% (95% CI: 8%-31%), 18% (95% CI: 5%-31%), and 14% (95% CI: 1%-31%) increased odds of SMM respectively, such that risk of SMM increased as exposure window increased. Associations were stronger for Hispanic/Latinx and Asian/Pacific Islander individuals than for white birthing people. Results were mostly null in neighborhoods with 1-2 incidents of FPV. Our findings underscore the urgent need to address the deleterious health consequences of policing and the imperative to prioritize preconception health in maternal health research.

Substance Use

Maternal preconception and pregnancy tobacco and cannabis use in relation to placental developmental markers: a population-based study Kim N. Cajachagua-Torres* Hanan El Marroun Irwin K.M. Reiss Vincent W.V. Jaddoe

Maternal tobacco and cannabis use during pregnancy is associated with adverse perinatal outcomes. We hypothesized that maternal tobacco and cannabis use are associated with placental adaptations, which subsequently lead to adverse perinatal outcomes. In a population-based prospective cohort study of 8,008 pregnant women, we assessed maternal tobacco and cannabis use by questionnaires. Placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) were measured in the first and second trimester and at delivery from blood samples. Placental weight and pregnancy complications were obtained from medical records. We observed that tobacco use before and during first-trimester only were not associated with any angiogenic factors. As compared to no tobacco use, continued use during pregnancy was associated with higher PlGF, lower sFlt-1 concentrations, and lower sFlt-1/PlGF ratio in second trimester (all p-values <0.05). Also, compared to no cannabis use, use before and during pregnancy were associated with higher PlGF concentrations and lower sFlt-1/PlGF ratio in first and second trimester (all p-values <0.05). First trimester only cannabis use was associated with higher sFlt-1 concentrations and higher sFlt1/PlGF ratio at delivery (all p-values <0.05). Compared to non-use, tobacco use before pregnancy was associated with a higher placental weight, whereas continued tobacco use during pregnancy was associated with a lower placental weight. Continued tobacco or cannabis use was related to higher placental weight to birth weight ratio and higher risk of pregnancy complications (all p-values <0.05). These results suggest that maternal tobacco and cannabis use lead to placental vascular maladaptation predisposing to adverse pregnancy outcomes.

Substance Use

Effect of perceived neighborhood environment on cannabis use during pregnancy among African American women Ban Al-Sahab* Dawn Misra

Background: Environmental context is an important predictor of health behavior. Understanding its effect on cannabis use among pregnant women is yet to be understood. **Objective:** To assess the impact of perceived neighborhood environment on prenatal cannabis use among African American women. **Methods:** Data is from the Life-Course Influences on Fetal Environments Study (LIFE), a retrospective cohort of postpartum African American women in Metropolitan Detroit, Michigan (2009-2011). Prenatal cannabis use was defined as ever use by calculating the last self-reported date of cannabis use relative to the mother's last menstrual period. Five perceived neighborhood scales were considered: social cohesion and trust, healthy food availability, walkability, social disorder and danger and safety. Higher scores for all of the neighborhood scales, except for social disorder, imply a better perceived environment. **Results:** Out of 1,369 women, 151 (11.0%) self-reported prenatal cannabis use. Younger, unmarried, unemployed, nulliparous and women with ≤ 12 years of education had higher odds of using cannabis during pregnancy. Cannabis use was also concurrent with prenatal tobacco smoking, alcohol drinking during pregnancy and ever use of other drugs. Comparing the means with a t-test, the means for all five neighborhood scales were significantly different by cannabis use status. Women who reported cannabis use during pregnancy had worse neighborhood scores than their counterparts. The mean differences in neighborhood scores between cannabis and non-cannabis users were: social cohesion and trust (-1.3, 95% confidence interval(CI): -2.12,-0.47), healthy food availability (-0.47, 95%CI: -0.85,-0.09), walkability (-0.81, 95%CI: -1.51,-0.12), social disorder (1.5, 95%CI: 0.63,2.36), and danger and safety (-1.69, 95%CI: -2.61,-0.76). **Conclusion:** Further studies are warranted to understand the relationship between individual and environmental determinants of prenatal cannabis use.

Substance Use

Polysubstance use during pregnancy – 25 U.S. states and jurisdictions, 2019 Denise, Beatriz, Clark, Brenda, Janae, Shin D'Angelo, Salvesen von Essen, Denny, Bauman, Dunkley, Kim*, Amy
Board Denise D'Angelo Beatriz Salvesen von Essen Clark Denny Brenda Bauman Janae Dunkley Shin Kim Janae Dunkley

Introduction: Substance use during pregnancy is often associated with poor health outcomes for the birthing parent and infant; however, research on polysubstance use during pregnancy is somewhat limited. This study assessed the prevalence of polysubstance use during pregnancy and identified commonly co-occurring substances.

Methods: We analyzed 2019 data from the Pregnancy Risk Assessment Monitoring System for 25 U.S. jurisdictions that included supplementary questions on opioid and other substance use during pregnancy, 11 of which also asked about alcohol use. The questions assessed alcohol and cigarette use during the last trimester of pregnancy, and use of all other substances at any point during pregnancy. Weighted prevalence estimates and 95% confidence intervals (CIs) were calculated.

Results: Overall, nearly one quarter of participants who reported use of any substance engaged in polysubstance use during pregnancy. Alcohol was the substance most commonly reported (7.4%; 95% CI 6.7-8.1%), followed by cigarettes (6.5%; 95% CI 6.0-7.0%), and marijuana (4.3%; 95% CI 3.9-4.7%). Approximately 1 in 4 participants who reported cigarette or e-cigarette use also reported marijuana use. Among participants who reported prescription stimulant use during pregnancy (0.6%; 95% CI 0.4-0.8%), 31.0% (95% CI 7.4-54.6%) also reported alcohol use and 24.2% (95% CI 9.9-38.6%) reported cigarette use. Although prevalence of heroin use was low (0.2%, 95% CI 0.1-0.2), use of illicit stimulants (amphetamines: 51.7%, 95% CI 32.1-71.3% or cocaine: 26.5%, 95% CI 11.9-41.1%) was frequently reported among pregnant persons using heroin.

Conclusions: Polysubstance use was reported for multiple substances during pregnancy in this sample. A multi-layered approach of evidence-based screening and risk counseling, enhanced availability of clinical and mental health services, and prompt access to quality substance use programs could be used to address substance use during pregnancy.

Substance Use

Associations between substance use and frequency of menopausal symptoms among US women with or at risk for HIV Brooke Bullington* Andrea Knittel Andrew Edmonds Catalina Ramirez Lisa Rahangdale Genevieve Neal-Perry Deborah Konkle-Parker Deborah Jones Weiss Caitlin Moran Elizabeth Topper Golub Helen Cejtin Dominika Seidman Seble Kassaye Tracey Wilson Anjali Sharma Adaora Adimora

Background: Half of US adults over age 50 report history of drug use. Menopausal symptoms can adversely affect well-being, but little is known about menopausal symptoms of women who use or used drugs.

Methods: We used longitudinal data from the Women's Interagency HIV Study from 2008-2020 to describe frequency of past or current substance use and menopausal symptoms among perimenopausal and postmenopausal women. We used alternating logistic regression to model associations between current (in past 6-12 months) and past (before menopause) heavy alcohol, heavy cigarette, heavy cannabis, crack/cocaine, and narcotics use and frequency of vasomotor, mood, and musculoskeletal symptoms. We estimated odds ratios (aOR) adjusted for other current substance use, cumulative substance use, race, ethnicity, menopausal stage, childhood and current sexual/physical trauma, income, and geographic location.

Results: Of 2,947 women, 66% were Black, 54% had an annual household income <$12,000, and 74% had HIV. Women reported heavy drinking (8%), heavy smoking (5%), heavy cannabis (5%), crack/cocaine (7%), and narcotics (12%). A total of 54%, 35%, and 46% of women without HIV and 41%, 51%, and 60% of women with HIV reported frequent vasomotor, mood, and musculoskeletal symptoms, respectively. Heavy alcohol use during menopause was associated with more frequent vasomotor symptoms (aOR: 1.22; 95% confidence interval [CI]: 1.10,1.37) and mood symptoms (aOR: 1.19; 95% CI: 1.05,1.33). Narcotics use during menopause was associated with more frequent mood symptoms (aOR: 1.19; 95% CI: 1.09,1.30) and musculoskeletal symptoms (aOR: 1.17; 95% CI: 1.07,1.28).

Conclusions: Substance use was common, including during the menopausal transition, and may affect menopausal symptoms, though there is potential for reverse causality given the exposure and outcome. Clinically assessing women's historical and current substance use may help to contextualize menopausal symptoms and guide management.

Substance Use

Associations of maternal cigarette and electronic cigarette use around the time of pregnancy with risk of diabetes XIAOZHONG WEN* Mariana Hand Alexia Pezzino Meghana Sana Brooke Pearce

Background: E-cigarette use during pregnancy has been increasing rapidly. But there is limited knowledge regarding e-cigarette use and maternal health, including diabetes.

Objective: To examine the associations of e-cigarette and cigarette use (ever and frequency) with diabetes before pregnancy and gestational diabetes.

Methods: This secondary data analysis used data from phase 8 (2016-2019) of the Pregnancy Risk Assessment Monitoring System (PRAMS, N=153,336). Postpartum mothers reported their e-cigarette and cigarette use within the 3 months before pregnancy and during the last 3 months of pregnancy. They also reported their diabetes status before pregnancy (preexisting diabetes) and during pregnancy (gestational diabetes). We used multivariable log-binomial regression models to estimate the adjusted odds ratio (aOR) for the associations of e-cigarette and cigarette use with diabetes, adjusting for significant covariates.

Results: Compared to non-users, mothers who exclusively used cigarettes before pregnancy (10.4% vs. 10.0%; aOR, 1.10 [95% confidence interval or CI, 1.05-1.16]) had an increased risk of gestational diabetes. Heavy smokers before pregnancy (≥11 cigarettes/day) had an increased risk of diabetes before pregnancy compared to light smokers (≤10 cigarettes/day) (4.4% vs. 3.5%; aOR, 1.20 [95% CI, 1.03-1.39]) or non-smokers (4.4% vs. 3.4%; aOR, 1.18 [95% CI, 1.03-1.34]; p-value=0.020). Heavy smokers before pregnancy (10.5% vs. 10.1%; aOR, 1.12 [95% CI, 1.03-1.22]) also had an increased risk of gestational diabetes, compared to non-smokers. However, e-cigarette use before or during pregnancy was not associated with diabetes before pregnancy or gestational diabetes.

Conclusions: Heavy cigarette smoking before pregnancy was associated with a high risk of diabetes before pregnancy and gestational diabetes. E-cigarette use seemed not to be a significant risk factor for maternal diabetes.

Violence or abuse victimization

Exposure to Domestic Violence and racial disparities in breastfeeding in North Dakota (ND PRAMS 2017-2019) Andrew Williams* MichaeLynn Kanichy Lexie Schmidt Grace Njau Matthew Schmidt Anastasia Stepanov

Background. In 2019, the overall breastfeeding initiation rate in the US was 84.1%, yet only 76.6% of American Indian (AI) women initiated breastfeeding. Exposure to domestic violence (DV) may influence breastfeeding via high stress and low social support. In ND, AI women have greater exposure to DV than other racial/ethnic groups. Evidence regarding DV and breastfeeding is limited, especially among AI women. We explored whether DV partially explains racial/ethnic disparities in breastfeeding initiation in ND.

Methods. Data for 2214 women were from 2017-2019 ND Pregnancy Risk Assessment Monitoring System. Breastfeeding initiation was maternal response to "Did you ever breastfeed or pump breast milk to feed your new baby, even for a short period of time?" (yes/no). DV was assessed for both 12 months before and during pregnancy based on maternal report (yes/no) of violence from a husband/partner, family member, someone outside of family, or ex-husband/partner. An "Any DV" variable was created if women reported "yes" to any DV. Logistic regression estimated odds ratios and 95% confidence internals for breastfeeding initiation among AI and Other race/ethnicity women compared to White women. In separate models, we included DV to assess whether DV accounted for racial/ethnic disparities. Models were adjusted for maternal demographic, medical, and behavioral factors.

Results. AI women had 51% reduced odds to initiate breastfeeding(OR:0.49 95%CI:0.31,0.59) compared to white women. Including the "Any DV" during pregnancy reduced the odds of breastfeeding initiation among AI women by 15%(OR:0.42 95%CI:0.30,0.59) compared to white women. Results were similar for DV before and during pregnancy.

Discussion. Findings suggest that AI women are less likely to initiate breastfeeding than white women, and DV does not explain the disparity but widens the disparity. Strengthening of cultural ties to the tradition of breastfeeding may improve breastfeeding rates in AI populations.

Women’s health

Characterizing the Risk of Type 2 Diabetes Mellitus by Gestational Diabetes: The APPLE NYC Cohort Katharine McCarthy* Shelley Liu Joseph Kennedy Hiu Tai Chan Luciana Vieira Victoria Mayer Gretchen Van Wye Mary Huynh Teresa Janevic

Diverse population-based data on the progression to Type 2 Diabetes (T2DM) from gestational diabetes mellitus (GDM) are lacking. We estimate the population-based risk of T2DM by GDM status and race/ethnicity with the A1c in Pregnancy and Postpartum Linkage for Equity (APPLE) cohort, a multiethnic retrospective cohort in New York City (NYC). We used a systematic match algorithm to identify unique women who gave birth between 2009 and 2011 and were followed for up to eight years postpartum using linked NYC birth record, hospital discharge and A1c diabetes registry data. Differences in time to T2DM by GDM status were assessed using Cox regression, adjusting for sociodemographic and clinical factors. We tested for effect measure modification between GDM status and race/ethnicity using tests for interaction and stratification. Models were generalized to accommodate non-proportional hazards by GDM by allowing interaction with time and through stratification by postpartum time interval. We applied a quantitative adjustment for bias due to disease misclassification using probabilistic bias analysis, hypothesizing non-GDM women may be less closely monitored and more likely to be underdiagnosed for T2DM. The cumulative incidence for T2DM was 8.2% and 0.5% among women with and without GDM, respectively. The adjusted hazard ratio (aHR) for the risk of GDM on developing T2DM was 15.7 (95% Confidence interval (CI) 13.9, 17.8) in the overall cohort and varied only slightly by race/ethnicity. When stratified by time, we found risk was highest in the first year following birth (aHR 17.2, 95% CI: 14.8, 20), and decreased with time to (aHR: 7.8, 95%CI: 6.2, 9.9) at 5-9 years postpartum. Under diagnosis of T2DM among women without GDM could reduce estimates by only one-third. Results demonstrate stark differences in the risk of T2DM by GDM which persist after accounting for diagnostic bias. These findings call for improved T2DM prevention in the postpartum period.

Women’s health

The Association between Delivery Type and Breastfeeding Initiation: A State-Specific Analysis Utilizing the Pregnancy Risk Assessment Monitoring System, 2016-2021 Evelyn Jones* Ksenia Primich

In Virginia, the percentage of infants who have attempted breastfeeding is higher than the national average, but gaps exist when looking at delivery type (cesarean section vs. vaginal). A growing amount of research has shown that the mode of infant delivery has an effect on breastfeeding practices, specifically on delay of breastfeeding initiation and early breastfeeding cessation. Because of the health benefits, the promotion and support of breastfeeding initiation is a public health issue. The purpose of this study was to determine whether delivery type is associated with breastfeeding initiation using Virginia Pregnancy Risk Assessment Monitoring System (VA PRAMS) data.

Data from VA PRAMS, a state-level, population-based survey, annually collects data on maternal behaviors and perinatal experiences that were used for this analysis. We included all live births to women of reproductive age (15-49) from 2016-2021 with information on the exposure and outcome variables. The exposure was delivery type, measured using birth certificate data. The outcome variable was breastfeeding initiation, which was assessed using the respective questions in VA PRAMS. Logistic regressions were performed to assess the relationship between delivery type and breastfeeding initiation. Multivariate logistic regressions were performed to control for covariates such as race, age, maternal education, insurance, WIC utilization, marital status, and previous live births. This data was a weighted percentage of mothers with live births reporting yes to breastfeeding initiation.

There were N=4,728 women included in our analysis. 71%(n=3,415) of women reported a vaginal delivery while 29%(n=1,427) of women reported a cesarean section delivery. Our initial analysis showed higher odds of breastfeeding initiation in women who had vaginal deliveries (Odds Ratio: 1.39; 95% Confidence Interval: 1.14, 1.70) compared with women who had cesarean section deliveries. However, results of adjusted analyses yielded this relationship as insignificant (OR: 1.30 95% CI: 0.92, 1.84).

In Virginia, women who had vaginal deliveries are more likely to initiate breastfeeding than women who delivered via cesarean section. Further analysis of barriers and how policies may support women delivering via cesarean section are recommended.

Women’s health

Association between pregnancy complications in the older sister and later cardiovascular death in the younger sister with uncomplicated pregnancies Aditi Singh* Liv Grimstvedt Kvalvik Kari Klungsøyr Rolv Arnold Skjærven

Background: Pregnancy complications like preeclampsia and preterm birth are associated with increased future cardiovascular (CVD) mortality. Studies have also shown an increased risk of preeclampsia in mothers who have sisters with preeclamptic pregnancies. It is unknown whether pregnancy complications in an older sister are associated with increased CVD mortality in a younger sister who did not herself experience complications.

Method: The Medical Birth Registry of Norway and the Population Registry was used to identify 83586 sister pairs who had their first births between 1967–2013 and where the younger sister had no pregnancy complications (defined as the absence preterm birth, preeclampsia, placental abruption, small or large for gestational age, diabetes, plural birth, perinatal death, malformations and caesarean section in all pregnancies). The Cause of Death Registry with follow-up until 2020 provided data on deaths.

Hazard ratios (HR) and 95% confidence intervals (CI) using Cox regression analyses were estimated for CVD deaths up to 69 years in younger sisters without pregnancy complications by specific pregnancy complications in the older sister’s pregnancy, adjusted for maternal age at first birth, year of first delivery and maternal education (three categories) in both sisters.

Results: CVD death was identified in 249 (9.1%) younger sisters, and an increased risk of CVD death was present if the older sister had preeclampsia in any pregnancy (HR 1.77; 95% CI 1.14-2.75). There were 22 CVD deaths (16.1%) in younger sisters with no complications when the older sister had preeclampsia, relative to 227 CVD deaths (8.7%) when the older sister did not have preeclampsia. Increased risk of CVD death in the younger sister was less evident for other specific pregnancy complications in the older sister’s pregnancies.

Conclusion: The risk of CVD death among younger sisters with no pregnancy complications was increased if the older sister had preeclampsia in any pregnancy.

Women’s health

The Affordable Care Act dependent coverage provision and unintended pregnancy Colleen MacCallum-Bridges* Robert Kaestner Zhehui Luo Claudia Holzman Tim Bruckner Claire Margerison

Background: Nearly 50% of pregnancies in the US are unintended (mistimed or unwanted), and these pregnancies disproportionately impact younger and lower income women. The Affordable Care Act dependent coverage provision (hereafter “the provision”) required that insurance plans cover dependents up to age 26, increasing access to health insurance coverage and contraceptives for young women. This had potential to reduce unintended pregnancies. The impact of this policy may have differed by dependent income level as those with lower income were less likely to be insured and thus more likely to benefit.

Objective: Estimate the association between the provision and unintended pregnancy, overall and by dependent income level.

Methods: We used data from the National Survey of Family Growth, cycles spanning 2006-2015. We estimated the impact of the provision on unintended pregnancy using an event study approach to compare trends in unintended pregnancy between those eligible to benefit (ages 18-25) and those ineligible to benefit (ages 26-44). We used 2007-2009 as the reference period, and we estimated unadjusted and adjusted associations overall and within income subgroups [<100% of the federal poverty level (FPL), 100-399% FPL, ≥400% FPL].

Results: There was no evidence of an association overall. However, among those with income <100% FPL, the provision was associated with an 8.7 (95% CI: 3.8, 13.6) percentage point decrease in unintended pregnancy between 2007-2009 and 2012-2014. Prior to the provision, the annual prevalence of unintended pregnancy among this group was 15%. Thus, the observed association is a decrease of >50%. No evidence of an association was found among other income groups.

Conclusion: Following the provision, a large decline in unintended pregnancy was observed among low-income women <26 years old. Additional work is needed to understand the interaction between parental and dependent income level and its implication for health equity.

Women's health

Impact of Medicaid Expansion on Contraception Use Among Low-income Women of Reproductive Age Nazeeba Siddika* Katlyn Hettinger Claire Margerison

Impact of Medicaid Expansion on Contraception Use Among Low-income Women of Reproductive Age

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Abstract:

The Affordable Care Act (ACA) Medicaid expansions have been found to be associated with increased enrollment in Medicaid among women of reproductive age and utilization of preventive care services, but it remains unknown whether these gains in coverage increased the use of contraceptives.

Objective: Our objective was to evaluate the impact of Medicaid expansion on contraception use among low-income, nonpregnant women of reproductive age.

Methods: We used data (35,274) from the National Survey of Family Growth (NSFG) waves 2006-2010, 2011-2013, 2013-2015, 2015-2017, and 2017-2019. The primary outcomes of interest were the current use of contraception (defined as self-reported any form of contraception in the month of the interview); use of 'most effective' contraceptives (as defined by the Centers for Disease Control and Prevention); and use of contraceptives that require interaction with a health care provider. We conducted a quasi-experimental study with a difference-in-differences (DID) design.

Results: Research using the NSFG dataset with state identifiers requires accessing data in a Research Data Center and obtaining disclosure permission for all results. We await disclosure of our results and were thus unable to report results by the abstract submission deadline. However, by June, we will report the estimated percentile point change in contraceptive use, use of effective contraception, and use of contraceptives requiring interaction with a health care provider associated with Medicaid expansion in the first 2 years after Medicaid expansion (2015-2017) and in the second 2 years after expansion (2017-2019) as well as an overall impact from 2015-2019. We will also report whether the impacts of Medicaid expansion were equitable across racial/ethnic groups.

Conclusions: Our findings will contribute to a growing understanding of the impact of the ACA on the health of women of reproductive age.

Women’s health

Maternal birthplace and risk of Postpartum Haemorrhage. A Norwegian population-based cohort study Katrine M Owe* Silje Pettersen Johanne Sundby Benedikte Lindskog Siri Vangen Ingvil K. Sørbye

Background: Postpartum hemorrhage (PPH) is a feared complication to childbirth and a leading contributor to maternal morbidity and mortality worldwide. Given the increasing trend in PPH in developed regions, we investigated maternal birthplace and its association with moderate and severe PPH by mode of delivery.

Methods: This was a nationwide registry-based cohort study of all singleton pregnancies lasting ≥22 gestational weeks registered in the Medical Birth Registry of Norway (2008-2017), and linked to the National Population Registry. The exposure was maternal birthplace, defined as the country where the woman was born, and categorized into regions. The outcome was PPH, defined as estimated blood loss of 500-1500ml (moderate) and >1500ml and/or blood transfusion (severe). Multinomial regression models simultaneously estimated adjusted relative risk ratios (RRR) for moderate and severe PPH, with 95% confidence intervals (CI) stratified by mode of delivery.

Results: Among 574,583 pregnancies, we identified 20.9% cases of PPH out of which 2.4% with severe PPH. Compared to Norwegian-born women, we observed a high risk of both moderate and severe PPH in women from Southeast/East Asia/Pacific who had a vaginal delivery (RRR 2.01, 95% CI 1.89–2.13, and RRR 2.18, 95% CI 1.89-2.51). Among women with an operative vaginal delivery, those from Southeast/East Asia/Pacific had high risk of moderate (RRR 2.06, 95% CI 1.83-2.32) and severe PPH (RRR 2.59, 95% CI 2.12-3.17), followed by women from Latin America/Caribbean (RRR 1.75, 95% CI 1.33-2.29, and RRR 2.03, 95% CI 1.28-3.21). Women from Sub-Saharan Africa and Southeast/East Asia/Pacific who had a Caesarean delivery, had almost twice the risk of severe PPH compared to Norwegian-born women (RRR 1.94, 95% CI 1.66-2.28; and RRR 1.94, 95% CI 1.63-2.32).

Conclusion: The risk of moderate and severe Postpartum hemorrhage differed by maternal birthplace, with a particular high risk in women from Asia & the Pacific, across modes of delivery.

Women’s health

Offspring birthweight in consecutive pregnancies and long-term maternal mortality, following spontaneous and iatrogenic term deliveries: A population-based study Yeneabeba Tilahun Sima* Rolv Skjaerven Liv Grimstvedt Kvalvik Nils-Halvdan Morken Kari Klungsoyr Linn Marie Sorbye

Background: Knowledge of the association between large offspring and maternal cardiovascular disease (CVD) mortality shows inconsistency. Most of these conclusions are based on first-born infants, not considering women’s consecutive births.

Objective: To assess long-term CVD mortality in women with consecutive pregnancies by trajectories of offspring birthweight by gestational age and explore whether the association was specific to spontaneous or iatrogenic deliveries.

Design: Population-based cohort study

Population: Women with first and second (453,741) singleton and term births in the Medical Birth Registry of Norway between 1967-2013, were followed up till 2020 by linkage to the Norwegian Cause of Death Registry.

Methods: Offspring birthweight by gestational age (z scores) was categorized into quartiles (Q) for women’s first and second birth. Exposure trajectories were made by combining Q1, Q2/Q3 and Q4 from women’s births, keeping women with consecutive birth in Q2/Q3 quartile as the reference. Risk of CVD mortality was estimated by cox regression model and expressed as hazard ratios (HR) with 95% confidence interval (CI), adjusting for women’s age and year of delivery. Results were stratified into spontaneous- and iatrogenic deliveries.

Results: Moving from a higher to lower quartiles of offspring birthweight in subsequent birth was associated with a higher risk of mortality. Women with a first offspring in Q2/Q3 and a subsequent birth in Q1 had higher risk of mortality (HR 1.4, 95% CI 1.2-1.6). Correspondingly, mortality was reduced in women with a first offspring in Q2/Q3 and second in Q4 (HR 0.7, 95% CI 0.6-0.9). Mortality was higher in women with iatrogenic than spontaneous deliveries.

Conclusions: Women with large offspring in subsequent deliveries had lower risk of CVD mortality while risk was higher for women with consecutive low birthweight infants. Maternal mortality risk was modified by birthweight of the successive offspring.

Big Data/Machine Learning/AI

Predictors of Unplanned Extubations Requiring Reintubation in Pediatric Critical Care

Krista Wollny* Deborah McNeil Stephana J. Moss Tolulope Sajobi Simon Parsons Karen Benzies Amy Metcalfe

Accidental removal of a breathing tube (*unplanned extubation)* is an adverse event in pediatric critical care. When a tube needs to be reinserted (*reintubation*), skilled clinicians must be available. This study explored predictors of unplanned extubation requiring reintubation.

We obtained data on children (≤18 years) who had an unplanned extubation in a PICU (2012-2020) from the Virtual Pediatric Systems database. We developed and trained a multilevel least absolute shrinkage selection operator (LASSO) logistic regression model in the 2012-2016 sample that accounted for between-PICU variations as a random effect to predict reintubation within 24 hours after unplanned extubation. The remaining sample (2017-2020) was used to externally validate the model. Predictors included age, weight, sex, primary diagnosis, admission type, and readmission status. Model calibration and discriminatory performance were evaluated using Hosmer-Lemeshow goodness-of-fit (HL-GOF) and area under the receiver operating characteristic (AUROC), respectively.

Of the 5,703 children included, 1,661 (29.1%) required reintubation. Variables associated with increased risk of reintubation were age (<2 years; OR: 1.61, 95% CI: 1.41-1.81), weight (<10kg; OR: 1.54, 95% CI: 1.37-1.73), and diagnosis (respiratory; OR: 1.51, 95% CI: 1.32-1.74). Scheduled admission was associated with decreased risk of reintubation (OR: 0.75, 95% CI: 0.64-0.87). With LASSO (lambda=0.008), remaining variables were age, weight, diagnosis, and scheduled admission. The predictors resulted in AUROC of 0.59 (95% CI: 0.57–0.61); HL-GOF showed the model was well calibrated (p=0.84). The model performed similarly in external validation (AUROC 0.58, 95% CI: 0.56-0.61).

LASSO logistic regression is a powerful feature selection technique that is useful for regression problems. Including clinical factors (e.g., oxygen and ventilatory requirements at the time of unplanned extubation) in the model may increase predictive capacity.

Birth defects

Maternal caffeine consumption and risk of birth defects in the National Birth Defects Prevention Study, 1997-2011 Eva Williford* Meredith Howley Sarah Fisher Kristin Conway Paul Romitti Matthew Reeder Andrew Olshan Mahsa Yazdy Marilyn Browne

Caffeine consumption is common during pregnancy. Existing evidence for the association between maternal caffeine consumption and birth defects is mixed. We updated estimates of associations between daily caffeine consumption in the year before pregnancy and 52 specific birth defects from the National Birth Defects Prevention Study (NBDPS) based on pregnancies from 1997-2011. The NBDPS was a large multisite, population-based case-control study conducted in 10 US states. We used logistic regression to estimate adjusted odds ratios (aORs) and 95% confidence intervals for the risk of specific birth defects associated with maternal pre-pregnancy daily caffeine consumption. We categorized self-reported total dietary caffeine consumption from coffee, tea, soda, and chocolate as: <10 mg/day, 10 to <100 mg/day, 100 to <200 mg/day, 200 to <300 mg/day, and 300 mg/day or more. For birth defects with at least five exposed cases, we adjusted for maternal race/ethnicity, age at delivery, body mass index, first trimester cigarette smoking, first trimester alcohol use, and study site. Our analysis included 30,516 cases and 11,502 controls, where 52% of case and 54% of control women reported consuming <100 mg caffeine per day, and 11% of both case and control women reported consuming 300 mg or more per day. Low levels of caffeine consumption were associated with small, statistically significant increases in aORs (1.2-1.7) for 10 birth defects. Associations with high levels of caffeine were generally weaker, except for two defects, craniosynostosis and aortic stenosis (aORs= 1.3 [1.1-1.6], 1.6 [1.1-2.3], respectively). Given the large number of estimates generated, some of the statistically significant results may be due to chance and thus the weakly increased ORs should be interpreted cautiously. No dose-response patterns were observed for any defect. Overall, our results support earlier NBDPS findings suggesting that caffeine consumption is not a risk factor for the studied defects.

Prenatal psychosocial stress is associated with lower infant gut microbiome alpha diversity in Cebu, Philippines Elijah Watson* Melissa Manus Sahana Kuthyar Delia Carba Thomas McDade Christopher Kuzawa Katherine Amato

Prenatal stress in mouse models has been linked to offspring microbiome development, but this relationship is understudied among humans. We used data from a subsample of mother-infant pairs from the Cebu Longitudinal Health and Nutrition Survey to examine associations between prenatal psychosocial stress measures and infant gut microbial alpha diversity. During pregnancy, mothers completed the Perceived Stress Scale (PSS) and a modified Center for Epidemiologic Studies-Depression scale (CES-D). Infant fecal samples were collected at two weeks (n=32) and six months (n=22) from 2017-2018. Infants reporting C-section birth, antibiotic use, or illness two weeks before sample collection were excluded. After 16S rRNA bacterial gene sequencing, infant gut alpha diversity was estimated using DivNet. Associations between prenatal psychosocial stress measures and infant gut alpha diversity were estimated using models accounting for incomplete microbial community structure. All models were run cross-sectionally at the two time points with either continuous PSS or CES-D as the main exposure and adjusted for a household asset index as a measure of socioeconomic status. Prenatal PSS scores ranged from 5-25 and CES-D scores ranged from 1-14. At two weeks, prenatal PSS (β=-0.07 [95% CI: -0.08, -0.06]) and CES-D (β=-0.14 [95% CI: -0.15, -0.13]) were associated with lower infant alpha diversity. Negative associations with alpha diversity persisted, but were attenuated, at six months with prenatal PSS (β=-0.05 [95% CI: -0.06, -0.05]) and CES-D (β=-0.05 [95% CI: -0.08, -0.06]). Our findings provide preliminary support for associations between prenatal psychosocial stress and infant gut microbiome alpha diversity. Larger samples, longer follow-up, and longitudinal modeling are needed to determine whether these associations persist and have developmental or health implications.

Child health and development

Effect of exposure to maternal diabetes during pregnancy on offspring’s brain cortical thickness and neurocognitive functioning Shyfuddin Ahmed* Miguel Ángel Cano Mariana Sánchez Nan Hu Gladys E Ibañez

Background

Maternal diabetes may affect the developing brain of the fetus. However, little is known about the long-term effects of maternal diabetes on offspring’s brain morphometry and neurocognitive functioning (NCF).

Objective

To examine the effect of prenatal exposure to maternal diabetes during pregnancy (DP) on brain structure and neurocognition in children between 9 and 10 years of age.

Methods

This study used cross-sectional structural neuroimaging and NCF data from the baseline wave of Adolescent Brain and Cognitive Development study. Exposure to maternal DP were extracted from developmental history questionnaire. Differences in brain cortical thickness (CTh) and five cognitive abilities (executive function, working and episodic memory, processing speed, and language abilities) were examined in diabetes-exposed and unexposed children. Linear mixed effect models and generalized linear models were used to adjust for the effect of confounding variables.

Results

A total of 9967 children (718 Diabetes-exposed, 9249 unexposed children) with an average age of 9.9 years (SD 6.2) were included in the analysis. Diabetes-exposed children had lower whole-brain CTh [mean: exposed vs unexposed= 2.725mm vs 2.732mm; mean difference(95%CI): exposed – unexposed= -0.007mm (-0.013, -0.001)] compared to unexposed children after adjusting for confounding variables. Diabetes-exposed children had lower CTh in most part of the occipital lobe of both hemispheres, right post-central gyrus and left superior parietal cortex. Diabetes-exposed children also had lower scores in processing speed task [mean: 85.9 vs 87.6; mean difference (95%CI): -1.7 (-2.8, -0.6)], and total cognition [mean: 83.2 vs 83.8; mean difference (95%CI): -0.6 (-1.2, -0.02)] compared to unexposed children.

Conclusions

Diabetes-exposed children have reduced CTh and NCF during preadolescence, which may have implications for psychomotor development during later life. Prospective studies are needed to confirm our findings.

Child health and development

Red blood cell folate modifies the association between serum per- and polyfluoroalkyl substances and antibody levels in U.S. adolescents Vicente, Yi-Xin, Yang, Zainab, Nicole, Angela, Carmen Mustieles, Wang, Sun, Bibi, Torres, Slitt, Messerlian*, Yu Zhang Vicente Mustieles Yi-Xin Wang Yang Sun Zainab Bibi Nicole Torres Angela Slitt Carmen Messerlian Alexandra Hillcoat

Background

Several per- and polyfluoroalkyl substances (PFAS) are considered immunotoxic and have been associated with reduced vaccine antibody response. Although red blood cell (RBC) folate has previously been associated with lower PFAS concentrations, no prior study assessed its role as an effect modifier between PFAS exposure and antibody levels.

Methods

We included 584 adolescents aged 12 to 19 years in the National Health and Nutrition Examination Survey 2003-2004 cycle. Concentrations of folate in RBC, four PFAS compounds [i.e., perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulphonic acid (PFHxS), and perfluorononanoic acid (PFNA)], and measles, rubella, and varicella antibodies were determined in serum. We stratified the population into lower vs. equal or higher than median RBC folate levels (RBC folate < vs. ≥ median). We used multivariable linear regressions to estimate the covariate-adjusted percent changes (PCs) and 95% CIs of antibody levels in relation to a 2.7-fold increase in individual PFAS concentrations, for low and high folate groups, respectively. We used quantile g computation (QGC) and Bayesian kernel machine regression (BKMR) to examine the joint effect of total PFAS mixtures on antibody levels for each folate group. We further restricted the analyses to participants with seropositive antibody levels (about 95% of the total population).

Results

In the total population, we found negative associations between serum PFOS and PFHxS concentrations and rubella antibody levels in the lower folate group, while the results were null in the upper folate group. Associations among the lower folate group were strengthened by restricting to the seropositive subpopulation. We further found negative associations between serum PFOA and rubella antibody levels, and PFOS and varicella antibody levels only among the lower folate group in the seropositive subpopulation. QGC and BKMR showed consistent negative associations between the total PFAS mixture and rubella antibody levels among the lower folate group, while the upper folate group showed no meaningful mixture results. No associations were found between PFAS exposure and measles antibody.

Conclusion

In this U.S. representative cross-sectional study, we found negative associations between select PFAS and the total PFAS mixture and rubella antibody levels only among adolescents with lower than median RBC folate levels. If confirmed in mechanistic studies, the findings have important implications for using folate as a mitigating measure for adverse PFAS immune effects.

The Language and Communication Development and School Readiness of U.S. Preschool-Aged Children Raised by Grandparent Caregivers Compared to Parents Sarah Keim*
Samrawit Yisahak Andria Parrott Rachel Mason

The early family environment is important to language and communication development and school readiness. More grandparents are in roles supporting child development when parental custody is impacted by substance misuse, incarceration, abuse and neglect, and other adverse childhood experiences (ACEs). We compared the prevalence of being “on track” with language and communication development and school readiness among US preschool children by household structure (grandparent- vs parent-headed) in the nationally-representative National Survey of Children’s Health. Caregivers completed modules about language and communication development and a “healthy and ready to learn” school readiness indicator. We used survey-weighted adjusted logistic regression to estimate the prevalence of being “on track” for these outcomes by household structure, stratified by ACEs, race, and poverty when interaction $p<.1$. We also used a 1:1 greedy matching algorithm and caliper of 0.5-SD for propensity score matching. Four percent of 38737 eligible children lived in a grandparent-headed household. 86% were on track for language and communication development; 30% were on track for school readiness. In unadjusted models, children in grandparent-headed households had a much lower odds of being on track with social-emotional development (OR=0.59; 95% CI: 0.35, 0.99). Adjusted results for all outcomes were null. Some interactions were detected, but only 1 association was statistically significant in stratified models: white children in grandparent-headed households had a higher odds of being on track with physical well-being and motor development than white children in parent-headed households (OR=1.41; 1.05, 1.90). Propensity score matching made no difference. Overall, many children are not on track with language and communication development and school readiness. Regardless of a child’s household structure, many families are in need of early development resources to promote school readiness.

Child health and development

Association of maternal autoimmune disease and offspring autism spectrum disorder and potential interaction with infection in early childhood: a population-based cohort study

Timothy Nielsen* Natasha Nassar Antonia Shand Hannah Jones Velda Han Shrujna Patel Adam Guastella Russell Dale Samantha Lain

Background: Both maternal autoimmune disease and early childhood infections have been associated with increased risk of autism spectrum disorder (ASD) in offspring. However potential synergistic effects between these exposures remain unexplored in human studies. The aim of this study was to examine potential synergistic effects between maternal autoimmune disease and early childhood infections and their association with offspring ASD.

Methods: We conducted a population-based cohort study of singleton children born at term gestation (37-41 weeks) in New South Wales, Australia from January 2002 to December 2008 and followed until 2017. Maternal autoimmune diagnoses and childhood infections before age 2 years were identified from linked maternal and child hospital admissions and child ASD by age 9 years was identified from linked disability services data. Multivariable logistic regression assessed the association between each exposure and ASD and additive interaction between exposures, controlling for potential confounders.

Results: A total of 18,451 children exposed to maternal autoimmune disease were propensity score matched (1:2) to 36,902 unexposed children. Any maternal autoimmune disease (adjusted odds ratio (aOR) 1.25, 95% confidence interval (CI) 1.07-1.47) and any childhood infection before age 2 years (aOR 1.38, 95% CI 1.15-1.67) were each associated with ASD. However, there was no evidence of additive interaction between the two exposures (relative excess risk due to interaction (RERI) 0.128, 95% CI -0.418-0.675) resulting in increased odds of ASD in offspring.

Conclusions: Both maternal autoimmune disease and early childhood infections were independently associated with offspring ASD, but we found no evidence of synergistic effects between these exposures. Future studies could examine potential interactions between other measures of maternal immune activation and childhood infection and impact on ASD.

Child health and development

Twins and singletons- who is healthier? Tamar Wainsotck* Israel Yoles Ruslan Sergienko Eyal Sheiner

Objective: Multiple gestation is a risk factor for many pregnancy complication, including mainly preterm delivery, low birthweight , gestational diabetes mellitus , and preeclampsia. The current study aimed to clarify whether offspring born after twin pregnancies are at an increased risk for long term health complications.

Methods: A retrospective cohort study was conducted in a single large tertiary medical center, including all live births between the years 1991-2021. Offspring with congenital malformations were excluded. Hospital based diagnoses of all offspring were categorized into main groups of morbidities: cardiac, respiratory, infectious, neurologic, neoplasm, and metabolic. Incidence of each main group was compared between twins and singletons, as well as time to first morbidity diagnosis in each group and pregnancy characteristics. Cox proportional survival models were used to study the association between twins versus singletons and main grouped morbidities, while adjusting for gestational age, mode of conception (spontaneous versus infertility treatments) and mode of delivery (cesarean versus vaginal).

Results: A total of 369,841 offspring were included in the analysis, of them 11,986 (3.2%) were twins and 357,855 (96.8%) were singletons. Twins were more likely to be delivered preterm (57.3% vs. 7.1%), by cesarean delivery (54.1% vs. 14.2%), and following infertility treatments (15.9% vs. 1.2%). Incidence of most morbidities was slightly, some significantly, higher among twins (Table). The differences can also be seen in the Kaplan-Meier survival curves. However, once adjusting for gestational age (among other confounding variables), twin offspring were no longer at an increased risk for morbidities, and were even at lower risk for health complications as compared to singletons.

Conclusion: Although twins seem to be at greater risk for long term health complications, once adjusting for prematurity, they may even be healthier than singletons.

Child health and development

Trends in adult survival, reproductive and educational outcomes for Norwegians born preterm from 1967 – 1991 Sage Wyatt* Truls Østbye Liv Grimstvedt-Kvalvik Kari Klungsøyr Rolv Skjærven

Introduction

While many effective interventions were developed during the 1980's to reduce short term risk of mortality for preterm infants, change in adult outcomes is unclear. The purpose of this study is to compare adult educational, reproductive, and survival outcomes of people born preterm over time.

Methods

We used data from 1249878 singleton births from Norwegian population registry data born from January 1967 to December 1991, divided into 5 cohorts of 5 years. Gestational age was divided into extremely preterm (22 – 32 weeks), moderately preterm (33 – 36 weeks) and term (>36 weeks). People were followed through June 2020.

Results

The total incidence of preterm birth (extremely preterm (EP): 1%, moderately preterm (MP): 4%) has remained stable over time, but percent who survive to age 18 has increased (EP 16% increase, MP 3% increase). People born preterm people are not at significantly different risk of adult death in 1986-1991 compared to term born people (EP: RR 1.20 CI95% 0.79-1.80, MP: RR 1.19 CI95% 0.94-1.49), but the risk has increased since 1967-1971 (EP: RR 1.09 CI95% 0.87-1.36, MP: RR1.05 CI95%0.93-1.18). People born preterm remain at lower odds than term born people of graduating high school in 1986-1991 (EP: OR 0.61 CI95% 0.56-0.67, MP: OR 0.76 CI95% 0.74-0.81) as they did 1967-1971 (EP: OR 0.61 CI95% 0.55-0.67, MP: OR 0.79 CI95% 0.75-0.83). People born preterm remain less likely than term born people to reproduce in 1986-1991 (EP: RR 0.65 CI95% 0.61-0.69, MP: RR 0.89 CI95% 0.86-0.92), but with less disparity than 1967-1971 (EP: RR 0.61 CI95% 0.55-0.67, MP: RR 0.79 CI95% 0.75-0.83).

Conclusions

Changes in clinical handling that drastically improved survival for preterm infants and children are not clearly reflected in wellbeing of the adult population. However, increasing early survival does not indicate an increase in greater adult disability, as indicators for quality of life show similar or higher levels to the initial period.

Child health and development

Unique and Joint Effects of Maternal Exposure to Phthalates and Experiences of Racism on Infant Behavior Amanda Wylie* Julia Rager Rebecca Fry Cathi Propper

Prior studies have revealed the adverse effects of early phthalate exposure, including to DEHP and DEP, on child neurodevelopment (Braun et al., 2013). Recent interest has surrounded whether the effects of chemical stressors, like phthalates, on outcomes may be conditional upon exposure to social stress. Though there is evidence that stressful life events and race (a proxy for race-related stress or effects of racism) moderates the effects of phthalates on child physical development (Barrett et al., 2016; Wenzel et al., 2015), the combined study of social stress and phthalates on child neurodevelopment is in its infancy. Leveraging data (N=97) from the Brain and Early Experience Study, we examine the unique, joint, and mediating effects of maternal prenatal self-reported experiences of racism (EOR) and phthalate exposure at 6-months postpartum (captured via silicone wristbands) on maternal report of infant behavior at 6-months. In linear regressions, DEHP was associated with increased infant negativity after controlling for maternal age, education, and infant's gestation-corrected age (β=.23, p=.03); there was weak (not significant) evidence that DEP was associated with infant surgency (β=.20, p=.07). DEHP and DEP were not associated with infant behavior after adjusting for EOR; rather, EOR was associated with the infant behavior at the same magnitude (negativity: β=.28, p=.02; surgency: β=.20, p=.07). Though mothers who identified as minoritized were exposed to higher DEHP and DEP (p<.02) than mothers who were white, we did not detect mediating effects. We also tested statistical interactions between phthalates and EOR on infant development but did not find meaningful effects. Thus, though minoritized mothers experienced higher phthalate exposure (which predicted infant behavior), EOR appears to be more salient than the chemical stressor. We will further probe relations between EOR, social stress, and phthalates, and extend outcomes to toddler behavior for SPER.

Child health and development

Pre-pregnancy maternal cardiovascular diseases and risk of offspring's neurodevelopmental disorders: a population-based cohort study M Zakir Hossin* Kyla McKay Lorena Cruz Anna Sandström Neda Razaz

Introduction: Maternal exposure to cardiovascular disease (CVD) during pregnancy is associated with adverse maternal and neonatal health outcomes. However, its association with offspring's long-term neurodevelopmental disorders (NDDs) is not yet known. Therefore, we aimed to investigate the association between mothers' pre-existing CVDs and offspring's NDDs.

Methods: This population-based cohort study included 2.4 million live singleton births recorded in the Swedish Medical Birth Register between 1990 and 2016. Information on maternal pre-pregnancy CVDs was extracted from the National Patient Register, including diagnosis of ischemic heart disease, heart failure, cerebrovascular disease, arrhythmia, cardiomyopathy, and congenital heart disease. Registered diagnoses of offspring NDDs included Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and intellectual disability (ID). Cox proportional hazards models were fitted to estimate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for the associations, adjusting for maternal characteristics including age, parity, education, smoking, psychiatric illness, pre-gestational diabetes and hypertension.

Results: A total of 141 027 individuals received a diagnosis of ADHD, 63 802 of ASD, and 22 385 received a diagnosis of ID. The adjusted analyses showed that offspring of mothers with CVD had 14% higher risk of ADHD (HR 1.14; 95% CI: 1.07-1.22) and 11% higher risk of ASD (HR 1.11; 95% CI: 1.01-1.21), compared with offspring of mothers without CVD. Specifically, maternal heart failure was associated with 2.12-fold increased risk of ASD (95% CI: 1.31-3.41) and maternal cerebrovascular disease was associated with 32% elevated risk of ASD (95% CI: 1.08-1.61) and 17% elevated risk of ADHD (95% CI: 1.01-1.35). No association was found between maternal CVDs and ID.

Conclusion: Maternal CVD before pregnancy may be a risk factor for ADHD and ASD in offspring, with varied risk by CVD subtype.

Child health and development

Prenatal exposure to toxicants and child language development in the Norwegian Mother, Father and Child Cohort Study (MoBa) Amanda Ramos* Amy Herring Gro Villanger Heidi Aase Stephanie Engel

Background/aim: Prenatal toxicant exposures have been associated with an increased risk of language difficulties in children. Much of this work has yet to explore which toxicant among correlated exposures might be most influential and whether there could be potential cascading developmental effects. Therefore, we examined the influence of prenatal exposure to phthalates, organophosphate esters (OPEs), and organophosphorous pesticides (OPPs) on children's language development from toddlerhood to the preschool period.

Methods: The study included 1055 pregnant women selected from the MoBa cohort run by the Norwegian Institute of Public Health. Prenatal concentrations of toxicant metabolites (6 phthalates, 4 OPEs, and 6 dialkylphosphate pesticides) were measured in maternal urine collected at 17 weeks gestation. Children's language was assessed with parent report on the Ages and Stages Questionnaire at 18 months, and parent and teacher report on the Child Development Inventory at preschool age. We ran structural equation models (parent and teacher model) to account for multiple exposures on on the longitudinal development of language ability.

Results: Prenatal OPPs were negatively associated with parent- and teacher-reported preschool language ability through earlier language deficits at 18 months (indirect effect: standardized beta (b)=-0.06, 95% Confidence Interval (CI): -0.11,-0.01; b=-0.04, 95% CI: -0.08,-0.004, respectively). Additionally, in the teacher model, prenatal low molecular weight phthalates were negatively associated with teacher-reported preschool language ability (b=-0.13, 95% CI: -0.24, -0.01). High molecular weight phthalates and OPEs were not associated with language development at either age nor were there differences by child sex for any toxicant.

Conclusions: Our results suggest that there could be unique and age-specific mechanistic pathways through which prenatal toxicant exposures influence child language ability.

COVID-19 Pandemic

Symptomatic and asymptomatic COVID-19-infected pregnant women: pregnancy and perinatal outcomes Zohra Lassi* Durray Khan Anna Ali Rehana Salam Jai Das

Background: There is a dearth of information on COVID-19's impact on pregnant women. However, literature reported trends of COVID-19 differ depending on the presence of clinical features upon presentation. This systematic review assessed differences in risk factors, management, complications, and pregnancy and perinatal outcomes in symptomatic vs. asymptomatic pregnant women with confirmed SARS-CoV-2 infection.

Methods: A search was run on electronic databases to identify studies reporting COVID-19 in pregnancy. Meta-analysis was performed using Review Manager 5.4.

Results: We included ten articles reporting data from 3158 pregnancies, with 1900 symptomatic and 1258 asymptomatic pregnant women. There was no significant difference in the mean age, gestational age, and body mass index between the two groups. The meta-analysis suggested that pregnant women who were obese, hypertensive, or had a respiratory disorder were more likely to be symptomatic when infected with SARS-CoV-2. Pregnant women with Black or Asian ethnicity were more likely to be symptomatic, while Whites were more likely to be asymptomatic. Cesarean-section was more likely amongst symptomatic pregnant women. The mean birth weight(g) was significantly lower, while the odds of low birth weight and preterm birth (<37 weeks) were higher amongst symptomatic pregnant women. Symptomatic pregnant women had a greater requirement for maternal intensive care unit (ICU) admission and mechanical ventilation while their neonates had a higher likelihood for Neonatal ICU admission.

Conclusion: The evidence suggests that the presence of risk factors increased the likelihood of pregnant women being symptomatic. Higher odds of complications were also observed amongst symptomatic pregnant women. However, more adequately conducted studies with adjusted analysis and parallel comparison groups are required to reach conclusive findings.

COVID-19 Pandemic

Immune response to SARS-CoV-2 in pregnant and non-pregnant women following infection
Marni Jacobs* Holly Valentine Celestine Magallanes Sierra Adkins Sydney C. Morgan Abbas Hakim Peter DeHoff Louise C. Laurent Priyadarshini Pantham

During pregnancy, the immune system undergoes adaptations to prevent fetal rejection. For certain pathogens, these adaptations cause increased disease susceptibility and altered immune response following infection. Recent research suggests that pregnant women are at higher risk for severe COVID-19 disease compared to non-pregnant patients. However, it is unclear whether this increased risk is associated with differences in immune response to infection. The present study assesses whether humoral immune response to SARS-CoV-2 is affected by pregnancy. Pregnant women with a positive SARS-CoV-2 test (n=20) were matched in a 1:2 ratio with non-pregnant reproductive aged women (n = 40) on number of days post-positive test at the time of blood sample. The final study population included 71 samples from 59 patients (1 vaccinated control excluded). Mean immunoglobulin G (IgG) and immunoglobulin M (IgM) levels to SARS-CoV-2 proteins were compared between groups using generalized estimating equations to account for repeated measures in some participants. Levels were log transformed prior to analysis. Median number of days post-positive at the time of sampling was 6 (range 2-97). No significant differences in mean age (29.6 vs. 26.9 years), ethnicity (40% Hispanic vs. 41%), or race (55% white vs. 37%) were noted between groups. No differences in mean antibody levels were seen between pregnant and non-pregnant groups (all $p \geq 0.53$). Results were similar when stratified by trimester of infection. Additionally, no differences were noted in IgG or IgM trajectories over time between groups. Overall, results suggest that humoral immune response following SARS-CoV-2 infection does not differ in pregnant women compared to their non-pregnant counterparts. While this study is small, findings should reassure patients and healthcare providers that pregnant patients appear to mount an appropriate immune response to SARS-CoV-2 following infection.

COVID-19 Pandemic

Association between SARS-CoV-2 Infection during Pregnancy and Postpartum Depression and Anxiety: Finding from the International Registry of Coronavirus Exposure in Pregnancy (IRCEP) Study Sonia Kim* Sonia Hernandez-Diaz Yanmin Zhu Diego Wyszynski Krista Huybrechts

While there has been widespread concern over the perinatal mental health implication of the COVID-19 outbreak, evidence on the risk of postpartum depression and anxiety following SARS-CoV-2 infection during pregnancy is limited. We studied this question using the web-based International Registry of Coronavirus Exposure in Pregnancy. Study participants were required to have been tested for SARS-CoV-2 between the date of last menstrual period and delivery. The exposure of interest was SARS-CoV-2 infection during pregnancy, as well as COVID-19 severity (Severe, Moderate, Mild, Asymptomatic). Women who tested negative and reported no clinical symptoms served as the reference group. The outcome was postpartum depression and anxiety, assessed by the 4-item Patient Health Questionnaire. The study collected baseline characteristics upon enrollment and prospectively followed the participants until 90 days post-delivery. The study also included retrospective cohort, who have been pregnant within the last 6 months and completed all questionnaires at enrollment. The analytic cohort consisted of 3,819 participants (Positive: 771, Negative: 3,048). We used inverse propensity weighting to adjust for confounding by socio-demographics, prior obstetric and maternal health comorbidities and used log-binomial models to estimate the adjusted relative risk (aRR) and 95% confidence intervals (95%CIs). Mothers exposed to severe COVID-19 had an increased risk of depression (aRR: 1.72; 95%CIs: 1.18-2.52) and anxiety (aRR: 1.40; 0.98-2.00). The strength of the association was attenuated for women with moderate COVID-19 (aRR=1.12; 0.86-1.44 for depression; aRR=1.18; 0.96-1.44 for anxiety). No increased risk was observed for mild or asymptomatic illness. Results were similar after restricting the cohort to individuals without pre-existing mental health illnesses. The results inform targeted interventions to minimize the risk of adverse COVID-19 related mental health outcomes for pregnant women.

COVID-19 Pandemic

Isolation and mental health among pregnant women during the coronavirus pandemic
Emily Harville* Moira Wood Elizabeth Sutton

Purpose: To examine the effect of social isolation due to the COVID-19 pandemic on the mental health of pregnant women, of particular concern, given potential effects on physical health, family functioning, and child development.

Methods: Pregnant women were recruited for the "Implications of and Experiences Surrounding being Pregnant during the COVID-19 Pandemic" at Woman's Hospital in Baton Rouge, Louisiana. Participants enrolled in the study at any point during their pregnancy and surveys were delivered weekly until the participant indicated that she had delivered her baby; a postpartum survey followed six weeks after delivery. This analysis includes 1037 participants with baseline, 596 with follow-up, and 302 with postpartum surveys. Questions on isolation behaviors were asked at baseline and grouped based on whether they involved isolation from work, friends and family, or public places. Symptoms of anxiety, stress, depression, and pregnancy-related anxiety were measured. Each type of isolation was examined as a predictor of mental health using linear model with control for confounders.

Results: The study population was largely white, married, and educated. Women who were younger, Black, single, had less education and income reported fewer isolation behaviors. After controlling for covariates, anxiety was associated with isolation from friends and family, and isolation from public events, while perceived stress postpartum and pregnancy-related stress were not associated with isolation. Associations were substantially diminished when controlled for baseline levels of anxiety symptoms.

Conclusion: Greater isolation was associated with more mental health symptoms, but worse mental health, particularly anxiety, may also have contributed to greater isolation behaviors.

COVID-19 Pandemic

Exposure to the early COVID-19 pandemic and early, late, and overall preterm births in the US: a conception cohort approach Claire Margerison* Tim Bruckner Colleen MacCallum-Bridges Ralph Catalano Joan Casey Alison Gemmill

Background: United States (US) data suggest fewer-than-expected preterm births (PTB) during March and April of 2020 and in November of 2020. To our knowledge, no study has examined the impact of exposure to the early COVID-19 pandemic at different points in gestation on the outcome of pregnancies. Our objective was to determine—among cohorts exposed to the population-level shock of the early COVID-19 pandemic—whether observed values of overall, early, and late PTB fell outside the expected range.

Methods: We used de-identified, national vital statistics birth certificate data from 2014 to 2020. We used month and year of birth (with randomly assigned day of birth) and gestational age to estimate month of conception for birth. We then calculated the count of overall (<37 weeks gestation), early (<33 weeks gestation), and late (33 to <37 weeks gestation) PTB by month of conception. We employed ARIMA time-series methods to estimate expected values of PTB for exposed conception cohorts and identified cohorts for whom the observed value of PTB fell outside the 95% detection interval of the expected value.

Results: Gestations conceived in June, August, or December of 2019—i.e., exposed to the early COVID-19 pandemic in the first or third trimester—yielded approximately 3,005 fewer late and 4,108 fewer overall preterm births than expected. In addition, gestations conceived in August, September, and October of 2019—i.e., exposed to the early COVID-19 pandemic in the late second to third trimester—produced approximately 631 fewer early preterm births than expected. Conclusions: The population shock of the early COVID-19 pandemic may have promoted longer gestation among close-to-term pregnancies, reduced risk of later preterm delivery among gestations exposed in the first trimester, or induced selective loss of exposed gestations. Future research should test these hypothesized mechanisms.

COVID-19 Pandemic

Determinants of COVID-19 vaccine initiation during the postpartum period in Ontario, Canada Deshayne Fell* Eszter Török Tavleen Dhinsa Gillian D. Alton Sheryll Dimanlig-Cruz Annette K. Regan Ann E. Sprague Shannon E. MacDonald Sarah A. Buchan Jeffrey C. Kwong Sarah E. Wilson Siri E. Håberg Christopher A. Gravel Kumanan Wilson Sandra Dunn Darine El-Chaâr Jon Barrett Nannette Okun Prakesh S. Shah Mark C. Walker Shelley D. Dougan

There is limited information on COVID-19 vaccine initiation in the postpartum period for individuals not yet vaccinated by the date of delivery. This study described temporal patterns and factors associated with postpartum COVID-19 vaccine initiation in Ontario. We included all deliveries ≥20 weeks' gestation between Dec 14, 2020 and Oct 31, 2021 from the provincial birth registry, linked to the COVID-19 vaccine database to capture all vaccinations up to Nov 30, 2021; individuals who had received ≥1 dose of COVID-19 vaccine before or during pregnancy were excluded. We constructed cumulative incidence curves for timing of vaccine initiation for each calendar month. Among deliveries between Apr and Oct 2021, we assessed sociodemographic, obstetrical, and behavioral factors associated with postpartum vaccination using Cox proportional hazards regression to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI). Among 78,615 individuals unvaccinated at delivery, 45,303 (57.6%) received ≥1 dose of COVID-19 vaccine by the end of Nov 2021; vaccine initiation was highest among those who gave birth in Jan through Apr 2021 (reaching about 70% by Nov 2021) and time-to-initiation was shortest among those who gave birth in Apr 2021. Lower maternal age (<25 vs. 30-34 years aHR: 0.68, 95% CI: 0.64-0.71), smoking during pregnancy (vs. non-smoking aHR: 0.61, 95% CI: 0.58-0.65), residing in a rural area (vs. urban aHR: 0.75, 95% CI: 0.72-0.78), lower neighborhood income (lowest quintile vs. highest aHR: 0.68, 95% CI: 0.65-0.71), higher material deprivation (highest quintile vs. lowest aHR: 0.73, 95% CI: 0.68-0.78), and exclusive breastfeeding (vs. combined or other feeding aHR: 0.91, 95% CI: 0.88-0.93) were associated with lower likelihood of vaccine initiation. Postpartum vaccine initiation was lower among certain sociodemographic subgroups and a substantial proportion of postpartum individuals had still not initiated COVID-19 vaccination by Nov 2021.

COVID-19 Pandemic

Birth Outcomes Among North Dakota Women Who Tested Positive for COVID-19 During Pregnancy Grace, Brenda Njau, McGrath*, Ramona Danielson Grace Njau Brenda McGrath Grace Njau

Background: Research on COVID-19 during pregnancy has shown an association with greater maternal and infant risk. However, other studies have found birth outcomes among women who have tested positive for COVID-19 to be similar to those who tested negative. The present study examined birth outcomes (i.e., low-birth weight; pre-term birth; neonatal intensive care unit stay; use of infant ventilation; poor Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score; delivery by Cesarean section) to explore if women with a positive COVID-19 test during pregnancy had worse birth outcomes than infants born to women without a record of a positive COVID-19 test during pregnancy. Methods: North Dakota Department of Health birth records from Apr.-Dec. 2020 were merged with COVID-19 testing data (N=2796); 311 of these records were women who had a positive COVID-19 test while pregnant. To isolate the effects of a positive COVID-19 test on birth outcomes, we used propensity score matching to ensure covariate balance using a variety of demographic and health-related characteristics that could potentially influence the likelihood of exposure to COVID-19 or that could impact birth outcomes. We also conducted a sensitivity analysis using birth records from Jan.-Mar. 2020. Results: No significant differences were detected in birth outcomes between women who tested positive for COVID-19 and women who gave birth in the three months prior to the presence of COVID-19 in ND or among women who gave birth during the same 9-month period but who did not have a positive test. Conclusions: Infants born to a ND woman with a positive COVID-19 test were not at an increased risk of poor birth outcomes compared to women without a positive COVID-19 test. This study is an important use of linking data files to learn about the impact of COVID-19 on women while accounting for factors that could make women at greater risk of exposure to COVID-19 or of poorer birth outcomes.

COVID-19 Pandemic

Prevalence of antibodies against SARS-CoV-2 among children and staff in Belgian schools between December 2020 and December 2021: a representative prospective cohort study

Joanna Merckx* Mathieu Roelants Milena Callies Ines Kabouche Isabelle Desombere Els Duysburgh

Background

Reported cases are insufficient to assess the epidemiologic distribution of SARS-CoV-2 infections in the school population and staff. Seroprevalence studies provide complementary estimates of past infection. We completed a prospective representative country-wide cohort study in Belgian primary and secondary school pupils and staff between December 2020 and December 2021.

Methods

We used a two-stage randomized cluster design with allocation by province and sociodemographic background for school selection and collected data at 5 testing periods (T1 to T5) from a convenience sample of pupils (grade 2-3 and grade 7-8) and staff. Only primary school pupils were included in T4/T5. A semi-quantitative IgG Rdb in-house adapted ELISA was used to detect antibodies in saliva. We collected survey data at inclusion and per test period. Point-prevalence estimates (95%CI) were estimated with generalized estimating equations accounting for clustering, without correction for test performance.

Results

In total, 44 and 40 schools providing in-person education participated including 710/575 pupils and 432/386 staff for primary and secondary school levels, respectively. From T1 to T3 (June 2021), seroprevalence in secondary school pupils increased from 13.6% (9.9 – 18.5) to 17.3% (12.5 – 22.0) and from *14.8 (12.2 – 18.0)* to 21.1% (16.9-26.3) in non-vaccinated staff. Point-prevalence estimates in primary school pupils were 11.0% (7.6 – 15.9), 17.1% (13.3 – 21.9), 15.5% (11.8 – 19.2), 26.6% (21.5 – 32.8) and 50.9% (43.7 – 59.2), at T1 to T5. A quarter of primary school pupils reported a confirmed acute infection since the pandemic start.

Conclusion

Belgian pupils and staff had similar increasing seropositivity in the second half of the 2020-2021 academic year. Primary school pupil seroprevalence increased strongly over the 2021 summer and 2021 fall, coinciding with the fourth Belgian wave. Less than half of the serology confirmed cases reported a SARS-CoV-2 acute infection.

Environment/climate change

Traffic-related air pollution and fetal growth in Eastern Massachusetts, USA Michael Leung* Anna M Modest Michele R Hacker Blair J Wylie Yaguang Wei Joel Schwartz Brent A Coull Francine Laden Marc G Weisskopf Stefania Papatheodorou

Background: Previous studies have examined the association between prenatal NO_2 —a traffic emissions tracer— and fetal growth based on ultrasound measures during pregnancy. Yet, most studies have used exposure assessment methods with low temporal resolution, which limits the identification of critical exposure windows given that pregnancy occurs over a relatively short period. Here, we used NO_2 data estimated from a high-resolution spatiotemporal ensemble model to examine the association between prenatal NO_2 exposure and fetal growth measures (ultrasound parameters and birth weight [BW]) and identify critical exposure windows in a Massachusetts-based pregnancy cohort. **Methods:** We used ultrasound and obstetric data from 9,446 singleton births at Beth Israel Deaconess Medical Center in 2011-2016. Fetal characteristics included biparietal diameter (BPD), head circumference, femur length, abdominal circumference, and BW. We fitted linear mixed-effects models to examine the associations between NO_2 and measures of fetal growth in three windows: 1) first 16 weeks of gestation, 2) cumulative exposure from conception to fetal growth measure, and 3) one-month prior to fetal growth measure. Fetal growth was assessed by anatomic scans (ultrasounds <24 weeks), growth scans (ultrasounds ≥24 weeks), and BW. All models were adjusted for sociodemographic characteristics, time trends, and temperature. **Results:** We found that higher NO_2 in all three exposure windows was associated with smaller fetal growth measures, with associations particularly strong for BPD and BW. For example, a 10-ppb increase in NO_2 in the first 16 weeks was associated with lower mean z-score of -0.06 (95% CI: -0.11, -0.02) for anatomic BPD scans, -0.07 (95% CI: -0.11, -0.03) for growth BPD scans, and -0.06 (95% CI: -0.09, -0.02) for BW. **Conclusion:** Higher NO_2 —a gaseous pollutant derived from traffic combustion— in three exposure windows during pregnancy was associated with smaller fetal growth measures.

Environment/climate change

Mid-pregnancy phthalate metabolites and phenols in relation to infant size and body composition: the Healthy Start study Danielle Stevens* Anne Starling Paige Bommarito Alexander Keil Dorothy Nakiwala Dana Dabelea Kelly Ferguson

Laboratory studies suggest prenatal phthalate and phenol exposure contribute to catch-up adipogenesis in males, but epidemiologic evidence is scarce. We aimed to examine associations between mid-pregnancy biomarkers of phthalate and phenol exposure and infant size and body composition in 438 mother-infant dyads from the Healthy Start prospective cohort. Sixteen phthalate metabolites and phenols were assessed in spot urine samples collected at 24-28 weeks' gestation. Infant outcomes measured at birth and 5 months included size (weight [grams]) and body composition (fat and lean masses [grams], percent fat mass). Single- (linear) and multi-pollutant (quantile g-computation) models adjusted for maternal sociodemographics, sample collection, and lifestyle factors, estimated associations of phthalates and phenols with infant outcomes at birth and 5 months, and effect modification by infant sex. On average, most phthalate metabolites and phenols were highly detected (~95%). Phenols were generally not associated with infant outcomes. In single-pollutant models, MBzP was inversely associated with weight (β:- 29.5 [95% CI: -60.9, 2.0] grams) and fat mass (-9.8 [-21.1, 1.5] grams) at birth, and MEP was inversely associated with weight (-47.5 [-111.4, 16.5] grams) and fat mass (-39.1 [-75.5, -2.6] grams) at 5 months; the magnitude of these associations was stronger in males. In multi-pollutant models, the phthalate mixture was generally inversely associated with fat mass among males but not females. For example, a one-quartile increase in the phthalate mixture was associated with reduced fat mass at 5 months (-125.9 [-228.1, -23.8] grams; -1.2 [-2.3, -0.2] percent) among males, but were null among females (-3.4 [-122.5, 115.7] grams; -0.2 [-1.5, 1.1] percent; p=0.11). In this US-based prospective cohort, prenatal phthalates were inversely associated with infant weight and fat mass, particularly in males. Additional follow-up is needed to assess catch-up adipogenesis past 5 months.

Environment/climate change

Maternal per- and poly-fluoroalkyl substances exposures associated with higher depression scores among immigrant women in the Chemicals in Our Bodies cohort Max Aung* Stephanie Eick Amy Padula Erin DeMicco Sabrina Smith June-Soo Park Tracey Woodruff Rachel Morello-Frosch

Background: Prenatal exposure to per- and poly-fluoroalkyl substances (PFAS) remains an important public health issue, partly due to their widespread detection in environmental media, slow metabolism in humans, and potential impacts on physiological processes such as neurological signaling. Maternal depression is highly prevalent in pregnancy and is an important neurological outcome that is potentially sensitive to PFAS. The health risks of PFAS may be further amplified in historically marginalized communities, including immigrant women.

Objective: We evaluated the extent to which maternal concentrations of PFAS were associated with depression scores during pregnancy and stratified by US-born and immigrant women.

Methods: Our analytical sample included 263 US-born and 213 immigrant pregnant women recruited in the Chemicals in Our Bodies cohort based in San Francisco, CA. Serum samples were collected in the 2nd trimester to measure seven PFAS metabolites. Depression scores were assessed using the Center for Epidemiologic Studies Depression Scale. Associations were estimated using multiple linear regression, adjusting for maternal age, education, and pre-pregnancy body mass index.

Results: On average, immigrant women had lower levels of all PFAS, which may partly be due to their shorter time spent in the US. A natural log unit increase in two PFAS was associated with higher depression scores in the overall combined sample, and stratified analyses showed that this association persisted only among immigrant women (*b* [95% confidence interval]: perfluorooctane sulfonic acid (1.25 [0.14-2.36]) and methyl-perfluorooctane sulfonamide acetic acid (1.68 [0.58-2.77]).

Conclusions: Findings provide new evidence that PFAS are associated with higher depression scores among immigrant women during pregnancy. Results can inform health risk assessments to better address depression rates in immigrants within the US.

Fertility and fecundity

Maternal risk of cardiovascular disease after use of assisted reproductive technologies: a Nordic registry linkage Maria C. Magnus* Abigail Fraser Siri E. Håberg Kristiina A Rönö Liv Bente Romundstad Christina Bergh Anne Laerke Pedersen Anja B. Pinborg Mika Gissler ulla-britt wennerholm Deborah A. Lawlor Signe Opdahl

Background: The current evidence regarding the risk of cardiovascular disease (CVD) among women who have undergone treatment with assisted reproductive technologies (ART) is limited by the small number of studies available, the heterogeneity between the studies, and the short follow-up.

Methods: We examined the association between delivery after ART and risk of CVD in a Nordic registry linkage including 4,149,279 women (out of whom 3% had used ART) who gave birth in Norway, Sweden, Finland and Denmark. Information on use of ART was available from birth or ART registries, while information on CVD was available from patient and cause of death registries. The risk of CVD was estimated using Cox regression, reporting hazard ratios (HR) and 95% confidence intervals (CI), adjusting for age, parity, and country.

Results: The rate of any CVD was 923 per 100,000 person years. Women who gave birth after ART had a modestly higher risk of any CVD, with an adjusted HR of 1.17 (95% CI: 1.15, 1.20) compared to those who had only conceived without ART. We observed a modestly higher risk of hypertensive disorders among women who gave birth after ART (adjusted HR 1.06; 95% CI: 1.01, 1.12), but no higher risk of ischemic heart disease (adjusted HR 0.95; 95% CI: 0.87, 1.03), cerebrovascular disease (adjusted HR 0.95; 95% CI: 0.86, 1.05), myocardial infarction (adjusted HR 0.91; 95% CI: 0.71, 0.95) or stroke (adjusted HR 0.91; 95% CI: 0.81, 1.02).

Conclusion: Women who gave birth after ART had a modestly higher risk of CVD. These women might benefit from regular monitoring of their cardiovascular health to initiate early interventions. Future studies should attempt to distinguish the role of underlying subfertility from aspects related to the ART procedure.

Fertility and fecundity

Factors related to participation in surveys of sexual health in a preconception cohort study
Julia Bond* Katharine White Amelia Wesselink Kenneth Rothman Lauren Wise

Introduction: Because sexual behavior is often considered a sensitive topic, several studies have examined the extent to which volunteer bias influences research on sexuality. This research has primarily focused on psychological attributes of survey participants and has often been conducted among undergraduate students, which may limit generalizability.

Methods: Pregnancy Study Online (PRESTO) is a North American prospective cohort study of couples trying to conceive. Female participants completed a baseline questionnaire and then shorter bimonthly follow-up questionnaires for 12 months or until conception, whichever came first. In March 2021, we added an optional supplemental survey entitled the “Sexual Health and Wellness Questionnaire” (SQ) to the PRESTO protocol. Thirty days after enrollment, participants were invited to complete the SQ via email. To restrict to participants who were engaged in the study, we included those who filled out the SQ or at least one follow-up survey. We calculated the percentage and corresponding 95% CI of participants who responded to the SQ across characteristics.

Results: Seventy-nine percent of the 1,053 participants completed the SQ. Seventy percent (95% CI 61, 80) of those who identified as Hispanic completed the SQ compared with 80% (95% CI 78, 83) of those who identified as non-Hispanic white. Seventy-eight percent (95% CI 75, 81) of participants doing something to increase chances of pregnancy completed the SQ, compared with 84% (95% CI 79, 89) of those who were not. There was a pattern of decreasing SQ response with increasing months of pregnancy attempt time at study entry, though it did not hold for the highest category of pregnancy attempt time.

Discussion: SQ response was influenced by demographic variables and characteristics related to intensity of pregnancy attempts. These findings have implications for the design and conduct of studies on sexual behavior and fertility.

Fetal loss/stillbirth/infant mortality

Time of delivery among low-risk women at 37-42 weeks of gestation and risks of stillbirth and infant mortality, and long-term neurological morbidity Neda Razaz* Giulia Muraca Katharina Fink Amelie Boutin Sid John Sarka Lisonkova Olof Stephansson Sven Cnattingius KS Joseph

Background: The most important knowledge gap in connection with obstetric management for time of delivery in term low-risk pregnancies relates to the absence of information on long-term neuro-developmental outcomes.

Objectives: We examined risks of stillbirth, infant mortality, cerebral palsy (CP), and epilepsy among low-risk pregnancies.

Methods: In this population-based Swedish study, we identified, from 1998 to 2019, 1,773,269 singleton infants born between 37 and 42 completed weeks in women with low-risk pregnancies. Poisson log-linear regression models were used to examine the association between gestational age at delivery and stillbirth, infant mortality, CP, and epilepsy. Adjusted rate ratios (aRRs) and 95% confidence intervals expressing the effect of birth at a particular gestational week compared with birth at a later gestational week were estimated.

Results: Compared with those born at a later gestation, aRRs for stillbirth and infant mortality were higher among births at 37 weeks' and 38 weeks' gestation. The aRRs for infant mortality were approximately 20% and 25% lower among births at 40 or 41 weeks compared with those born at later gestation, respectively. Infants born at 37 and 38 weeks also had higher aRRs for CP (vs infants born at ≥38 and ≥39 weeks, respectively), while those born at 39 gestation had similar aRRs (vs infants born at ≥40 weeks); infants born at 40 and 41 weeks had lower aRRs of CP (vs those born at ≥41 and 42 weeks, respectively). The aRRs for epilepsy were higher in those born at 37 and 38 weeks compared with those born at later gestation.

Conclusion: Among low-risk pregnancies, birth at 37 or 38 completed weeks' gestation is associated with increased risks of stillbirth, infant mortality and neurological morbidity, while birth at 39 to 40 completed weeks is associated with reduced risks compared with births at later gestation.

Fetal loss/stillbirth/infant mortality

Preconception pain medication use and spontaneous abortion: a prospective cohort study

Holly Crowe* Lauren Wise Elizabeth Hatch Kenneth Rothman Ellen Mikkelsen Henrik Sørensen Amelia Wesselink

Pain medications are used by >50% of women in the preconception period. Previous research focused on prescription medication recorded in administrative databases. We examined the association between self-reported use of prescription or over-the-counter pain medications and incidence of spontaneous abortion (SAB, loss of pregnancy <20 weeks' gestation) using data from a North American preconception cohort study. Participants reported medication use in the 4 weeks before baseline and during follow-up on self-administered bimonthly questionnaires and SABs on questionnaires during preconception (every 8 weeks) and pregnancy (~8 and ~32 weeks of gestation). We used Cox proportional hazards models with gestational weeks as the time scale to compute hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for demographics, lifestyle, and reproductive/medical history. We analyzed data from 8,128 participants enrolled during 2013-2021 who conceived over 12 months of follow-up. Twenty percent reported SAB. Overall, 5533 (68%) participants reported recent pain medication use on their last preconception follow-up, commonly for headache and muscle pain. Ibuprofen was the most reported medication (44% of participants), followed by acetaminophen (34%), naproxen (7%), aspirin (6%), and opioids (3%). Preconception use of any pain medication, compared with non-use, was not appreciably associated with SAB incidence (HR=0.94, CI: 0.85-1.06) nor was use of specific medications: 0.89 (CI: 0.80-0.99) for ibuprofen use, 0.90 (CI: 0.73-1.10) for naproxen use, 1.00 (CI: 0.81-1.25) for aspirin use, 1.05 (CI: 0.94-1.17) for acetaminophen use, and 0.95 (CI: 0.70-1.29) for opioid use. Results were similar after stratifying by medication use timing relative to conception. Our results indicate that preconception pain medication use of any type is not appreciably associated with increased risk of SAB. However, we were not able to consider dose, indication, or use after pregnancy detection.

Fetal loss/stillbirth/infant mortality

Estimates of stillbirths, preterm birth, small-for-gestational age, low birth weight and neonatal mortality in Ethiopia Frederick, Bezawit, Yahya, Mesfin, Sebastien, Chalachew, Delayehu Goddard, Hunegnaw, Mohammed, Hunegnaw, Haneuse, Bekele, Bekele*, Grace Chan
Frederick Goddard Bezawit Hunegnaw Yahya Mohammed Mesfin Hunegnaw Sebastien Haneuse Chalachew Bekele Delayehu Bekele Frederick Goddard

Introduction
Globally, data on birth outcomes and early mortality are scarce especially in settings with limited resources, programs, and data systems. Total births, stillbirths or live births, are often not counted; yet such data are critical for policy makers and researchers to allocate resources and target interventions to improve survival. Our study aims to report the number and estimate the prevalence of stillbirths, preterm births, small-for-gestational-age (SGA), low birth weight (LBW) births, and neonatal deaths in a region of the world where these key maternal and child health indicators remain largely unknown.

Methods
We conducted a pregnancy cohort study in Amhara, Ethiopia between December 2018 and November 2020. Women were regularly visited during pregnancy through delivery. Gestational age was estimated by ultrasound, maternal recall of last menstrual period or number of months pregnant, and fundal height. Birth weight was measured with digital scales within three days of delivery, and vital status of the newborn at birth was collected. We estimated the prevalence of livebirths, stillbirths, preterm, SGA, and LBW births. We calculated the prevalence of neonatal (overall, early, and late) and perinatal mortality.

Results
We enrolled 2801 pregnant women of which 2628 (94%) completed follow-up; 101 (4%) resulted in an early loss <28 gestational weeks. Among 2527 remaining women there were 2564 births (37 twins), 97.5% were livebirths and 2.5% were stillbirths. The prevalence of babies born preterm, SGA or LBW was very high (38%); 16% of live births were preterm, 23% SGA, and 9% LBW. Among live births, the overall prevalence of neonatal mortality was 3.2%. Mortality was higher among preterm births 6.6%, LBW births 12.5%, and SGA births 4.4% The prevalence of early neonatal mortality (2.1%) was almost twice as high as the prevalence of late neonatal mortality (1.1%). The perinatal mortality prevalence was 4.6%.

Conclusion
There is a high prevalence of stillbirths, preterm, SGA, LBW, and neonatal mortality, and even higher prevalence of mortality among those who are born preterm, SGA and LBW. Our results have important implications for newborn health and survival. For researchers and programmers, our results provide evidence for resource allocation, to evaluate progress, and to develop and deliver interventions that improve survival.

Fetal loss/stillbirth/infant mortality

Ambient air pollution and risk of spontaneous abortion among couples trying to conceive Katrine, Sinna P., Matthias, Amelia K., Lauren A., Elizabeth E., Jibran, Jørgen, Kenneth J., Henrik T., Ellen M. Eriksen, Ulrichsen, Ketzel, Wesselink, Wise, Hatch, Khan, Brandt, Rothman, Sørensen, Mikkelsen*, Anne Sofie Dam Laursen Katrine Eriksen Sinna P. Ulrichsen Matthias Ketzel Amelia K. Wesselink Lauren A. Wise Elizabeth E. Hatch Jibran Khan Jørgen Brandt Kenneth J. Rothman Henrik T. Sørensen Ellen M. Mikkelsen Ellen M. Mikkelsen

Evidence from cohort studies on air pollution and spontaneous abortion (SAB) remains inconsistent across specific pollutants. We estimated associations between ambient residential air pollution concentrations and the risk of SAB (loss before 22 completed weeks' gestation) in a Danish preconception cohort. From 2007-2019 we recruited couples who were trying to conceive. We ascertained pregnancies through bimonthly follow-up questionnaires completed up to 12 months after enrollment. We identified SABs by self-report on follow-up questionnaires and through the Danish National Patient Registry. We geocoded time-updated residential addresses and used the DEHM/UBM/AirGIS dispersion modelling system to estimate mean daily concentrations of nitrogen dioxide (NO_2), nitrogen oxides (NOx), carbon monoxide (CO), ozone (O_3), particulate matter <2.5 µg ($PM_{2.5}$) and <10 µg (PM_{10}), and sulfur dioxide (SO_2), modeled as weekly updated time-varying cumulative average exposures during the four weeks before conception through pregnancy. We used Cox proportional hazard regression models with gestational weeks as time scale to compute hazard ratios (HRs) and 95% CIs for associations for an interquartile range (IQR) difference in air pollutants with SAB. We analyzed data from 6,195 women who became pregnant within 12 months of enrollment of whom, 17% had an SAB. Adjusted HRs for one IQR higher residential air pollution concentration were 1.00 (95% CI: 0.77-1.28) for NOx, 0.91 (95% CI: 0.60-1.37) for NO_2, 1.19 (95% CI: 0.74-1.93) for O_3, 0.97 (95% CI: 0.70-1.36) for CO, 0.97 (95% CI: 0.66-1.41) for PM_{10}, 1.13 (95% CI: 0.77-1.66) for $PM_{2.5}$ and 1.16 (95% CI: 1.03-1.29) for SO_2. Overall, we observed little association between risk of SAB and higher cumulative concentrations of air pollutants through gestation. For O_3, $PM_{2.5}$ and SO_2, HRs suggested an elevated risk of SAB, although for O_3 and $PM_{2.5}$, the lower CIs were also consistent with a lower risk of SAB.

Genetics

Examination of newborn DNA methylation among women with and without self-reported polycystic ovary syndrome and hirsutism Kristen Polinski* Sonia Robinson Diane Putnick Raji Sundaram Erin Bell Paule Joseph James Segars Veronica Gomez-Lobo Weihua Guan Edwina Yeung

Objective: To assess associations of maternal polycystic ovary syndrome (PCOS) with and without hirsutism and DNA methylation (DNAm) alterations in the dried blood spots (DBS) of 830 neonates. **Methods:** Women enrolled in the Upstate KIDS cohort self-reported diagnoses of PCOS and hirsutism (i.e., excessive body hair) 4 months after delivery. Women were categorized as having PCOS with hirsutism, PCOS without hirsutism or no PCOS. DBS DNAm was measured using the Infinium MethylationEPIC BeadChip in singletons and one randomly selected twin of a pair. Multivariable robust linear regression was used to evaluate associations of PCOS with DNAm β-values. Minimally adjusted (infant sex, plurality, cell type count and batch effects) and fully adjusted models (inclusion of maternal characteristics) were considered. **Results:** Overall 12.3% (102/830) had a PCOS diagnosis (8.3% PCOS without hirsutism; 4% PCOS with hirsutism). These women were more likely to have a higher pre-pregnancy body mass index, gestational diabetes, or seek fertility treatment to conceive. Exposure to PCOS with hirsutism compared to no PCOS was associated with differential DNAm at cg08471713 near the *MEOX1* gene [β(SE):0.0768 (0.014); false discovery rate (FDR) p=0.04], which may have roles in somite development and hemopoietic stem cell differentiation. After adjustment for maternal characteristics, PCOS with hirsutism remained marginally associated with cg08471713 [β(SE):0.0716 (0.014); FDR p=0.12]. PCOS without hirsutism compared to no PCOS was not associated with individual CpG probes. **Conclusion:** The observed but limited effects among those exposed to PCOS with hirsutism suggests that excess circulating maternal androgens may potentially alter DNAm of offspring. This is supported by evidence from animal studies in which a hyperandrogenic state, such that is present in hirsutism, modifies offspring DNAm. Replication and further research are needed in additional cohorts.

Genetics

Epigenetic gestational age and the relationship with developmental milestones in early childhood: Upstate KIDS cohort Kristen Polinski* Sonia Robinson Diane Putnick Weihua Guan Jessica Gleason Sunni Mumford Raji Sundaram Stephanie London Edwina Yeung

Objective: DNA methylation clocks can estimate gestational age (DNAm GA) and deviations in observed and estimated DNAm GA may be useful markers in evaluating early childhood outcomes, such as identifying future developmental delay risk. We examined associations of measures of DNAm GA and probable developmental delay based on the Ages & Stages Questionnaire® (ASQ).
Methods: Data came from 855 singletons and one randomly selected twin of a pair whose parents completed the ASQ when their child was 4, 8, 12, 18, 24, 30 and 36 months of age. The ASQ is a validated screening instrument designed to detect whether a child has reached developmental milestones in 5 domains. We examined probable delays on specific ASQ domains as well as overall delay on any domain as outcomes of interest. Dried blood spot DNAm was profiled using the EPIC 850K BeadChip and DNAm GA was estimated using a cord blood DNAm GA clock specific to the EPIC 850K BeadChip (Haftorn 2021). In addition, gestational age acceleration (GAA) was calculated as standardized residuals from a linear regression of DNAm GA on observed GA. **Results:** Using generalized linear mixed models, each week increase in DNAm GA was protective of overall delay (OR 0.76; 95%CI 0.65-0.90) and delay in all domains except for problem solving skills after adjustment for maternal age, race, education, smoking or alcohol during pregnancy, prepregnancy BMI, plurality and child sex, i.e., fine motor (OR 0.71; 0.56-0.91), gross motor (OR 0.68; 0.53-0.89), communication (OR 0.74; 0.60-0.91), and personal-social (OR 0.75; 0.59-0.94). Associations remained in singletons (n=688) but not twins (n=167). Results were similar when restricted to term births (73%). However, no associations were observed with GAA. **Conclusion:** Longer gestational age is known to be protective of developmental delay. While DNAm estimated gestational age mirrored those known associations, GA acceleration was not associated with risk of early developmental delay.

Global health

Global prevalence of preterm birth among Pacific Islanders: a systematic review and meta-analysis Bohao Wu* Kendall Arslanian Kate Nyhan Elizabeth Izampuye Sarah Taylor Veronika Shabanova Bethel Muasau-Howard Nicola Hawley

Preterm birth (live birth <37 weeks) is one of the most common causes of neonatal mortality. The global preterm birth prevalence estimate was 10.6% in 2014 and inequities exist both between and within countries. Pacific Islanders are underrepresented in health research, yet the disproportionately high prevalence of obesity among this group may put them at risk for preterm birth. This is the first systematic review and meta-analysis to estimate preterm birth prevalence among Pacific Islanders globally. We searched MEDLINE, EMBASE, Web of Science Core Collection, the Cochrane Library, CINAHL, Global Health, and two non-indexed regional journals. Observational studies reporting preterm birth prevalence among Pacific Islanders published before December 3rd, 2021 were included. Case-control studies were excluded due to the inability to estimate prevalence. We used random-effects models for estimates in order to not limit our findings to just the published studies. Heterogeneity was assessed with τ^2 statistic. We estimated preterm birth prevalence among Pacific Islanders in the US (11.1%, 95% CI 10.5%-11.6%, τ^2=0.02), the US Affiliated Pacific Islands (USAPI, 6.7%, 95% CI 5.0%-9.0%, τ^2=0.13), New Zealand (7.7%, 95% CI 7.1%-8.4%, τ^2=0.01), Australia (6.2%, 95% CI 4.8%-7.8%, τ^2=0.05), and Papua New Guinea (8.6%, 95% CI 4.9%-14.5%, τ^2=0.40). Our results suggest that Pacific Islanders in the US had a relatively higher preterm birth prevalence than in other global settings, including Papua New Guinea (although heterogeneity among studies in that setting should be acknowledged). Our findings imply it is essential to explore risk factors for preterm birth among Pacific Islanders in the US. The disaggregation of Pacific Islanders from other races in the US, New Zealand, and Australia is needed to better identify their unique risk factors and the true burden of adverse pregnancy outcomes.

Global health

Socioecological Predictors of Breastfeeding Practices in Rural Eastern Ethiopia Marina Magalhães* Amanda Ojeda Karah Mechlowiz Kaitlin Brittain Jenna Daniel Kedir Roba Jemal Yousuf Mark Manary Wonwossen Gebreyes Arie Havelaar Sarah McKune

Estimates by the World Health Organization indicate that over 800,000 global neonatal deaths each year are attributed to deviations from recommended best practices in breastfeeding. Identifying factors promoting ideal breastfeeding practices may facilitate efforts to decrease neonatal and infant death rates and progress towards achieving the Sustainable Development Goals set for 2030. Though numerous studies have identified the benefits of breastfeeding in reducing the risk of childhood undernutrition, infection and illness, and mortality in low- and middle-income countries, no studies have explored predictors of breastfeeding practices in rural eastern Ethiopia, where undernutrition is widespread. This study uses data collected during the Campylobacter Genomics and Environmental Enteric Dysfunction (CAGED) project among 102 households in the Haramaya woreda, Eastern Hararghe Zone, Eastern Ethiopia, and investigates factors influencing breastfeeding practices: untimely initiation, prelacteal feeding, and untimely complementary feeding. Nearly half (47.9%) of infants in this study were non-exclusively breastfed (n=96). Generalized liner mixed effects models of breastfeeding practices revealed that prelacteal feeding may be a common practice in the region (43.9%, n=98) and characterized by gender differences (p=.04). No statistically significant differences were identified for untimely initiation and complementary feeding. Respective prevalences of 18% and 14% may, however, be clinically meaningful in a region burdened by high rates of undernutrition, particularly as severely food insecure mothers had more than 71% lower odds of early initiation and participants who self-reported to consumed khat daily had 3 times greater odds of untimely complementary feeding (95% CI, [0.60 – 16.57]). The findings of this study raise questions about gender norms and the factors that may affect breastfeeding practices in this region. This information may be used to guide future research questions and inform intervention strategies.

Gynecological health

Breastfeeding history and adenomyosis risk using data from a population-based case-control study employing two control groups Mandy S. Hall* Claudia Holzman Ana I. Vazquez Sawsan As-Sanie Holly R. Harris Kristen Upson

Adenomyosis is characterized by the presence of endometrial tissue within the muscular wall of the uterus and is associated with substantial morbidity. While the etiology of adenomyosis remains unknown, an estrogenic milieu is recognized to contribute to disease pathogenesis. We hypothesize that lactation, in which infant suckling inhibits ovulatory cycles and induces a hypoestrogenic state, is associated with decreased adenomyosis risk. We investigated this hypothesis using data from a case-control study of adenomyosis conducted among female enrollees ages 18-59 years of a large, integrated healthcare system in Washington State. In that study, incident, pathology-confirmed adenomyosis cases diagnosed 2001-2006 were identified (n=386) and two control groups were employed: 1) randomly selected age-matched enrollees with intact uteri (“population controls”, n=323) and 2) hysterectomy controls (n=233). Data on breastfeeding history were collected by in-person interview; for each live birth reported, each participant was asked if she breastfed the infant and for how long. We restricted the analytic sample to those with at least one live birth (331 cases, 246 population controls, and 198 hysterectomy controls) and used logistic regression to estimate ORs and 95% CIs for the associations between adenomyosis and 1) ever breastfeeding and 2) lifetime total breastfeeding duration, adjusting for age, reference year, smoking, education, and parity. In analyses using population controls, history of ever breastfeeding was associated with a 40% decreased risk of adenomyosis (OR 0.6, 95% CI: 0.3-1.0). The magnitude of association was stronger with longer total breastfeeding duration (≥12 months vs. 0-<3 months: OR 0.4, 95% CI: 0.3-0.6). In our analyses using hysterectomy controls, we observed similar patterns of associations that were attenuated in magnitude. Our results indicate that a potentially modifiable factor, breastfeeding, may decrease adenomyosis risk among parous women.

Gynecological health

A population-based cohort study of risk after pregnancy complications in a woman's last birth Nadia Arshad* Rolv Skjærven Linn Marie Sørbye Kari Klungsøyr Janne Mannseth Liv Grimstvedt Kvalvik Nils-Halvdan Morken

Introduction: In the United States and around the world, maternal mortality (MM) dropped, however, there is still an opportunity to further reduce maternal deaths related to pregnancy.

Aim: To provide an overview of recent trends in maternal mortality ratio in Norway and to assess association between pregnancy complications and maternal mortality.

Method: Data was obtained from Medical Birth Registry of Norway, 1967-2020. Outcome was risk of MM within one year after childbirth with complications in any and in last pregnancy: placental abruption, preeclampsia, preterm birth (PB), perinatal mortality (PM), small for gestational age, gestational diabetes, and hypertension alone. Log binomial regression was used to calculate odds ratios (OR) with 95% confidence interval (CI) for association between exposures and outcome.

Results: Out of 1 501 063 mothers who gave birth, 636 died within one year after childbirth from 1967 to 2020. The overall MMR was 4.23/100 000 live births. The MM decreased by 7%. The highest absolute risk was after PB 26%, followed by preeclampsia, and PM 11% in any pregnancy. In the last pregnancy, the risk was 21% after PB, 8.4% after preeclampsia, and PM. The association between complications and risk of MM was strongest after PM [unadjusted OR 5.4 (4.1-7.1)], followed by 3.1 (1.9-5.1) after placental abruption, and 3.0 (2.5-3.7) after PB in any pregnancy compared with mothers without complications in any pregnancy. In last pregnancy, compared with no complications in the last, OR 22.0 (16.1-29.9), 5.5 (3.1-9.5), and 5.1 (4.1-6-3) after PM, placental abruption, and PB respectively. The associated persisted after adjustment for maternal education, age, and year of last childbirth.

Conclusion: Placental abruption, preeclampsia, PB, and PM in any and last pregnancy were associated with an increased risk of MM. Screening for and detection of pregnancy complications in lifetime and in last pregnancy is an essential step towards promoting safe maternal care.

Health equity

A Descriptive Analysis of Optimal Birth Outcomes in the US 2018-2019 Lauren Dyer* Caryn Bell Katherine Theall Maeve Wallace

Background: Adverse outcomes represent only one facet of many in the full experience of pregnancy and pregnancy outcomes. A shift in focus towards healthy reproductive outcomes may reveal opportunities for novel interventions and strategies to promote optimal health. Yet studies on optimal birth experiences and outcomes remain sparse.
Methods: Optimal births were those that met the following criteria: pregnancies without maternal clinical complications, vaginal delivery at a gestational age of 37 weeks or later, and infant birth weight of >2,500 grams with no congenital anomalies, no abnormal conditions, and 5-minute APGAR score >7. We calculated Empirical Bayes smoothed (EBS) rates of optimal birth for the total population and by maternal race/ethnicity by applying the smoothing tool in GeoDa version 1.18.0.10 We defined counties achieving greater racial birth equity as those where the total population EBS optimal birth rate was higher than the national 75th percentile and the absolute difference between maternal racial/ethnic categories was smaller than the national 25th percentile difference.
Results: During the 2018-2019 period, 49.80% of overall births could be classified as an “optimal birth” according to the study definition. There was significant local clustering of births based on spatial analyses (Moran’s I=0.471; p<.001). Of the 3140 US counties, only 282 (8.98%) appeared to advance White-Black equity in optimal births, and 205 (6.53%) appeared to advance White-Hispanic equity in optimal births.
Conclusions: In the effort improve maternal health, we should focus not only on the absence of negative outcomes, but also the occurrence of positive outcomes, a paradigm shift that may prove insightful and effective. Our analytic results suggest that optimal births can be measured and that spatial patterns exist at the county level for this outcome.

Infectious disease

Emergency Department Pediatric Readiness Does Not Improve Pediatric Sepsis Outcomes
Morgan Swanson* James Torner Hilary Hewes Lawrence Cook Ryan Carnahan Monica Lieng Knute Carter Kang Zhao Nicholas Mohr

Objective

Pediatric sepsis is a life-threatening condition leading to high pediatric morbidity and mortality. We hypothesized increased emergency department (ED) pediatric readiness would be associated with better clinical outcomes among pediatric sepsis patients.

Study Design

A retrospective cohort of pediatric sepsis subjects were identified from administrative claims datasets (2010 – 2019) of ED and hospital visits in Iowa, New York, and Florida. ED pediatric readiness scores were obtained from the 2013 National Pediatric Readiness Assessment database, which is an assessment of EDs based on readiness to care for sick and injured children (scores range from 0 to 100). An instrumental variables approach, using an instrument of differential distance, estimated associations between pediatric readiness and the primary outcome, 28-day hospital-free days. Hospital-free days is a composite outcome of death, length-of-stay, and readmission; deaths are 0 hospital-free days. Models were adjusted for demographics, co-morbidities, payer, state, and year.

Results

There were 3,675 pediatric sepsis subjects in 311 hospitals; the median pediatric readiness score was 78 out of 100 (interquartile range: 61 to 90). Overall, median 28-day hospital-free days were 23 and 2.5% of subjects died during the hospital encounter. Presenting to a top-quartile pediatric-readiness ED was not associated with 28-day hospital free days (adjusted 2SLS estimand: -0.10, [95%CI: -2.36 to 2.16], p=0.928). Transfer was less common in subjects presenting to high-readiness hospitals (adjusted odds ratio: 0.38, [95%CI: 0.24 to 0.60]).

Conclusions

We found no association between ED pediatric readiness and clinical outcomes in pediatric sepsis patients. This suggests current regionalization practices may work to deliver pediatric sepsis patients to the level of definitive care that is needed. Further work could investigate optimal transfer practices for pediatric sepsis patients.

Mental health

Residential segregation and prenatal depression in non-Hispanic Black and Hispanic mothers in North Carolina, 2005-2009 Sarah Haight* Lea Ghastine Catherine Hoyo Chantel Martin

Research on residential segregation and mental health is inconsistent and rarely assessed during pregnancy, a high-risk time for depression. We investigate this relationship in a sample of non-Hispanic (NH) Black and Hispanic mothers. Demographics, residence, and self-reported depressive symptoms (Center for Epidemiological Studies Depression [CESD] screener), were obtained from the Newborn Epigenetic Study (NEST), a North Carolina pregnancy cohort (2005-2009). Using U.S. Census data (2006-2010), census tract residential segregation (NH Black vs NH white and Hispanic vs NH white) was measured with the Index of Concentration at the Extremes (ICE). ICE scores range from -1 (highest concentration of low privilege) to 1 (highest concentration of high privilege). Generalized linear mixed models estimated average change in CESD score associated with ICE score, accounting for neighborhood clustering and adjusting for individual's age, education, parity, marital status, smoking, and neighborhood deprivation. Among 773 participants, average CESD scores (ranging 0-60) were 14.1 (SD=9.7) and 12.1 (SD=10.2) for NH Black and Hispanic mothers, respectively. Average ICE scores were 0.21 (SD=0.45) and 0.11 (SD=0.29) for NH Black and Hispanic, respectively. For NH Black mothers, a 1-unit increase in ICE score (towards an extreme concentration of NH white) was associated with a reduction of 1.5 in CESD score (95% CI=-5.3, 2.3). After adjustment, estimates crossed over the null indicating increased depressive symptoms for NH Black mothers living in areas with increased concentrations of NH white populations (b=8.0; 95% CI=-3.7, 19.7). Among Hispanic mothers, a 1-unit increase in ICE score was associated with an average reduction of 2.7 in CESD score (95% CI=-6.8, 1.5). The impact of residential segregation on prenatal mental health may differ by race/ethnicity and effects may attenuate after accounting for individual- and neighborhood-level factors.

Mental health

Early age at sexual debut, risky sex behaviors and depressive symptomatology among young adults in the United States Andrew Williams* Amy Breigenzer

Background: In the United States, depression is most common among adults aged 18-29. Early sexual debut and risky sex behaviors may influence depression, but current evidence is mixed. We examined associations between sex behaviors and depression among US adults aged 20-25.

Methods: Data were from 2,580 adults aged 20-25 in the National Health and Nutrition Examination Survey(2005-2016). Depression was measured with the Patient Health Questionnaire-9(PHQ-9, (9 questions scored 0-3, range 0-27). Severe depression was PHQ-9 score >10. Three sex behaviors were assessed: early age at sexual debut(first sexual intercourse ≤age 16), chlamydia diagnosis in prior 12 months, and herpes diagnosis ever. Chlamydia and herpes diagnoses were considered proxies for lack of barrier protection during sex. Logistic regression models estimated odds ratios(OR) and 95% confidence intervals(95%CI) for the association between sex behaviors and severe depression, adjusted for demographic factors. Sensitivity analyses examined differences by gender and the effect of age at menarche.

Results: Early age at sexual debut and risky sex behaviors were associated with increased risk for severe depression. Compared to later sexual debut, early age at sexual debut was associated with two-fold higher risk for severe depression(OR:2.00 95%CI:1.99,2.01). Chlamydia diagnosis was associated with a 35% increase(OR:1.35 95%CI:1.35,1.37) and herpes diagnosis was associated with a 16% increase(OR:1.16 95%CI:1.15,1.17) for severe depression. In sensitivity analysis, early age at sexual debut was a stronger predictor of severe depression among women(OR:2.52 95%CI:2.51,2.53) than men(OR:1.29 95%CI:1.28,1.30)(p-interaction<.01). Age at menarche did not change results among women.

Conclusions: Risky sex behaviors increase risk of depression in young adults. Early age at sexual debut was the strongest predictor of depression and may be a stronger predictor of depression among women.

Mental health

Prevalence of Mental Disorder Co-Occurrence and Outcomes Associated with Multiple Disorder Co-occurrence in the Project to Learn about Youth Mental Health (PLAY-MH) Lina Dimitrov* Corey Lipton Melissa Danielson Rebecca Bitsko Angelika Claussen Jennifer Zubler Joseph Holbrook Lorraine Kubicek Kate Flory Julie Owens Steven Cuffe

The aim of this study was to determine the prevalence of co-occurring mental disorders, as determined by a Diagnostic and Statistical Manual of Mental Disorders, 4^{th} Edition criteria-based approach, and to understand associations of co-occurring disorders with school discipline, child and family functioning, and suicidal ideation/attempts among a K-12 sample of children. We analyzed data from the Project to Learn About Youth-Mental Health which used a two-stage design to draw samples from school districts in Colorado, Florida, Ohio, and South Carolina. First, teacher screeners were used to classify a child as high vs. low risk for externalizing, internalizing, or tic disorders. In stage two, parents of selected children (sample stratified by risk status, gender, and school level) completed interviews, including the Diagnostic Interview Schedule for Children, version IV to identify those who met criteria for a mental disorder, including attention-deficit/hyperactivity disorder, behavioral disorders, anxiety disorders, and depression. Analyses were restricted to 305 children with at least one disorder and accounted for the complex sample design to produce weighted percentages and 95% confidence intervals (CI) using SAS v9.4 survey procedures (SAS Institute, Inc.; Cary, NC). Among children who met criteria for at least one disorder, 39.4% had two or more (2^{+}) total mental disorders and children with depression were most likely to have 2^{+} disorders (90.3%). Compared to children with one disorder, parents reported children with 2^{+} disorders were more likely to have sleep problems (92.6% vs. 72.7%, p=0.001), to have ever been suspended from school (42.5% vs. 29.4%, p=0.01), or to have experienced suicidal ideation (17.5% vs. 1.3%, p=0.01) and that their children's' mental disorders were more likely to cause family financial problems (17.7% vs. 4.9%, p=0.01). These results demonstrate the impact of mental disorders and inform mental health service resource allocation.

Nutrition/obesity

Impact of pre-pregnancy body mass index on adverse pregnancy outcomes: Analysis from the Longitudinal Indian Family hEalth (LIFE) cohort study Fouzia Farooq* Monica Gudipally Kalpana Basany Fouzia Farooq Catherine Haggerty Gong Tang Govindrao Kusneniwar Guru Rajesh Jammy Clareann Bunker P.S. Reddy

Background: Maternal pre-pregnancy body mass index (BMI) and gestational weight gain are measures of maternal health and nutrition that are key to meeting the nutrient demands of pregnancy. These factors are also vital for fetal development as well as infant health. While sufficient prenatal dietary intake is critically important, excessive maternal weight is associated with pregnancy complications, childhood obesity and adverse cardiovascular outcomes. Both low and high maternal BMI are linked to adverse pregnancy outcomes (APOs), yet data in developing countries including India are sparse. Methods*:* We modeled the relationships between pre-pregnancy BMI and adverse APOs including low birth weight (LBW), preterm birth, Cesarean delivery, intrauterine growth restriction, miscarriage, and fetal death among 675 women aged 15-35 years with singleton pregnancies in the Longitudinal Indian Family hEalth study, a population-based prospective pregnancy cohort study conducted in Telangana State, India. Pre-pregnancy BMI was assessed at a mean of 12.3 months prior to pregnancy. Odds ratios and 95% confidence intervals for each APO were adjusted for confounders. Results: Women categorized as obese prior to pregnancy had a 3-fold increased risk of Cesarean delivery (OR 3.13, 95% CI (1.56, 6.29)) compared to normal weight women. Women categorized as overweight preconception had a marginally increased risk of Cesarean delivery, albeit not statistically significant (OR 1.17, 95% CI (0.61, 2.24). Women who were underweight had a modestly increased risk of LBW compared to those categorized as having normal weight prior to pregnancy (OR 1.12, 95% CI (0.71, 1.77). On the other hand, women categorized as obese and overweight pre-pregnancy had marginally decreased risks of LBW (OR 0.71, 95%CI (0.28, 1.77); OR 0.61, 95% CI (0.24, 1.51), respectively). Conclusion: Our data suggest that women with elevated pre-pregnancy BMI may have a higher risk of APOs, especially Cesarean delivery. Targeted pre-pregnancy intervention studies and programs that include counseling on preconception health and lifestyle modification are in developing countries are warranted and may improve subsequent pregnancy outcomes among overweight and obese women.

Nutrition/obesity

Prospective associations of sleep with diet, adiposity, and growth among toddlers born preterm Samrawit Yisahak* Kelly Boone Joseph Rausch Sarah Keim

Associations of sleep with diet and adiposity are understudied during toddlerhood when lifestyle habits and taste preferences establish. Prior studies focused on total sleep duration, though day and nighttime sleep could have different associations due to circadian regulation of appetite. Further, studies mostly focus on too little sleep. In a secondary analysis of a randomized trial of toddlers born preterm, we examined prospective associations of sleep duration and timing with diet, adiposity, and growth. Children born at <35 weeks' gestation were randomized at 10-17 months (age corrected for prematurity) to placebo or fatty acid supplementation for 180 days. Caregivers reported toddlers' sleep habits at baseline using the Brief Infant Sleep Questionnaire. After 180 days, caregivers reported the child's past month diet in a food frequency questionnaire. We computed a toddler diet quality index (TDQI, max 100 points), reflecting adherence to 2020 Dietary Guidelines for Americans for < age 2. Anthropometry was measured at baseline and follow-up using standardized protocols. We used WHO growth standards to calculate weight-for-height, triceps skinfold, and subscapular skinfold z-scores. We used linear and logistic regression for assessing associations of sleep with outcomes at follow-up, and linear mixed models with sleep*time interaction for changes in anthropometry (growth). Nearly 30% of 284 toddlers slept shorter or longer than recommended. Night and daytime sleep (per hour) were associated with higher (β=1.01 (95% CI: 0.16, 1.85)) and lower TDQI (β -1.62 (CI: -2.71, -0.52)), respectively. Associations of short and long sleep with TDQI were β=-2.24 (CI: -5.71, 1.24) and β=-0.24 (CI: -3.62, 3.14), respectively. Associations with adiposity at follow-up were null, but daytime sleep was associated with changes in weight-for-height z (P=0.02). Nighttime, but not daytime sleep maybe favorable for diet quality and longer than recommended sleep may not be unfavorable.

Nutrition/obesity

Associations Between Dietary Carbohydrate Intake During Pregnancy and Placental Glucose Transporter Expression Amber Kautz* Lauren Aleksunes Sadia Chowdhury Ying Meng Richard K. Miller Thomas O'Connor Emily Barrett

Background: Prenatal dietary carbohydrate intake has been positively associated with infant size at birth, however, mechanisms are poorly understood. Maternal delivery of glucose via placental transporters may play a role.
Objective: To examine the association between carbohydrate intake during pregnancy and placental expression of the glucose transport proteins GLUT1 and GLUT3.
Methods: We analyzed data from women with healthy pregnancies enrolled in the Understanding Pregnancy Signals and Infant Development Study (UPSIDE) who reported dietary intake in the second trimester and had placental glucose transporter data available (N=157). Based on 24-hour dietary recalls, we quantified proportion of calories from carbohydrate and added sugar, as well as glycemic load. Transporter concentrations were measured in membrane fractions of term placental tissue using quantitative targeted proteomics. We fit multivariable linear regression models adjusted for gestational age at birth, infant sex, maternal age, early pregnancy body mass index, lifetime smoking status, and transporter batch.
Results: Median (25th, 75th percentiles) for glycemic load and proportion of calories from added sugar and total carbohydrate were 141.06 (115.36, 180.80), 0.110 (0.075, 0.159) and 0.507 (0.455, 0.561), respectively. We observed positive associations between proportion of calories from carbohydrate and GLUT1 that were strengthened after adjustment for covariates (β: 208.316, 95% CI: -3.539, 420.172). Proportion of calories from carbohydrate was additionally positively associated with GLUT3 (β: 4.723, 95% CI: 0.605, 8.840). Proportion of calories from added sugar and glycemic load were not associated with GLUT1 or GLUT3.
Conclusions: Proportion of calories from total carbohydrate was positively associated with expression of glucose transport proteins in human placentae. Future research to confirm the impact of dietary intake on placental nutrient transporters is planned.

Nutrition/obesity

Findings from Hispanic Community Health Study/Study of Latinos (HCHS/SOL) on prospective influence of maternal psychosocial stressors and BMI on birth outcomes Tracy, Krista, Michelle, Hridya, Carmen, Liana, Ian, Christina, Martha, Linda, Lindsay Manuck, Perreira, Kominiarek, Rao, Isasi, Preudhomme, Paul, Cordero, Daviglus, Gallo, Fernández-Rhodes*, Cristin McArdle Tracy Manuck Krista Perreira Michelle Kominiarek Hridya Rao Carmen Isasi Liana Preudhomme Ian Paul Christina Cordero Martha Daviglus Linda Gallo Lindsay Fernández-Rhodes Lindsay Fernández-Rhodes

Objective: We assessed the overall effect of maternal psychosocial stressors of Latina mothers using measured/self reported 1-5 years pre-pregnancy Body Mass Index (BMI) on adverse birth outcomes (gestational diabetes (GDM), preterm birth (PTB: <37 weeks), small or large for gestational age (SGA: <10th percentile; LGA>90th percentile), hypertension (HTN) and Caesarean section).

Methods: In this study, 508 mother-infant dyads met inclusion criteria from the target population of 16,415 self-identified Hispanic/Latinos enrolled in the Hispanic Community Health Study/Study of Latinos. Sociodemographic, and clinical measurements of pre-pregnancy BMI were measured as World Health Organization categories: underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese ($\geq$30 kg/m^2) at visit 1. Pregnancy characteristics (age at birth, birth year, smoking, parity, gestational weight gain, and birth outcomes were self-reported at Visit 2 and converted to standardized or dichotomous scores for analysis. HCHS/SOL participants with a valid pre-pregnancy BMI value who experienced a singleton birth between visit 1 and visit 2 with complete information (N=508, survey weighted n=868.1) were included. Logistic regression analysis was performed to quantify the association between pre-pregnancy BMI category and birth outcomes, adjusting for biopsychosocial factors including maternal and pregnancy factors, self-identified race/ethnicity, intergenerational educational mobility, marital status, and acculturation.

Results: Almost 35% of the study population (weighted n = 298.2) comprised births to women with normal BMI. For birth outcomes we report 12.3% SGA, 13.4% LGA, 9.89% PTB, 3.0% GDM, 9.0% Hypertension, and 38.8% Cesarean Section. In logistic regression, we found pre-pregnancy BMI was positively associated with LGA, and PTB after adjustment for biopsychosocial factors for both underweight and obese categories of BMI, while SGA, GDM, HTN were weaker and monotonic by BMI category. The adjusted odds ratio (OR_a) for pre-pregnancy BMI obese category compared to normal LGA OR_a:1.3 95%CI: (1.0, 5.3); PTB OR_a 2.6 (95%CI:0.9-7.3); SGA OR_a 0.9 (95%CI: 0.5-2.1).

Conclusions: In this community-based cohort of Hispanic/Latinos from diverse backgrounds we report attenuated but persistent effects of pre-pregnancy BMI, with increased odds of adverse birth outcomes given exposure to biopsychosocial stressors. However, these associations were not significant. Future exploratory analysis will examine structural equation modelling to better understand the potential mediation pathways for this association.

Obstetric health

Obstetric anal sphincter injury by maternal origin and length of residence: a nationwide cohort study Sukhjeet, Siri, Johanne, Benedikte, Katrine Mari Bains, Vangen, Sundby, Lindskog, Owe*, Ingvil Krarup Sørbye Sukhjeet Bains Siri Vangen Johanne Sundby Benedikte Lindskog Katrine Mari Owe Katrine Marie Owe

Objective: To estimate the association between maternal origin and obstetric anal sphincter injury (OASI), and assess if associations differed by length of residence.

Design: Population-based cohort study.

Setting: The Medical Birth Registry of Norway.

Population: Primiparous women with vaginal livebirth of a singleton cephalic fetus between 2008 and 2017 (n = 188 658).

Methods: Multivariable logistic regression models estimated adjusted odds ratios (aORs) for OASI with 95% CI by maternal region of origin and birthplace. We stratified models on length of residence and paternal birthplace.

Main outcome measures: OASI.

Results: Overall, 6373 cases of OASI were identified (3.4% of total cohort). Women from South Asia were most likely to experience OASI (6.2%; aOR 2.24, 95% CI 1.87-2.69), followed by those from Southeast Asia, East Asia & the Pacific (5.7%; 1.59, 1.37-1.83) and Sub-Saharan Africa (5.2%; 1.85, 1.55-2.20), compared with women originating from Norway. Among women born in the same region, those with short length of residence in Norway (0-4 years), showed the highest odds of OASI. Migrant women across most regions of origin had the lowest risk of OASI if they had a Norwegian partner.

Conclusions: Primiparous women from Asian regions and Sub-Saharan Africa had up to two-fold risk of OASI, compared with women originating from Norway. Migrants with short residence and those with a foreign-born partner had higher risk of OASI, implying that some of the risk differential is due to sociocultural factors. Some migrants, especially new arrivals, may benefit from special attention during labour to reduce morbidity and achieve equitable outcomes.

Obstetric health

Mode of delivery and maternal sexual wellbeing: a longitudinal investigation of the UK ALSPAC cohort Florence Martin* Paul Madley-Dowd Viktor Ahlqvist Egill Jónsson Bachmann Abigail Fraser Harriet Forbes

Background The rate of cesarean section is increasing globally. Qualitative evidence suggests that cesarean section is perceived to be protective of sexual function, however, this is evidenced by a few short-term, and almost no long-term, quantitative studies. Emerging evidence suggests that cesarean section may be associated with sex-related pain postpartum, but further longitudinal studies are needed. We investigated the relationship between mode of delivery and subsequent maternal sexual enjoyment, sexual frequency, and sex-related pain.

Methods Using the UK-based Avon Longitudinal Study of Parents And Children (ALSPAC) cohort, eligible women had data available for mode of delivery (from obstetric records) and at least one self-reported sexual outcome (via questionnaire). Sexual enjoyment and frequency were measured repeatedly between 33 months and 18 years postpartum; sex-related pain, both in the vagina during sex and elsewhere after sex, was measured at 11 years postpartum. Missing covariate and outcome data were imputed and associations between mode of delivery and sexual outcomes were investigated using ordinal logistic regression.

Results In our sample of 10,327 women, 1,094 (11%) participants gave birth via cesarean section. Mode of delivery (cesarean section vs vaginal delivery) was not strongly associated with sexual enjoyment at any timepoint (e.g., adjusted odds ratio (aOR) 1.12, 95% confidence interval (CI) 0.98–1.28, P-value=0.10 at 33 months) or sexual frequency (aOR 0.99, 95% CI 0.88–1.11, P=0.84 at 33 months). Cesarean section was, however, associated with an increased odds of both types of sex-related pain at 11 years postpartum as compared with vaginal delivery in the adjusted models (aOR 1.68, 95% CI 1.42–2.01, P<0.001 and aOR 1.42, 95% CI 1.09–1.86, P=0.01, respectively).

Conclusions Cesarean section was not associated with improved sexual enjoyment and frequency up to 18 years postpartum (compared to vaginal delivery), however, it was associated with increased sex-related pain at 11 years postpartum as compared with vaginal delivery. These findings contradict perceptions of sexual wellbeing in the mode of delivery debate, suggesting that women who have delivered via cesarean section can suffer from sex-related pain that is not limited to abdominal scarring.

Obstetric health

Frequency and correlates of short interpregnancy interval: analysis of PRAMS data from 44 sites in 2009-2018 Amanda Luff* Michelle Menegay Maria Gallo

Objectives: Short interpregnancy interval (SIPI) is associated with unintended pregnancy. We aimed to identify frequency and correlates of SIPI.

Methods: We assessed data from the 2009-2018 Pregnancy Risk Assessment Monitoring System, a representative survey of gestational parents with live births in US locations at 2-6 months post-delivery. We classified SIPI based on respondent reporting of not needing contraception because of current pregnancy. Using survey weights, we calculated SIPI prevalence and adjusted prevalence ratios (aPRs) with 95% confidence intervals (CIs) for correlates, accounting for age, race/ethnicity, site, year, and time since delivery.

Results: Of 367,775 responses in 44 sites, 2,178 (0.49%; 95% CI: 0.45-0.53) reported pregnancy at time of survey. Non-Hispanic Black people had a higher aPR compared to non-Hispanic White people (1.40; 95% CI: 1.13-1.73). aPRs were higher among those with less than high school education (1.96; 95% CI: 1.64-2.37) and earning less than 250% of the federal poverty level (2.03, 95% CI: 1.59-2.60). Among those receiving prenatal care, people who discussed contraception with a healthcare worker before birth had a lower aPR (0.57; 95% CI: 0.40-0.81). Those who were uninsured postpartum had a higher aPR (1.42; 95% CI: 1.02-1.99), but no association was detected for insurance preconception or prenatally. People who attended a postpartum check-up had a lower aPR (0.45; 95% CI: 0.37-0.55) compared to those without a check-up.

Conclusions: Racial and socioeconomic disparities in SIPI prevalence suggest inequity in contraceptive counseling and access. Contraceptive options should be discussed prenatally, especially among patients at risk of losing insurance postpartum.

Obstetric health

Ovulation Tracking to Elucidate Length of Gestation and First-Trimester Growth Ginna Doss* Julie Daniels Sunni Mumford Charles Poole Anne Steiner Anne Marie Jukic

Background. Gestational age is approximated using observable measures like last menstrual period (LMP) and crown-rump length (CRL). Ovulation detection kits provide a more accurate estimate of the beginning of pregnancy. Our objectives were 1) to compare the proportion of births defined as preterm and postterm at delivery by LMP vs. by ovulation and 2) to present first trimester CRL growth curves when gestational age was defined by LMP vs. ovulation.

Methods. The Effects of Aspirin in Gestation and Reproduction (EAGeR) trial was a prospective time-to-pregnancy study that enrolled participants with a history of pregnancy loss. This analysis included singleton pregnancies conceived during prospective follow-up with known ovulation and LMP dates and with CRL measured at a first trimester ultrasound (n=464). Regression models for log-transformed and untransformed CRL with several functions of gestational age were fit for both ovulation and LMP-based gestational age assessment. Optimal models were selected by the highest adjusted coefficient of determination (R^2). Among participants who went on to have a live birth (n=406), we compared the proportion of births defined as preterm (<37 weeks) or postterm (>42 weeks) when gestational age was defined by ovulation or LMP. We report the weighted kappa for agreement between gestational age measures.

Results. A slightly larger proportion of births were assessed as preterm at delivery by ovulation (8.3%) than by LMP (6.9%) and as postterm by LMP (1.0%) than by ovulation (0.2%). The agreement between gestational age estimation methods was moderate, weighted kappa = 0.70 (95% CI: 0.56, 0.87). Using each method of gestation age estimation, we fit a model of first trimester growth. The LMP-based model predicted smaller CRL than the ovulation-based model at later ultrasounds.

Conclusion. The comparison of LMP vs. ovulation-based gestational age at ultrasound and delivery suggest that LMP exhibits a slight tendency to overestimate gestational age relative to ovulation, potentially altering growth models. This is consistent with previous research.

Obstetric health

Prognosis for Adverse Neonatal Outcomes among Small- and Large-for-Gestational age infants: Should We Look at Maternal Stature? Lauren Yearwood* Jeffrey N Bone Emma Wen Giulia M Muraca Janet Lyons Neda Razaz KS Joseph Sarka Lisonkova

Objective: To assess the rates of adverse health outcomes among small-for-gestational age (SGA) and large-for-gestational age (LGA) infants born to mothers of short, average, and tall stature.

Methods: A retrospective cohort study of singleton live births in the USA, 2016-2017 (N=7,325,741), using data from the National Center for Health Statistics. Short and tall stature was defined as <10^{th} and >90^{th} centile of the maternal height distribution (<154.9 cm and >172.7 cm, respectively). SGA and LGA were defined as <10^{th} and >90^{th} percentile of birth weight for gestational age, respectively. The primary outcomes included being born preterm (<37 weeks' gestation), neonatal intensive care unit (NICU) admission, and composite severe neonatal morbidity and neonatal death. Logistic regression was used to estimate adjusted odds ratios (AOR) and 95% confidence intervals (CI) adjusted for maternal risk factors.

Results: Compared with LGA infants of average stature mothers, LGA infants of short mothers had increased odds of being born preterm (5.5% vs 2.3%; AOR=1.68, Cl 1.59-1.78), NICU admission (9.9% vs 6.1%; AOR=1.32, Cl 1.27-1.38), and composite severe neonatal morbidity/neonatal death (3.7% vs 2.3%; AOR=1.30, Cl 1.21-1.39), whereas LGA infants of tall mothers had between 0.81 and 0.75-fold (95% CI range: 0.71-0.84) decreased odds. In contrast, SGA infants of tall vs. average stature mothers had increased odds of all adverse outcomes, particularly the composite severe neonatal morbidity/neonatal death (6.0% vs 4.6%; AOR=1.14, CI 1.08-1.21). SGA infants of short vs average stature mothers had comparable odds of all outcomes.

Conclusion: Neonatal prognosis in SGA and LGA infants is influenced by maternal height. SGA infants of tall women and LGA infants of short women have higher rates of neonatal death and/or severe morbidity compared with their counterparts born to women of average stature.

Obstetric health

What factors modify the association between pre-pregnancy obesity and adverse perinatal outcomes? Jeffrey Bone* KS Joseph Laura Magee Chantal Mayer Sarka Lisonkova

Background

Obesity is one of the most common pre-pregnancy risk factors for adverse perinatal events. Our aim was to assess whether this effect of obesity is modified by other concomitant maternal risk factors.

Methods

This was a retrospective cohort study of all singleton births in the United States, 2016-2017, using data from the National Centre for Health Statistics. Logistic regression was used to estimate the adjusted odds ratios (AOR) and 95% confidence intervals (CI) between obesity and a composite outcome of stillbirth, neonatal death, and severe neonatal morbidity. Modification of this association by maternal age, nulliparity, chronic hypertension and diabetes mellitus was assessed on both multiplicative and additive scales.

Results

The study population included 7,576,417 singleton pregnancies; 1,062,177 (14.4%), 516,693 (7.0%), 365,357 (5.0%) had class I, II and III obesity, respectively. Rates of the composite outcome increased with increasing obesity class, compared with women with normal BMI. Nulliparity, hypertension and diabetes modified the association between obesity and the composite perinatal outcome on both the additive and multiplicative scales. Nulliparous vs. multiparous women had a higher rate of increasing risk with increasing BMI, e.g., in class 3 obese nulliparous women aOR was 1.77 (95%, CI 1.73-1.83) vs. aOR 1.35 (95%, CI 1.32-1.39) in multiparous women. Women with hypertension or diabetes had higher outcome rates overall, but no dose response relationship with increasing BMI. While overall outcome rates increased with age, the risk curves by maternal age were similar across obesity classes.

Conclusions

Obese women are at increased risk of adverse perinatal outcomes, and the magnitude of these risks is modified by diabetes mellitus, chronic hypertension and nulliparity. These risk differences between subgroups of obese women should be emphasized in guidelines for the care of obese women.

Obstetric health

Pre-pregnancy Body Mass Index and Childhood Asthma Risk Natalie Rosenquist* Megan Richards Matthew Strickland Jeannette Ferber De-Kun Li Lyndsey Darrow

Background: Pre-pregnancy BMI may affect the intrauterine environment and increase a child's risk of developing asthma.

Methods: Electronic medical records (EMR) and pharmacy dispensing records were collected from the Kaiser Permanente Northern California (KPNC) integrated healthcare system. Children were included if they were born from 2005-2014, their mother received prenatal care in the KPNC system, and they were followed until at least age 6 (n=63,084). Asthma was defined using a combination of ICD codes and prescription dispensings. Pre-pregnancy BMI was ascertained using anthropomorphic measurements recorded in the EMR up to 6 months before pregnancy, or if missing, within the first 8 weeks after conception. Risk ratios (RR) and 95% confidence intervals for child's asthma were estimated using Poisson regression with robust error variance for (1) maternal pre-pregnancy BMI categories (underweight [<18.5], normal [18.5-25], overweight [25-30], obese I [30-35], and obese II & III [35+]) and (2) continuous pre-pregnancy BMI modeled using cubic splines with knots at BMI category boundaries. Models were adjusted for covariates including maternal age, education, race, asthma, allergies, smoking, diabetes, hypertension, and total gestational weight gain; and child's birth year, parity, sex, gestational age, and BMI (at age 5).

Results: 7.5% of children had asthma at age 6. Half of mothers had a normal pre-pregnancy BMI, 2.5% were underweight, 27% were overweight, 12% were obese I, and 9% were obese II & III. Relative to normal BMI, RRs were 0.95 (0.78, 1.16) for underweight, 1.09 (1.02, 1.17) for overweight, 1.13 (1.04, 1.24) for obese I, and 1.14 (1.03, 1.27) for obese II & III. The covariates that had the most impact on BMI estimates were gestational age and child's BMI. When continuous BMI was modeled with splines, asthma risk increased linearly between BMI values of 20 and 40.

Conclusions: Child's asthma risk is associated with higher maternal pre-pregnancy BMI.

Obstetric health

Relative income and pregnancy outcomes after embryo transfer: real-world evidence from the National Health Insurance data *, Seung-Ah Choe Tammy Kim

Unsuccessful pregnancy including early pregnancy loss, ectopic pregnancy, molar pregnancy, fetal death in utero or stillbirth can occur after in vitro fertilization and embryo transfer (IVF-ET). In addition to the physical and financial burden, any types of abortive outcome have a devastating emotional impact on couples undertaking IVF-ET cycles. In October 2017, South Korean government started provision of insurance coverage for in vitro fertilization procedures in people who were diagnosed infertility. We explored the association between socioeconomic status and the risk of pregnancy outcome among women with clinical pregnancy after IVF-ET. This is a retrospective observational study using the data from the National Health Information Database of National Health Insurance (NHI) Service in South Korea. We constructed a national cohort of pregnant women who had diagnostic code of pregnancy (starting with 'O') and had ever taken health examination at least once utilizing the NHI data available up to those in December 2019. We identified clinical pregnancy after embryo transfer by identifying the appearance of diagnostic code for pregnancy within 8 weeks of treatment code for embryo transfer. To identify pregnancy outcomes including delivery, our analyses restricted to 44,038 clinical pregnancy episodes of 29,847 women who underwent embryo transfer between October 2017 and February 2019. We used individually linked data of household income decile. The income levels of individual data were divided into four groups (1, 0-30%; 2, 30-50%; 3, 50-70%; 4, 70-100%) for analytical convenience. Log-binomial regression analysis was applied to calculate relative risk (RR) of abortive pregnancy outcome after embryo transfer, adjusted for age, body mass index, parity, cause of infertility, region, and season of embryo transfer. Sixty percent of the pregnancies were in women with employment and living in Seoul capital area. Among the 44,038 clinical pregnancies after embryo transfer**,** 30,783 (69.9%) ended with live births. Majority of pregnancy outcome was live birth (30,783, 69.9%). Among the rest of cases, 11,215 (25.5%) cycles ended with miscarriage or early pregnancy loss, 1779 (4.0%) cycles were ectopic pregnancy, 45 (0.1%) was coded as molar pregnancy, and 224 (0.5%) were fetal death in utero or stillbirth. In all ET cycles, the association between risk of abortive outcome and relative level of income was close to null. In the stratification analysis, lowest income group showed lower risk of abortive outcome compared to those with highest income in the pregnancies after frozen embryo transfer. We observed generally null association between relative income and risk of abortive outcome in IVF-ET pregnancies in the setting of universal coverage of IVF-ET procedure.

Obstetric health

Maternal cigarette and electronic cigarette use around the time of pregnancy associated with the risk of hypertension XIAOZHONG WEN* Meghana Sana Mariana Hand Alexia Pezzino Brooke Pearce

Objectives: Despite the rapid increase in electronic cigarette (e-cigarette) use among pregnant women, there is limited knowledge regarding the effects of e-cigarette use on maternal health. We examined the association between maternal e-cigarette use and gestational hypertension.

Methods: We obtained data from phase 8 (2016-2019) of the Pregnancy Risk Assessment Monitoring System (PRAMS, N=153,336). Postpartum mothers reported their e-cigarette and combustible cigarette use within the 3 months before pregnancy and during the last 3 months of pregnancy. Additionally, they retrospectively reported their hypertension status before pregnancy (preexisting hypertension) and hypertension that developed during pregnancy (gestational hypertension). We used multivariable logistic regression models to estimate the adjusted odds ratio (aOR) of hypertension (preexisting and gestational) associated with maternal e-cigarette use and frequency of use at various time points, controlling for socio-demographic and pregnancy confounders.

Results: Compared to non-users, mothers who exclusively used cigarettes (8.6% vs. 5.6%; aOR, 1.37 [95% CI, 1.29-1.45]) within 3 months before pregnancy had an increased risk of hypertension before pregnancy. Exclusive e-cigarette smokers in the 3 months before pregnancy had a higher risk of gestational hypertension compared to non-users (12.8% vs. 11.4%; aOR, 1.18 [95% CI, 1.03-1.35]). Other associations were not statistically significant.

Conclusion: Combustible cigarette use before pregnancy was associated with an increased risk of hypertension before pregnancy. E-cigarette use before pregnancy was associated with an increased risk for gestational hypertension.

Obstetric health

Explaining Black-White differences in CS rates among low-risk pregnancies: Applying the Kitagawa decomposition technique with the Robson classification system Trang Pham*
Kristin Rankin Arden Handler

Intro:
The U.S. C-section (CS) rate is over 30% and CS rates in non-Hispanic Black (Black) birthing persons surpass those of their non-Hispanic White (White) counterparts. The Robson Classification System (Robson group-RG) provides a method of risk stratification useful for comparing CS rates across groups with different risk profiles, but is under-utilized in the US.
Methods:
Live births to Black and White U.S. residents (2019 Natality Data) were classified into 12 mutually exclusive RGs based on: parity, gestational age, onset of labor, fetal presentation, plurality and history of CS. Low-risk pregnancies comprise 6 RGs (1, 2a, 2b, 3, 4a, and 4b), which include term nulliparous or multiparous (without prior CS) pregnancies with spontaneous labor, labor induction or pre-labor CS. RGs 5-10 which include pregnancies at high risk for medical intervention (e.g., breech, multiples, preterms), were excluded. We applied the Kitagawa decomposition technique to estimate the distributional versus rate components to the excess CS rate among low-risk Black (vs. White) birthing persons in the U.S.
Results:
Low-risk CS was 20.0% in Blacks and 15.9% in Whites (RD=4.1 percentage points, 95% CI 4.0-4.2). While Whites were more likely to undergo labor induction, Blacks had higher CS rates across all low-risk RGs. The decomposition analysis revealed that 77% of the excess CS rate among Blacks was attributable to the RG-specific CS rates, primarily due to higher CS rates after induction for Black primiparas and multiparas. The distribution of birthing people across RGs accounted for only 23% of the disparity.
Conclusion:
The high CS rate in low-risk birthing persons with and without prior birth is attributed, in part, to unnecessary medical intervention, particularly among Black birthing persons. Reducing inequities in unnecessary CS may play a significant role in postpartum health, an area of focus since the majority of pregnancy-related deaths occur in the postpartum period.

Omics

Maternal Microbial Metabolites and Risk of Fetal Growth Extremes: A Longitudinal Multi-racial/ethnic Cohort Study Rana Chehab* Adrienne Kwok Oliver Fiehn Ines Thiele Amanda Ngo Dinesh Barupal Charles Quesenberry Assiamira Ferrara Yeyi Zhu

Fetal growth extremes [small and large for gestational age (SGA and LGA)] represent high-risk phenotypes for cardiometabolic disorders. Profiling the in-utero milieu via metabolomic profiling may elucidate pathophysiology of fetal growth extremes. We aimed to identify microbial metabolites associated with SGA and LGA. A random sample of 140 SGA, 134 LGA and 140 appropriate for gestational age (AGA) was drawn from the PETALS cohort study. 1167 annotated metabolites were measured by gas and liquid chromatography (LC)/time-of-flight mass spectrometry (TOF-MS) and hydrophilic interaction LC/quadrupole TOF-MS using fasting serum at gestational weeks (GW) 10-13 and 16-19. 165 microbial metabolites were linked with the Virtual Metabolic Human Database. We identified significant pathways (P_{FDR} <0.05) associated with SGA and LGA vs. AGA using chemical similarity enrichment analysis. Branched-chain amino acids (AA), dicarboxylic acids (DA), medium-chain hydroxy acids at GW 10-13 were positively associated with SGA risk, while phosphatidylcholines, saturated fatty acids (FA) and glucogenic AA were inversely associated with SGA risk. At GW 16-19, positive associations with branched-chain AA and DA persisted, in addition to saturated FA and ceramides, while unsaturated triglycerides (TG) were inversely associated with SGA risk. LGA risk was positively associated with glucogenic AA, DA, hippurates, phenylacetylglutamine and cresols at GW 10-13, and inversely associated with phosphatidylcholine and unsaturated TG. At GW 16-19, carnitine, saturated TG, cyclic AA, DA, glyceric acids, phenylacetylglutamine and cresols were positively associated with LGA risk, while aromatic, basic and sulfur AA, sugar alcohols, phosphatidylcholines and unsaturated TG were inversely associated with LGA risk. Our findings suggest distinct microbial metabolites in early to mid-pregnancy are associated with SGA and LGA risk, calling for further investigation into microbiome-metabolome-host interactions.

Paternal health

Relationship with the father of the baby and depressive symptoms among pregnant Black women Rosemary Adaji, Carmen Giurgescu, and Dawn Misra Rosemary Adaji* Carmen Giurgescu Dawn Misra

Background: Black women report higher levels of depressive symptoms during pregnancy compared to white women. Supportive relationships with the father of the baby (FOB) may be protective and decrease depressive symptoms. Yet, research with pregnant Black women that considers the role of the FOB remains sparse. This study examined the association between the relationship with the FOB and depressive symptoms among pregnant Black women.

Methods: A sample of 421 Black women (18-45 years) participating in the Biosocial Impacts on Black Births (BIBB) study completed questionnaires at 19-29 weeks' gestation. Relationship with the FOB indicators included satisfaction with FOB relationship, FOB involvement during pregnancy, support and conflict with FOB, warmth of relationship with FOB before and during pregnancy, and frequency of contact with FOB. Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D). CES-D scores ≥23 were considered high levels of depressive symptoms. Descriptive and multivariate logistic regression analyses were used. The regression model was adjusted for maternal socio-demographic characteristics, health behaviors, and medical history.

Preliminary results: All indicators of relationship with FOB were associated with high levels of depressive symptoms (CES-D score ≥23) in bivariate analyses. Adjustment for potential confounders showed that conflict with FOB, marital/cohabitation status, and frequency of contact with FOB were independently associated with depressive symptoms ($p < 0.05$). Findings from the adjusted model may be reflective of likely correlation among relationship indicators. Further analysis will explore a latent class model to account for this correlation.

Conclusion: Findings from this study will inform research on the potential contribution of FOB to birth outcomes through indirect pathways such as maternal depressive symptoms.

Pregnancy outcomes

Maternal hair cortisol concentration is associated with insulin resistance in mid-pregnancy

Diana Juvinao-Quintero* Gloria Larrabure-Torrealva Sixto Sanchez Clemens Kirschbaum Michelle Williams Bizu Gelaye

Background: Intrauterine exposure to chronic stress, elevated levels of glucocorticoids and to an abnormal maternal glucose metabolism, may limit fetal development and determine early-life programming of disease. ***Aim***: We conducted the present study to evaluate the extent to which elevated hair cortisol concentration (HCC), reflective of dysregulation of hypothalamic-pituitary-adrenal (HPA) axis, in pregnancy is associated with increased risk of gestational diabetes (GDM) and/or insulin resistance. ***Methods***: We included data from 528 pregnant women (mean gestational age 25 weeks) attending prenatal clinics in Lima, Peru. We extracted cortisol concentrations from hair samples with methanol using liquid chromatography tandem mass spectrometry. Each participant provided 6-cm hair samples: 3 cm hair segment closest to the scalp reflected HCC in mid-pregnancy (13-24 weeks), and 3-6 cm from the scalp reflected HCC in early pregnancy (1-12 weeks). A standardized oral glucose tolerance test (OGTT) was administered in mid-pregnancy to diagnose GDM and to calculate indices of insulin resistance (HOMA-IR) and beta-cell function (HOMA-B). Multivariate regressions were used to estimate the association of HCC with GDM status and other glycemic traits. ***Results***: GDM was detected in 123 (23.3%) women. Mean HCC were 3.7 (± 3.4) pg/mg and 4.8 (± 3.4) pg/mg in early and mid-pregnancy, respectively. We found that a unit increase in HCC in early and mid- pregnancy, were statistically significantly associated with higher fasting insulin (Beta=0.69 µIU/mL), HOMA-IR (Beta=0.14-0.15) and HOMA-B (Beta=12.0-17.2). Glucose values measured during the OGTT and GDM status, were not associated with maternal HCC. ***Conclusions***: High maternal HCC was associated with an abnormal insulin homeostasis in pregnancy, but not with risk of being diagnosed with GDM. Dysregulation of the HPA axis, as reflected by high HCC, may be an additional factor contributing to insulin resistance syndrome in pregnancy.

Pregnancy outcomes

Preconception dietary glycemic index and risk of large-for-gestational age births Anne Marie Darling* Mahsa Yazdy Suzan Carmichael Gary Shaw Eirini Nestoridi

Background: Prenatal diets with a high glycemic index (GI), which leads to elevated postprandial glucose levels and hyperinsulinemia, have been inconsistently linked to an increased risk of large-for-gestational age (LGA) births. The impact of pre-pregnancy dietary GI on LGA risk is unknown, however. We examined the association of maternal pre-pregnancy dietary GI with LGA among 9,661 mother-infant dyads from the National Birth Defects Prevention Study (NBDPS) as well as joint associations of GI and maternal overweight/obesity, infant sex, and maternal diabetes on this association.

Methods: Dietary intake for mothers of infants born without birth defects between 1997-2011 was ascertained using a 58-item food frequency questionnaire. We dichotomized dietary GI into high and low categories using spline regression models. Infants with a birth weight $\geq$ the 90^{th} percentile for gestational age and sex according to a U.S. population reference were considered LGA. We used logistic regression to obtain unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association.

Results: 831 participants (8.6%) were classified into the high dietary GI category (58.8). 1250 infants (12.9%) were born LGA. Unadjusted analysis suggested an inverse association between high dietary GI and LGA (OR 0.81, 95% CI 0.65, 1.02). No association was observed after adjustment for demographic, lifestyle, and reproductive factors when comparing high dietary GI intake between LGA births and all other births (OR 0.99 95% CI 0.78, 1.27) or when excluding small-for-gestational age (SGA) births (OR 1.01 95% CI 0.79, 1.28). Further, no joint associations with maternal overweight/obesity, infant sex, or maternal diabetes were observed.

Conclusion: High pre-pregnancy maternal glycemic index was not associated with LGA births either independently or jointly with other factors.

Pregnancy outcomes

EPoCH: a web-app to explore potentially causal effects of parental prenatal health behaviours on child health Kayleigh Easey* Gemma Sharp

Background: Observational evidence shows that maternal (and paternal) health behaviours around pregnancy are associated with offspring health. It is often difficult to infer whether associations represent causal effects or arise due to confounding. We have conducted a multi-cohort, multi-exposure, multi-outcome study, applying several approaches that can strengthen causal inference. We have developed a web-app to make our results available to the research community.

Methods: In a reduced phenome-wide association study (PheWAS), we separately regressed over 200 child health outcomes on up to four parental health behaviour classes at several timepoints, or polygenic risk scores (PRS) for these health behaviours. To increase power, we ran the PheWAS in four cohorts and meta-analysed results (maximum N=106,396). Finally, we developed a web-app (EPoCH) to search, visualize and download results.

Results: Our EPoCH web-app facilitates triangulation of approaches to strengthen causal inference. Users are shown associations (effect estimates and 95% confidence intervals): 1) adjusted for various confounders; 2) from different cohorts, allowing cross-context comparisons; 3) for (i) maternal and paternal exposures, and (ii) pre- and post-natal exposures, enabling negative control comparisons; 4) for different pregnancy exposure timepoints, enabling exploration of the importance of exposure timing; 5) for different doses of ordinal exposures, enabling exploration of dose-response effects; 6) for PRS, facilitating Mendelian Randomisation analyses.

Impact: The EPoCH app provides a useful resource for improving causal inference in parental prenatal effects research. Findings can help identify the most appropriate prenatal targets for more effective interventions to improve child health.

Pregnancy outcomes

Associations between weekly gestational exposure of nitrogen dioxide and preterm birth in a North Carolina birth cohort, 2003-2015 Alison K. Krajewski* Thomas J. Luben Joshua L. Warren Kristen M. Rappazzo

Preterm birth (PTB) is associated with exposure to criteria air pollutants, though variability in the magnitude and consistency of associations exists. We evaluated the associations between weekly gestational exposure to nitrogen dioxide (NO_2) with PTB (less than 37 weeks completed gestation) in a North Carolina (NC) birth cohort from 2003-2015 (N=1,367,757). Daily NO_2 concentrations from a hybrid model with a spatial resolution of 1 km x 1 km were aggregated to census tract level estimates and linked to residential address at delivery, and then averaged to obtain exposure estimates for each week of pregnancy. Modified Poisson regression with robust errors was used to estimate risk differences (RD) and 95% confidence intervals (CIs) per 10 ppb increase in NO_2, adjusted for gestational parent marital status, race/ethnicity, age at delivery, Medicaid status, and month of conception. The associations between NO_2 exposure and PTB were generally null throughout pregnancy. RDs for weekly exposure during gestation ranged from -7 (95% CI: -14, 1) to 0 (-6, 5) per 10,000 births. However, when adjusting for estimated $PM_{2.5}$ (from hybrid model) and ozone (from EPA's Community Multiscale Air Quality (CMAQ) model) concentrations to account for potential copollutant confounding, there was a consistent pattern of decreased risk of PTB per 10 ppb increase in NO_2 exposure in each week of gestation. RDs in the copollutant model ranged from -29 (-36, -22) to -10 (-15, -5) per 10,000 births for NO_2, 5 (4,6) to 12 (10, 14) per 10,000 births for $PM_{2.5}$, and -17 (-24, -10) to 4 (-3, 11) per 10,000 births for ozone. While NO_2 exposure was not associated with PTB in the single pollutant model, there was decreased risk with PTB when adjusting for other criteria air pollutants.

Pregnancy outcomes

Causal effects of maternal coffee consumption on perinatal health: a systematic Mendelian randomization study based on four European cohorts Peiyuan Huang* Gemma Sharp Deborah Lawlor Robyn Wootton Carolina Borges

Background: Current guidelines for restricting caffeine intake during pregnancy are based on observational evidence for an association with pregnancy loss, low birth weight, and preterm birth, which may be biased by confounding. This Mendelian randomization (MR) study systematically examined the possible causal effect of maternal coffee consumption on perinatal health.

Methods: This two-sample MR study used eight coffee consumption-related genetic variants identified by a European genome-wide association study (N=91,462) as instruments. Genetic associations with 35 common perinatal health outcomes were obtained from two British (ALSPAC and UK Biobank), a Norwegian (MoBa) and a Finnish (FinnGen) study, with a total sample size of up to 390,000. MR results were meta-analyzed across studies. A range of sensitivity analyses were performed to test instrument strength, instrument-confounder associations, and potential pleiotropy.

Results: Genetically predicted coffee consumption increased the risk of maternal anaemia during pregnancy (pooled odds ratio: 1.80 [95% confidence interval: 1.03-3.16]) and reduced the risk of antenatal depression (0.61 [0.40-0.93]), but neither result passed the criteria for multiple testing corrections using the false discovery rate method. Little evidence was found for causal effects on other outcomes, including pregnancy loss (0.98 [0.91-1.05]), low birth weight (1.01 [0.56-1.85]), or preterm birth (1.03 [0.85-1.26]). Results were imprecise for some outcomes. MR sensitivity analyses validated the genetic instrument in pregnant women and found no evidence for pleiotropy via offspring genotype, lifestyle factors, or plasma caffeine levels.

Conclusions: In contrast to previous observational studies, we found limited evidence for a causal effect of maternal coffee consumption on adverse perinatal health outcomes, suggesting that findings from previous observational studies may be biased and that drinking coffee during pregnancy may not be harmful.

Pregnancy outcomes

Plasma Persistent Organic Pollutants in Early Pregnancy and Fetal Growth among Pregnant Women with Obesity Sifang Kathy Zhao* Edwina Yeung Yan Qiao Marion Ouidir Katherine Grantz Dian He Roger Newman William Grobman Micahel Bloom Kurunthachalam Kannan Germaine Buck Louis John Vena Kelly Hunt Rajeshwari Sundaram Cuilin Zhang

Background: Maternal persistent organic pollutants (POPs) has been related to fetal growth and may alter adipogenesis and fat storage. However, it remains unclear as to associations of POPs with longitudinal fetal growth specifically for pregnant women with obesity.

Methods: Among 452 women with obesity in the NICHD Fetal Growth Studies, non-fasting blood samples collected at 10-14 weeks' gestation were analyzed for lipids and 76 POPs: 11 poly-and-perfluorinated alkyl substances, 1 polybrominated biphenyl, 9 polybrominated diphenyl ethers (PBDE), 44 polychlorinated biphenyl congeners (PCBs), some detected infrequently, and 11 organochlorine pesticides (OCPs). Fetal biometrics were obtained from 5 ultrasound visits in pregnancy by certified sonographers. Relations of each of the 76 POPs to longitudinal fetal growth were examined using generalized linear mixed models, adjusting for confounders. Using group lasso variable selection, we identified important chemicals associated with fetal growth from the mixture and estimated the mixture effect on fetal growth at each visit.

Results: Higher plasma concentrations of 3 PCBs (PCB167, PCB172/192, PCB196/203) and 1 OCP (trans-Nonachlor) were associated with larger fetal size. For example, β (95% confidence interval) comparing 3rd tertile (median 1.12 ng/g lipid) with 1st tertile (median 0.29 ng/g lipid) of PCB-196/203 was 0.17 g (0.02, 0.32) for estimated fetal weight. Of note, PCB167 and PCB172/192 were detected infrequently (<10% above limits of detection). When we examined the mixture effect in multi-pollutant models, the 3rd compared to 1st tertile of mixture concentrations was associated with larger abdominal circumference at 24-29 (0.08 mm [0.02,0.15]) and 30-33 weeks' gestation (0.07 mm [0.03,0.12]), mainly related to PCB-199 and PBDE-100.

Conclusion: Among pregnant women with obesity, higher levels of several individual and mixtures of POPs in early pregnancy were associated with accelerated fetal growth.

Pregnancy outcomes

Preconception vitamin D and miscarriage in a prospective cohort study Anita Subramanian* Anne Z. Steiner Clarice R. Weinberg Ginna L. Doss Anne Marie Z. Jukic

Background: In humans, low vitamin D has been associated with prolonged menstrual cycles, delayed ovulation, and a lower probability of conception. Animal and in vitro data indicate that vitamin D may affect implantation. Our objective was to estimate the association between preconception vitamin D level and risk of miscarriage.

Methods: Participants were trying to conceive naturally for 3 months or less at enrollment and aged 30-44 years. A preconception blood sample was collected and 25-hydroxyvitamin D [25(OH)D] was measured. Women who conceived (n=362) were at risk of a miscarriage from the day of a reported positive pregnancy test until either a participant-reported pregnancy loss or 20 weeks post day of ovulation, whichever came first. Gestational age was defined by ovulation. Time to miscarriage (days) or censoring was modeled using a multivariate Cox proportional hazards model. Multiple imputation was performed for missing covariates and missing day of ovulation.

Results: The mean age was 33 years (standard deviation (SD): 3.0 years). Mean 25(OH)D was lower among those who reported their race as African-American and those with higher BMI. After adjustment for age, race, BMI, education, exercise, alcohol, and caffeine intake, compared to the referent group (30-<40 ng/ml), the hazard ratio (HR) and 95% confidence interval (CI) for those with a 25OHD level of less than 30 ng/ml was 1.10 (CI: 0.63, 1.93). Among participants with a higher 25OHD level (≥ 40 ng/ml), the HR was 1.04 (CI: 0.61, 1.79).

Conclusion: In this population of women conceiving naturally, preconception vitamin D levels do not appear to predict miscarriage. Future research should focus on women at greater risk for miscarriage or in populations at risk for vitamin D deficiency or on supplementation.

Pregnancy outcomes

Associations of hypertensive disorders of pregnancy and gestational diabetes mellitus with menopausal symptoms at midlife in Project Viva Diana Soria* Wei Perng Sheryl Rifas-Shiman Lidia Minguez-Alarcon Marie-France Hivert Jan Shifren Emily Oken Jorge Chavarro

Objective. To evaluate the associations of a lifetime history of hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM) with menopausal symptoms in midlife.

Methods. Secondary analysis of 676 women participating in Project Viva, an ongoing cohort enrolled during pregnancy. The exposure was lifetime history of HDP or GDM assessed for the index pregnancy by review of outpatient and hospital medical records and for all other pregnancies by interview or questionnaire at study entry (1999-2002) and the midlife visit (2017-2021). The primary outcome was the Menopause Rating Scale (MRS) applied at the midlife study visit. We used linear or logistic regression models adjusted for covariates such as baseline age, race/ethnicity, education, married/cohabiting, household income, baseline parity, age at menarche, and body mass index at midlife.

Results. The mean (SD) age was 52 (3.9) years at the midlife visit, and 48% of the participants had experienced menopause. There were no consistent differences in total symptoms, domain-specific or individual symptoms in women with history of HDP (18%) or GDM (7%). A history of HDP and/or GDM was not associated with age at the onset of natural menopause.

Conclusions. Our findings do not support an association of a history of HDP or GDM with the severity of menopausal symptoms or age at the onset of natural menopause. Larger studies of women with history of these pregnancy complications are needed to clarify their association with menopausal symptoms.

Pregnancy outcomes

Application of fetal growth standards in the Nulliparous Pregnancy Outcomes Study (nuMoM2b) cohort Jessica Gleason* Uma Reddy Zhen Chen William Grobman Ronald Wapner Katherine Grantz

No fetal growth standard is currently endorsed for universal use in the US, and it is unclear how international standards perform compared to US-based standards at identifying small or large for gestational age at birth (SGA, <10th%ile; LGA, >90th%ile) or predicting neonatal morbidity/mortality in US populations. Using estimated fetal weight (EFW) from ultrasounds at 16-21 and 22-29 weeks in a prospective pregnancy cohort (n=9530; 2010-14), we compared area under the curve (AUC) and sensitivity of 5 commonly-referenced fetal growth standards (INTERGROWTH-21 (IG), World Health Organization (WHO), Hadlock 1991, National Institute of Child Health and Human Development (NICHD) race/ethnic-specific and unified) to predict SGA or LGA, and SGA or LGA with perinatal morbidity/mortality. At 22-29 weeks, WHO classified 9.2% of fetuses as SGA, while the other 4 classified a lower proportion: NICHD race/ethnic-specific 7.7%, IG 6.2%, Hadlock 6.1% and NICHD unified 5.1%. Hadlock and IG classified the lowest (8.3%) and highest (21.3%), respectively, as LGA. EFW at 22-29 weeks had better ability to predict SGA or LGA than EFW at 16-21 weeks, though AUC was low at both gestational age ranges. When predicting severe neonatal morbidity, WHO had the highest AUC of 0.525 (0.512, 0.531) when EFW was <10th %ile at 22-29 weeks, but the AUCs were similar among standards (range 0.517-0.521). Sensitivity was generally low across standards (22.7-29.1%). When predicting SGA with severe neonatal morbidity or mortality, when EFW was <10th percentile at 22-29 weeks, WHO had highest AUC (0.65; 95% CI 0.61, 0.69) and IG had lowest (AUC=0.59; 95% CI 0.57, 0.63), though all standards had low sensitivity (9.4-13.1%) and positive predictive values (25.3-38.2%). Despite classifying different proportions of fetuses as SGA or LGA, all standards performed similarly in predicting perinatal morbidity and mortality. Our findings highlight the importance of knowing how standards perform in local populations.

Pregnancy outcomes

Prevalence and risk factors of vulnerable newborn phenotypes in rural Amhara, North West Ethiopia Estifanos Baye* Firehiwot Workneh Abate Michelle Eglovitch Mulatu Melese Derebe Ingrid E. Olson Fisseha Shiferie Sitota Tsegaye Kalkidan Yibeltal Workagegnhu Tarekegn Grace J. Chan Parul Christian Sheila Isanaka Yunhee Kang Luke C. Mullany Rose L. Molina Amare Worku Tadesse Blair J. Wylie Alemayehu Worku Yemane Berhane Anne CC Lee

Introduction: Low birthweight (LBW) (<2500 g) is often used as an indicator of newborn vulnerability. However, this classification does not distinguish preterm birth versus small for gestational age (SGA) newborns and excludes those preterm or SGA with a birthweight of >=2500 g (not LBW (NLBW)), who also carry increased risk. In low-income countries like Ethiopia, the quality of data on SGA/preterm prevalence is low and there is limited data on the simultaneous occurrence of these conditions.

Methods: A prospective pregnancy-birth cohort was followed in 12 rural health centers in Amhara region, Ethiopia. Preterm birth was defined as a live birth before 37 completed weeks' gestation. SGA was defined as a birthweight <10^{th} percentile using the Intergrowth 21^{st} standard, appropriate size for gestational age (AGA) between 10 – 90^{th} percentiles, and large for gestational age (LGA) >90^{th} percentile. Live births were classified using 10 discrete combinations ("vulnerable newborn phenotypes") of LBW, preterm, and SGA status.

Results: 556 singleton consecutive live births were included. Overall, 7.7% were born preterm, 37.1% SGA, 1.4% LGA, and 16.4% LBW. The predominant birth phenotype was Term-AGA-NLBW (55%), followed by Term-SGA-NLBW (25%). Prevalences of Term-SGA-LBW, Preterm-AGA-LBW and Preterm-LGA-LBW were 11.2%, 3.6% and 0.2%, respectively. Compared to women with no education, those who completed secondary education and above had a 70% lower risk of having a preterm infant (adjusted odds ratio [AOR]=0.3, 95% confidence interval [CI]: 0.1 – 0.8). The odds of delivering a LBW infant among women with mid-upper arm circumference (MUAC) <23cm were two times higher than those with MUAC >=23cm (AOR=1.8, 95% CI: 1.1 – 2.9).

Conclusion: A high prevalence of LBW and SGA was observed in this rural Ethiopian setting. Implementation and scale-up of effective interventions are needed to prevent these vulnerable birth outcomes, thereby reducing associated morbidity and mortality.

Pregnancy outcomes

Neighborhood Evictions and Preterm Birth among Black Individuals Shawnita, Elizabeth S., Cathrine, Chantel L. Sealy-Jefferson, McClure, Hoyo, Martin*, Lea Ghastine Shawnita Sealy-Jefferson Elizabeth S. McClure Cathrine Hoyo Chantel L. Martin Chantel Martin

Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation, is the leading cause of infant mortality among Black infants. Evictions (involuntary displacement of occupants from a rented residence) are a key aspect of neighborhood housing instability, a neighborhood characteristic that impacts social cohesion and public health. Building upon previous findings suggesting familial distress as a potential driver of increased PTB among Black pregnant people exposed to high neighborhood eviction rates, this study explores whether the association of neighborhood evictions with PTB differs depending on the presence or absence of children in the household among 397 singleton births to Black pregnant people in the Newborn Epigenetics Study from 2009-2011. This study is based in Durham, North Carolina, which is experiencing a decades long eviction crisis that disproportionately affects Black residents. Using publicly available data, we calculated neighborhood eviction rates as evictions per 100 renter-occupied households in a census block group for the year of pregnancy. Presence of children in the household (0 or ≥1) was self-reported and PTB was abstracted from medical records. Logistic regression models were adjusted for maternal age at delivery, educational attainment, marital status, and neighborhood poverty. In our sample, 10% of births were preterm. A 1-SD increase in neighborhood eviction rate was associated with twice the odds of PTB among Black pregnant people with children in the household (OR=1.97, 95% CI: 1.14, 3.42). However, this association was not observed among those without children in the household (OR=0.85, 95% CI: 0.49, 1.39). These findings suggest that Black families with children are particularly vulnerable to neighborhood evictions. To reduce the disproportionate burden of PTB in Black communities, neighborhood level interventions to prevent evictions should prioritize Black families with children.

Pregnancy outcomes

Associations between gestational weight gain adequacy and cesarean delivery in twin pregnancies: a secondary analysis of the JUMODA national cohort Melissa Amyx* Diane Korb Jennifer Zeitlin Thomas Schmitz Camille Le Ray

Objective: to evaluate the association between gestational weight gain (GWG) adequacy and cesarean sections (CS) in twin pregnancies in France

Methods: We included livebirths (N=7208) from the national, prospective, population-based JUMODA twin cohort (2014-15). GWG was calculated as end of minus beginning of pregnancy weight. GWG adequacy based on rate of GWG (insufficient [IGWG]; adequate [AGWG]; excessive [EGWG]) was determined by dividing lower and upper bounds of the 2009 IOM GWG recommendations (normal weight: 16.8-24.5, also for underweight; overweight: 14.1-22.7; obese: 11.4-19.1kg) and a previously derived French classification (underweight: 13-21; normal weight: 13-20; overweight: 11-19; obese: 7-16kg) by 37. The percentage of women delivering by CS (either twin CS; both vaginal delivery [VD]) and CS timing (prelabor, intrapartum) was determined by GWG adequacy. Adjusted generalized linear mixed models evaluated these associations (adjusted odds ratios [aORs], 95% confidence intervals [CIs]), stratified by BMI (under/normal weight; overweight; obese).

Results: Among under/normal weight women with twin pregnancy, per IOM recommendations, CS increased with EGWG (IGWG: 48.2%; AGWG: 49.9%; EGWG: 59.7%; p<.05), with similar trends after adjustment (IGWG: aOR 0.9, 95%CI 0.8, 1.0; EGWG aOR 1.2, 95%CI 1.0, 1.5). Specifically, prelabor CS increased with increasing GWG (IGWG: 26.7%; AGWG: 28.8%; EGWG: 34.4%; p<.05), remaining significant with adjustment (IGWG: aOR 0.8, 95% CI 0.7, 1.0; EGWG aOR 1.4, 95% CI 1.0, 1.9). Trends were similar for intrapartum CS (IGWG: aOR 0.8, 95%CI 0.7, 1.0; EGWG aOR 1.3, 95%CI 0.9, 1.9). For overweight and obese women with twin pregnancy, no consistent results were found. Results were similar with the French classification.

Conclusion: Among under/normal weight women with twin pregnancy, EGWG was associated with increased CS, particularly prelabor CS. More research is needed to determine appropriate GWG guidelines in this population.

Social determinants of health

High Health Care Financial Burden Is Associated with Postpartum Care Seeking among Commercially Funded Hospital Births, Oregon 2012-2017 Menolly Kaufman*

Background: Birthing people with commercial insurance tend to have better birth and postpartum health outcomes at the population level compared to Medicaid-funded births. However, the quality and cost of commercial insurances can vary widely, and it is increasingly common for private plans to have direct costs to the patient that are excessively high. Research is limited as to how high patient health care costs affect postpartum morbidity and access to care.

Objective: To assess how direct costs for health care (i.e. out-of-pocket spending) before and during birth impact postpartum care-seeking.

Methods: We conducted a retrospective cohort of commercially funded births in Oregon from 2012-2017 using an All-Payer All Claims database. Our primary exposure was out-of-pocket spending (deductibles, co-payments, and co-insurance, all health care costs that fall directly on the patient) for the birthing person from the first of the calendar year through delivery discharge. We utilized multivariable log-binomial regression to estimate how out-of-pocket spending impacts readmissions and emergency department visits within one-year postpartum and postpartum visit attendance within 12 weeks. We stratified the final models by pre-term birth status to assess if an out-of-pocket financial burden has a different impact on “higher risk” births.

Results: Among our population of commercial insured birthing people (N=78,147), 28.7% (N=22,406) had out-of-pocket health care costs over $2,500. Compared to births with $0 in out-of-pocket financial burden through delivery discharge, births with over $5,000 were 15% less likely to attend their comprehensive postpartum visit within 12 weeks (RR: 0.85, 95% CI: 0.83, 0.88) and 20% less visit the emergency department (RR: 0.80, 95% CI: 0.73, 0.88). We observed no statistically significant differences between out-of-pocket financial burden and readmissions.

Conclusion: The financial burden of health care may influence care-seeking, including for birthing and postpartum people. As policymakers and clinicians seek solutions to reduce inequities in postpartum health outcomes, the financial burden related to birth should be considered.

Social determinants of health

The hospital burden of intergenerational contact with the welfare system Alexandra Procter* Catherine Chittleborough Rhiannon Pilkington Odette Pearson Alicia Montgomerie John Lynch

Intergenerational welfare contact is a policy issue because of the personal and social costs of ‘entrenched disadvantage’ across generations. Yet few studies have quantified the hospital burden. We estimated the proportion of children who experienced intergenerational welfare contact and other welfare contact types; and estimate their cause-specific hospital burden.

This linked administrative data study of children born in South Australia, 1991-1995 (n=94,358), and their parent/s (n=143,814) used de-identified data from the Better Evidence Better Outcomes Linked Data platform. Using Australian Government Centrelink data, welfare contact was defined as parent/s receiving a means-tested welfare payment (low-income, unemployment, disability or caring) when children were aged 11-15, or children receiving payment at ages 16-20. Intergenerational welfare contact was welfare contact occurring in both parent and child generations. Children were classified as: No welfare contact, parent only welfare contact, child only welfare contact, or intergenerational welfare contact. Hospitalisation rates and cumulative incidence were estimated by age and welfare contact group.

Intergenerational welfare contact affected 34.9% of children, who had the highest hospitalization rate (133.5 per 1,000 person-years) compared to no welfare contact (46.1 per 1,000 person-years), parent only welfare contact (75.0 per 1,000 person-years), and child only welfare contact (87.6 per 1,000 person-years). Of all intergenerational welfare contact children, 43.0% experienced at least one hospitalization between 11-20, frequently related to injury, mental health, and pregnancy.

Children experiencing intergenerational welfare contact represent a third of the population aged 11-20. Compared to children with parent-only welfare contact, intergenerational welfare contact children had 78% higher hospitalization rates from age 11 to 20, accounting for over half of all hospitalizations in this age group.

Social determinants of health

Prenatal neighborhood stress and maternal sex steroid hormone levels across pregnancy
Megan Hansel* Thomas O'Connor Christina Wang Emily Barrett Zorimar Rivera-Núñez

Neighborhood stressors have been associated with adverse pregnancy outcomes. A potential mechanism is disruption of maternal endocrine pathways. While stress hormones (e.g. cortisol) have received much attention, other relevant hormones, such as sex steroids, have been overlooked. We examined associations between maternal neighborhood stressors and sex steroid hormones measured serially across pregnancy. Pregnant women in the Understanding Pregnancy Signals and Infant Development (UPSIDE) study contributed biospecimens, questionnaire, and medical record data in each trimester (n=262). Exposure to neighborhood stress was measured through the validated City Stress Inventory, which includes two subscales: 11-item *neighborhood disorder* (e.g., vacant buildings, crime), and 7-item *exposure to violence* (personal experiences of violence). Composite scores were calculated and examined categorically (quartile (Q) for neighborhood disorder and any/none for exposure to violence). Total testosterone [TT], free testosterone, estrone, estradiol, and estriol were measured in maternal serum in each trimester using LC/MS-MS. We fit linear regression models adjusting for confounders (including sociodemographic factors) and stratified by fetal sex. Results are presented as percentage change (Δ%) and 95% confidence interval (CI) in hormones. Most participants (73%) reported one or more exposures to neighborhood disorder; 22% reported any exposure to violence. In adjusted models, neighborhood disorder was associated with higher TT in all trimesters, with the strongest associations observed in the third trimester (Q2:%Δ=36, 95%CI:9,70; Q3:%Δ=29, 95%CI:4,60; Q4:%Δ=30, 95%CI:2,65). Associations were stronger in women carrying male fetuses (%Δ range:50-74). The exposure to violence sub-score was not associated with any hormone. Our analyses suggest that neighborhood disorder may impact prenatal maternal testosterone levels with potential implications for maternal and child health.

Social determinants of health

Subjective and objective financial deprivation in adolescence and lifetime experience of gestational diabetes Julia Porth* Bobby Cheon

Background: Gestational diabetes mellitus (GDM) develops in 2-10% of pregnancies annually in the United States. Adverse experiences in adolescence are associated with GDM but limited research has examined relationships between adolescent socioeconomic conditions and GDM. This analysis explored associations between objective and subjective financial deprivation and later GDM diagnosis.

Methods: Data came from Waves I and V of the National Longitudinal Study of Adolescent to Adult Health. Wave 1 income was used to identify families falling below 130% of the federal poverty level (objective deprivation). Subjective deprivation was assessed retrospectively at Wave V (ages 33-39) by asking whether, when growing up, one's family was better or worse off financially than the average family. Women reported ever receiving diagnosis of GDM at Wave V. Odds ratios (ORs) and average marginal effects (AME) of relationships between subjective and objective financial deprivation in adolescence and later GDM were obtained from logistic regressions accounting for complex survey design.

Results: The analytic sample included 651 women, 10% of whom had ever been diagnosed with GDM. Neither subjective (better off OR: 0.74, 95% CI: 0.28, 1.95; AME: -0.027, 95% CI: -0.11, 0.058; worse off OR: 1.69, 95% CI: 0.79, 3.64; AME: 0.062, 95% CI: -0.040, 0.17) nor objective (OR: 0.78, 95% CI: 0.36, 1.68; AME: -0.025, 95% CI: -0.099, 0.049) financial deprivation in adolescence were associated with later GDM. The multiplicative interaction between subjective and objective deprivation was also statistically insignificant (p=0.64).

Conclusions: While associations between adversity in adolescence and later GDM have been observed, this exploratory analysis suggests neither objective nor subjective financial deprivation in adolescence are alone or jointly associated with later GDM. Financial deprivation in the absence of other adverse childhood events may be insufficient to influence GDM risk later in life.

Social determinants of health

Prenatal Alcohol and Tobacco Exposure as a Mediator between Socioeconomic Status and Adverse Childhood Experiences Alec Yingjing Xia* Minhazul Mohsin Stefanie Bodison Deborah Jonker Eric Kan Kirsten Ann Donald Dan J Stein Elizabeth Sowell Kristina Andrea Uban

While alcohol is a known teratogen that alters cognitive, physiological, and neurobehavioral development, less is known about how the broader context of social disparities influences maternal consumption, postnatal environment, and subsequent child outcomes. Here we examine prenatal exposure to alcohol (PAE) and tobacco (PTE) as a mediator between socioeconomic status (SES) and adverse childhood experience (ACE) in a prospective birth cohort study in Cape Town, South Africa. 176 mother and child dyads were included in the analysis. PTE was grouped into no exposure and exposed, while PAE was grouped into no exposure, early exposure, and continued exposure. SES was measured by monthly household income (I) and maternal education (ME). ACE was measured by the total score of a 14-item questionnaire. Following the Baron and Kenny criteria for mediation analysis, PAE and PTE were each regressed on I and ME, respectively. ACE was then regressed on I and ME, and lastly regressed on PTE, I and ME. All analysis was performed in R. PTE was significantly associated with I (OR = 0.9989, 95% CI[0.9980, 0.9997]) and ME (OR = 0.80, 95%CI[0.64, 0.99]). On average at the same ME level, an increase in $R 200 reduced the risk of PTE by 20% (OR by 200-unit change = 0.795). ACE was significantly predicted by ME (β1= -0.31, $p <$ 0.01) and marginally significantly predicted by I (β2= – 0.0008, $p = 0.056$). The effects of I (β1= -0.0005, $p = 0.26$) and ME (β2= – 0.25, $p < 0.05$) on ACE were reduced when PTE (β3= 1.42, $p <$ 0.001) was in the model, which supported PTE as a partial mediator between SES and ACE. Our preliminary findings suggest that socioeconomic disparity partially influences early life adversity through prenatal exposure to tobacco. Further research is needed to disentangle the impact of socioecological factors on prenatal substance exposure in diverse contexts, which will inform our understanding on the differential impact of teratogenic substance use across communities.

Substance Use

Assessing Prenatal Alcohol Exposure History Among Pediatric Patients: Practices Among U.S. Primary Care Providers Janae Dunkley* Nicholas Deputy Clark Denny Jacquelyn Bertrand Shin Kim

Introduction: Documenting a history of prenatal alcohol exposure (PAE) for children enables early identification and treatment of fetal alcohol spectrum disorders (FASDs). However, little is known about how commonly PAE history is obtained by pediatric clinicians. This study examined the proportion of pediatric clinicians obtaining a PAE history and the methods used.

Methods: We analyzed DocStyles 2020 Fall survey data for 769 clinicians who see pediatric patients in the U.S. The sample was derived from 1,754 survey respondents who were active members of SERMO, a social network for clinicians. The survey included two questions about the frequency (never, sometimes, often, always) and process of obtaining PAE history for several groups of children. Frequency distributions were calculated overall and by provider type (family practitioner [FP], pediatrician, and nurse practitioner/physician assistant [NP/PA]). Chi-square and Bonferroni post hoc tests were used to determine whether frequency of obtaining a PAE history varied by specialty.

Results: Overall, PAE history was always obtained for 40.8% of children with developmental/behavioral issues, 35.2% of newborns, 32.4% of adopted/foster children, 23.7% of infants, and 20.5% of new patients. The frequency of never obtaining a PAE history was highest when pediatric clinicians saw new patients (18.3%) and infants (14.0%). More FPs (41.4%) and NP/PAs (45.2%), compared to pediatricians (29.0%, $p=0.003$ and $p=0.002$, respectively), reported often/always obtaining PAE history for new patients. A higher proportion of pediatricians (71.4%) than FPs (58.6%, $p=0.002$) reported often/always obtaining PAE history for adopted/foster children. Most respondents reported using interviews conducted by physicians or PAs to obtain PAE history (70.6%).

Conclusions: Clinicians are not routinely obtaining PAE history for pediatric patients, suggesting enhanced efforts may help increase awareness and practice supports for obtaining PAE history.

Substance Use

Preconception cannabis use and gestational diabetes mellitus (GDM): the PrePARED Brittany M., Jorge E., Erica P., Jaime, Anne Marie, Sylvia, Gita D., Sunni L., Enrique, Jeffrey G., Lauren A., Emily W. Charlton, Chavarro, Gunderson, Hart, Jukic, Ley, Mishra, Mumford, Schisterman, Shaffer, Wise, Harville*, Ke Pan Brittany M. Charlton Jorge E. Chavarro Erica P. Gunderson Jaime Hart Anne Marie Jukic Sylvia Ley Gita D. Mishra Sunni L. Mumford Enrique Schisterman Jeffrey G. Shaffer Lauren A. Wise Emily W. Harville Emily Harville

Background

Cannabis use might increase the risk of gestational diabetes mellitus (GDM) by increasing appetite and promoting fat deposition and adipogenesis. We aim to assess the association between preconception cannabis use and GDM.

Method

Individual-level data from 8 prospective studies in the PrePARED consortium were obtained. Pregnancies (with GDM status) lasting ≥20 weeks of gestation after cannabis use was first measured are referred to as the index pregnancy. GDM was exclusively self-reported in 4 studies and, in the other 4 studies, identified from medical records or a combination of self-report and medical/birth records. Pooled analysis of individual data was used using logistic regression to estimate study-type-specific odds ratios (ORs), with random effect meta-analysis to combine study-type-specific ORs. Stratified analyses assessed interaction effects between cannabis and tobacco use (never, former, and current smokers).

Results

Out of 17,880 total participants, 1,198 developed GDM in the index pregnancy. Before the index pregnancy, 12% used cannabis in the past year and 4% used more than weekly. The length of time between cannabis use measure and the start of pregnancy was 24.8±44.7 months. 57% of those who used cannabis in the past year were current/former tobacco smokers. Overall, no association between preconception cannabis use in the past year and GDM was detected (aOR=0.97, 95%CI: 0.79, 1.19) regardless of use frequency, adjusting for potential confounders. Among participants who never smoked tobacco, those who used cannabis more than weekly had a higher risk of developing GDM compared to those who did not use cannabis in the past year (aOR=2.95, 95% CI: 1.24, 7.03, p-value for interaction=0.10).

Conclusion

Preconception cannabis use might be associated with a higher risk of developing GDM among those who do not smoke tobacco. Future studies might investigate the role of concurrent use of cannabis and tobacco and potential residual confounding.

Substance Use

Preconception cannabis use, gestational hypertension, and pre-eclampsia: the PrePARED consortium Brittany M., Jorge E., Erica P., Jaime, Anne Marie, Sylvia, Gita D., Sunni L., Enrique, Jeffrey G., Lauren A., Emily W. Charlton, Chavarro, Gunderson, Hart, Jukic, Ley, Mishra, Mumford, Schisterman, Shaffer, Wise, Harville*, Ke Pan Brittany M. Charlton Jorge E. Chavarro Erica P. Gunderson Jaime Hart Anne Marie Jukic Sylvia Ley Gita D. Mishra Sunni L. Mumford Enrique Schisterman Jeffrey G. Shaffer Lauren A. Wise Emily W. Harville Emily Harville

Background

Cannabis use may affect the cardiovascular system and the development of placenta. We aim to evaluate the association between preconception cannabis use and gestational hypertension (GH) and pre-eclampsia (PE).

Method

We obtained individual-level data from 8 prospective studies participating in the PrePARED consortium. Pregnancies (with GH/PE status) lasting ≥20 weeks of gestation after first cannabis use were defined as the index pregnancy. GH/PE was exclusively self-reported in 4 studies and, in the other 4 studies, identified from medical records or a combination of self-report and medical/birth records. GH and PE were examined individually and as a combined outcome. Pooled analyses of individual data were undertaken using logistic regression to estimate study-type-specific odds ratios (ORs). Random effect meta-analysis was used to combine study-type-specific ORs. Stratified analyses assessed the association between preconception cannabis use and GH/PE depending on tobacco use status (never, former, and current smokers).

Results

Out of 18,121 total participants, 2,031 developed GH/PE in the index pregnancy. Before the index pregnancy, 15% of participants used cannabis in the past year. Among participants who used cannabis in the past year, 39% were current tobacco smokers. Overall, there was no association between cannabis use in the past year and GH/PE (adjusted odds ratio (aOR)=0.86, 95% CI: 0.66, 1.12). Among current tobacco smokers, cannabis users had a lower risk of GH compared with non-cannabis users (≤weekly cannabis use vs. no: aOR=0.38, 95% CI: 0.15, 0.96; >weekly vs. no: aOR=0.39, 95% CI: 0.11, 1.36, p-value for interaction=0.48). No association was identified among never/former tobacco smokers.

Conclusion

Preconception cannabis use was not associated with an increased risk of GH/PE during pregnancy. Future studies should investigate the role of concurrent use of cannabis and tobacco in preconception health.

Substance Use

Opioid Use During Pregnancy and Risk of Postpartum Hospital Admission in Florida

Amanda L. Elmore* Jason L. Salemi Alexander McLain Suzanne McDermott Nansi Boghossian

Background

Opioid use during pregnancy remains prevalent and has been associated with higher risk of postpartum hospital readmission. However, previous studies were limited to 90-day outcomes. We examined the association between prenatal opioid use and hospital readmission up to 5-years postpartum.

Methods

A retrospective cohort was developed using birth certificates linked to the delivery hospital administrative records in Florida (1/1/09-12/31/13). We categorized maternal opioid use for the mother-infant dyad as a binary 'Yes' or 'No', based upon the presence of a maternal opioid-related diagnoses OR an infant diagnosis of NAS. We examined the risk of all-cause maternal hospital admission from 1-2 and 2-5 years after delivery using Modified Poisson regression with doubly robust propensity score adjustment for maternal and hospital confounders. Results are presented as adjusted risk ratios (aRR) and 95% confidence intervals (CI). We also described the most frequent principal diagnoses for postpartum admissions among exposed women.

Results

Between 1-2 years after index delivery, 63% of women with prenatal opioid use had at least one hospital admission compared to 33% of the unexposed. Nearly 60% of exposed women were admitted three or more times between 2-5 years postpartum. The risk of postpartum readmission for women with opioid use was 21% higher from 1-2 years (aRR: 1.21, 95% CI: 1.18-1.24) and 14% higher from 2-5 years (aRR: 1.14, 95% CI: 1.10-1.18) compared to women without opioid use. The most common diagnoses for women with opioid use were abdominal pain, other complications of pregnancy, and disorders of teeth and jaw for both postpartum timeframes.

Conclusion

Women with prenatal opioid use had a higher risk of all-cause hospital admission and over 5 times the risk of admission for an opioid overdose or adverse effects of opioid use. Therefore, this study provides important information for the long-term postpartum management of women with prenatal opioid use.

Substance Use

Prenatal Substance Exposure on White Matter Development in Children Aged 9-10 Years

Vida Rebello* Kristina Uban

Prenatal substance exposure (PSE) including alcohol, marijuana, tobacco, and cocaine exposure causes teratogenic harm to the developing fetus. Moreover, these effects have been shown to have a lasting impact on the child's cardiovascular and neuroendocrine systems. Here, we investigate the association between PSE and structural white matter connectivity in the parahippocampal cingulum and the cortico-spinal/pyramidal tracts. These tracts are responsible for memory, movement, and spatial processing.

Methods

Baseline measures of four diffusion tensor imaging brain metrics (Average Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD), and Fiber Volume (FV)) were assessed in 7867 participants aged 9-10 in the ongoing Adolescent Brain Cognitive Development (ABCD) cohort. Linear mixed-effects models were performed on bilateral regions of interest to evaluate the association between PAE and white matter connectivity adjusting for key covariates.

Results

Based on our analyses on exposed vs non-exposed participants (N= 7728), we saw asymmetrical differences in white matter connectivity. Compared to exposed children, children with no PSE had a higher fiber volume ($46.6mm^3$, $p< 0.01$) seen in the parahippocampal and right corticospinal tract seen unilaterally in the right hemisphere.

Conclusion

Prenatal exposure to substances was associated with lower fiber volume suggesting that exposure to these substances during critical periods of development may have important implications for children's neurological health.

Women’s health

Vitamin D and uterine fibroid development: a prospective study Quaker Harmon* Stacy Patchel Sheri Denslow Frankie LaPorte Donna Baird

Fibroids are benign tumors with significant morbidity. Black women have a high burden of disease with onset 10 years earlier than White women and 3 times higher rates of hysterectomy. Laboratory investigations and cross-sectional epidemiological studies suggest that vitamin D may offer protection from fibroid development. We assessed the association between repeated measures of serum 25-hydroxyvitamin D [25(OH)D] and fibroid growth, incidence, and loss in the Study of Environment, Lifestyle & Fibroids (SELF). SELF followed 1,610 women self-identified as “African American” or “Black”, ages 23-35 from the Detroit, Michigan area with ultrasound every 20 months for 4 visits (5 years). Serum 25(OH)D was assayed at every visit and categorized with clinical cut points: 73% had deficient 25(OH)D (<20ng/ml) at enrollment. Fibroid growth, scaled to 18-months, was estimated for individual fibroids as the difference in log-volume between visits. Women with incident fibroids (n=294) were identified among those who were fibroid free at enrollment (n=1230). Fibroid loss was defined as a reduction in fibroid number between two successive visits. All statistical models used time-varying annual mean 25(OH)D, accounted for within-woman and within-fibroid correlations, and adjusted for time-varying demographic, reproductive, fibroid related and contraceptive factors. Higher 25(OH)D (≥20ng/ml) was associated with a 10% reduction in fibroid growth (95% Confidence Interval (CI) -17, -1) compared to 25(OH)D <20ng/ml. Suggestive associations for fibroid incidence and loss were observed when comparing participants with 25(OH)D ≥30ng/ml at the prior visit to those with 25(OH)D <30ng/ml: fibroid incidence [hazard ratio 0.8 (95% CI 0.5, 1.3)] and fibroid loss [risk ratio 1.3 (95% CI 0.9, 1.8)]. The results provide support for the hypothesis that vitamin D can reduce fibroid development, but are limited by the few women with a 25(OH)D measurement ≥30ng/ml (only 8% of measurements).

Women’s health

Soy-based infant formula feeding and uterine fibroid incidence in a prospective ultrasound study of African American women Christine R. Langton* Quaker E. Harmon Kristen Upson Donna D. Baird

Uterine fibroids are highly prevalent, benign tumors and the leading indication for hysterectomy. African American women are disproportionally burdened by fibroids, and few established risk factors have been identified. Exposure to exogenous estrogens during sensitive developmental windows may adversely affect reproductive systems. Soy-based infant formula contains phytoestrogens; in animal studies, postnatal administration of phytoestrogens has demonstrated detrimental effects on uterine development that persists into adulthood including increased fibroid risk in the Eker rat. Limited prior epidemiologic studies also have suggested increased fibroid development with soy formula infant feeding.

We evaluated the association between soy formula feeding and fibroid incidence among African American women aged 23-35 years in the Study of Environment, Lifestyle & Fibroids (SELF). Soy formula was assessed via an early life questionnaire administered to the participant’s mother when she was available (89% of analytic sample). A standardized ultrasound examination was conducted during 4 clinic visits over 5 years to detect fibroids ≥0.5 cm in diameter. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs for the association between soy formula feeding and incident fibroids adjusted for early life and adult factors.

Of 1,121 fibroid-free participants at baseline, 150 (13%) were ever fed soy formula as infants and 269 (24%) developed incident fibroids. We did not observe an association between ever being fed soy formula and incident fibroid risk (HR = 1.08; 95% CI: 0.75, 1.54). However, participants fed soy formula within 2 months of birth and for >6 months (n=53) (vs. never fed soy formula), had an elevated risk of fibroid incidence (HR = 1.56; 95% CI: 0.92, 2.65).

Results from this first ultrasound-based, prospective fibroid study add support to prior data suggesting increased fibroid incidence among women fed soy formula early in infancy.

Women’s health

Postpartum mental health among women with common pregnancy conditions Katherine Ahrens* Kristin Palmsten Mariah Pfeiffer Catherine Gelsinger Heather Lipkind Christina Ackerman

Background: Postpartum mental health disorders are common, serious, and can affect the health and wellbeing of the entire family. The objective of our analysis was to estimate the risk of having a new mental health diagnosis in the first 24 months postpartum among women with common pregnancy conditions.

Methods: We used the Maine All Payer Claims Database to identify women with deliveries during 2007-2019 (n=123,125). We estimated the cumulative hazard of being diagnosed with each of the following in the first 24 months since delivery: depression, anxiety, bipolar disorder, posttraumatic stress disorder (PTSD), and schizophrenia/psychotic disorder. We used Cox models to estimate hazard ratios (HR) for prenatal depression, gestational diabetes, and hypertensive disorders of pregnancy (separately), adjusting for maternal demographics and pregnancy characteristics. Observations were censored upon loss of health insurance coverage, start of next pregnancy, or at 24 months, whichever came first; those with pre-existing mental health diagnoses were excluded.

Results: The cumulative hazard of being diagnosed in the first 24 months since delivery with depression was 29%, anxiety 25%, bipolar disorder 3%, PTSD 6%, and schizophrenia/psychotic disorder 1%. Women with prenatal depression were at higher risk of having a postpartum mental health diagnosis (adjusted HRs ranged from 2.7 to 4.0). Risks of having depression and anxiety were modestly higher among women with hypertensive disorders of pregnancy (aHR= 1.2 and aHR=1.1) and having anxiety was higher among those with gestational diabetes (aHR=1.1).

Conclusion: The cumulative hazard of being diagnosed with a new mental health condition in the first two years following delivery is substantially elevated among women with prenatal depression. Effective interventions aimed at preventing, screening, and treating mental health conditions among women with pregnancy complications for an extended time postpartum are warranted.

Women’s health

Vitamin D status and markers of inflammation, iron deficiency, and anemia in a cohort of reproductive-age women Kristen Upson* Parminder Suchdev Lisa Tussing-Humphreys Elizabeta Nemeth Quaker Harmon Gregory Travlos Ralph Wilson Donna Baird

Vitamin D may decrease the risk of iron deficiency and anemia by decreasing proinflammatory cytokines, which in turn suppresses hepcidin expression and increases iron bioavailability for erythropoiesis and hemoglobin synthesis. We examined vitamin D status and markers of inflammation, iron deficiency, and anemia in an epidemiologic cohort of women. We used enrollment data from the Study of Environment, Lifestyle & Fibroids, a cohort of 1,693 Black women ages 23-35 years who reside in the Detroit, Michigan area. Among a subset of 1,214 non-pregnant, never smokers, data were available on serum 25-hydroxyvitamin D (25(OH)D), serum C-reactive protein (CRP) (inflammation marker), serum ferritin (SF), and blood hemoglobin (Hgb) concentrations. Since SF is an acute phase reactant, we adjusted SF concentrations for CRP using a recommended regression correction approach. We defined elevated CRP, iron deficiency, and anemia as follows: CRP ≥5 mg/L, adjusted SF<15 µg/L, and Hgb <12 mg/dL; 25(OH)D was categorized in quartiles. Log-binomial regression was conducted to estimate the prevalence ratio (PR) and 95% CI for the association between 25(OH)D quartiles and elevated CRP, iron deficiency, and anemia, adjusting for age, education, passive cigarette smoke exposure, birth in last year, and current hormonal contraceptive method use. We observed a 20% lower prevalence of elevated CRP with higher 25(OH)D concentrations (top vs. lowest quartile: PR 0.80, 95% CI: 0.64, 1.00). The highest quartile of 25(OH)D concentrations (vs. lowest) was associated with a 42% decreased prevalence of iron deficiency (PR 0.58, 95% CI: 0.41, 0.81) and a 39% decreased prevalence of anemia (PR 0.61, 95% CI: 0.47, 0.78). These results are consistent with the proposed role of vitamin D in ameliorating inflammation, iron deficiency, and anemia, and supports further investigation into vitamin D as a potential intervention to improve iron status and anemia in women.

Women's health

Pregnancy complications in last pregnancy and mothers' long-term mortality risk: do relations differ from that of first pregnancy? A population-based study Abdu Seid*

Pregnancy complications in last pregnancy and mothers' long-term mortality risk: do relations differ from that of first pregnancy? A population-based study

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Background: Studies have shown that women with pregnancy complications in first pregnancy are at increased risk of later cardiovascular (CVD) morbidity and mortality. However, there is little knowledge about complications in the last pregnancy and later CVD. We therefore studied complications (preeclampsia, preterm, and small for gestational age) in women's last pregnancy and maternal CVD death, after accounting for the women's complete reproduction. **Data and Methods**: In this nationwide population-based cohort study, we used registry-based data from the Medical Birth Registry of Norway (1967-2020) linked to the national Cause of Death Registry. We followed mothers whose first birth was during 1967-2013, from the date of last childbirth until death or December 31st 2020, whichever occurred first. Cox proportional hazards regression was used to analyze risk of CVD death between 40 and 69 years of age, according to pregnancy complications and number of lifetime births, adjusting for maternal age at birth and education, and focusing first and last pregnancy. **Results**: Women with complications in their pregnancy were at higher risk for premature CVD death compared to mothers with two lifetime births and no complications. The higher risk for premature CVD death was particularly evident among women with a complication only in the last than women with a complication in the first pregnancy only.

Conclusions: The risk for premature CVD death was higher among mothers who end their reproduction with a complicated pregnancy than women without complications and women with complications in their first pregnancy.

Women’s health

The association between ADHD, pregnancy, and induced abortion in girls and young women Jacqueline M- Cohen* Maria C. Magnus Kari Furu Øystein Karlstad Chaitra Srinivas Olga Basso

Background: Attention-deficit/hyperactivity disorder (ADHD) is defined by symptoms of inattention and hyperactivity-impulsivity that interfere with social, academic, or occupational functioning. The impulsivity associated with ADHD might lead to more unplanned pregnancies and induced abortions.

Objective: To determine if young women with ADHD have higher rates of pregnancy and induced abortion than their peers without ADHD.

Methods: We identified all women ages 15-30 living in Norway from 2010-2020. We defined ADHD as having filled two or more prescriptions for ADHD medication at any time from 2004-2020. Pregnancies, including spontaneous and induced abortions, and births were identified from registers of primary and specialist healthcare, and the Medical Birth Registry. We estimated risk ratios (RRs) and 95% confidence intervals (CIs) for having a pregnancy or induced abortion by Poisson regression comparing people with and without ADHD, separately for ages 15-19, 20-25, and 26-30, adjusted for birth year and country of birth. We also estimated the proportion of pregnancies that resulted in an induced abortion at each age.

Results: Our study population included 937,791 women born 1979-2005 and 3.1% had ADHD. Those with ADHD were more likely to become pregnant at ages 15-19 (RR 2.4, 95% CI 2.2-2.5), and 20-25 (RR 1.4, 95% CI 1.4-1.5), but less at ages 26-30 (RR 0.7, 95% CI 0.7-0.8). However, those with ADHD were more likely to have an induced abortion in all three age groups: RRs 2.2, 1.7, 1.8. Individuals with ADHD were as likely as peers to choose to have an abortion if they became pregnant before age 22, and more likely if they became pregnant at later ages (30% versus 10% at age 30).

Conclusions: Girls and women with ADHD are at increased risk of experiencing an induced abortion. This suggests a need for more public health attention to these individuals to improve contraceptive use and reduce the rates of unplanned pregnancies.

Women’s health

Will reproductive age women participate in a follow-up study 10 to 14 years after initial study enrollment? Findings from the Effects of Aspirin in Gestation and Reproduction (EAGeR) Follow-up Study May Shaaban* Zachary Shepelak Joseph Stanford Enrique Schisterman Stefanie Hinkle Sunni Mumford Robert Silver Karen Schliep

Background: Our primary goal was to assess the feasibility of recruiting women and offspring to study key relationships between maternal reproductive health exposures and subsequent health outcomes 10–14 years after initial study participation.

Methods: The EAGeR trial (2007–2011) was a longitudinal randomized control trial enrolling 1228 women who had one to two prior pregnancy losses and were actively trying to conceive. Follow-up recruitment focused on EAGeR participants from Utah (n=999). Between 05/01/2020 and 07/01/2021, multiple outreach strategies were utilized, including email, text, postal mail, and phone calls. Study participants completed a short online questionnaire on reproductive, cardiometabolic, and respiratory health. Amazon gift cards ($10) were emailed to participants after completion.

Results: Sixty-five percent (649/999) of women have participated in the follow-up study, with 70% (347/499) participating who had a live birth during the EAGeR trial, and 60% (302/500) among women who did not have a live birth; 2% (n=23) opted out. The most successful recruitment method was a personalized email with a questionnaire link followed by 3 follow-up reminder emails (421 [42%] completions). Postal mail (1.4%), text (5.4%), and call (16.0%) campaigns beyond the initial emails resulted in 228 additional completions but required significantly more time and cost than the email campaign.

Conclusions: Despite no communication with EAGeR participants between the end of the original trial and the start of the follow-up study, we show relatively high feasibility with 65% of women participating and only 2% opting out. Next steps to reach >80% recruitment goal (150 additional women of 330 still eligible) include chart review to obtain current contact information after securing IRB approval. This work demonstrates the feasibility of recruiting participants for long-term follow-up after studies; additional work is needed to determine strategies for improved reach.