



Eunice Kennedy Shriver National Institute
of Child Health and Human Development



2020 ANNUAL REPORT

**Division of Intramural
Population Health
Research, NICHD**

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MESSAGE FROM THE DIRECTOR

The mission of the Division of Intramural Population Health Research (DIPHR) is to conduct research leading to the promotion of population health and well-being.

2020 was a year like no other due to the circumstances of the COVID-19 pandemic, which affected the Division similarly to many academic and research centers across the United States and around the world. The extreme situation forced a sudden shift in how the Division operates. In March 2020, the NIH began encouraging staff to take advantage of workplace flexibilities, including expanded telework. Since then, everyone has been required to work remotely, with unparalleled restrictions on in-person interaction and under unique conditions of uncertainty—not to mention the overwhelming impact on daily lives. At the time these contingency measures were initiated, I had been serving as Acting Director of DIPHR for barely a month. The NICHD Director Dr. Diana Bianchi entrusted me to take on this role after Dr. Constantine Stratakis stepped down from the position in February 2020.

DIPHR has addressed and adapted to the disruptions from the pandemic, aspiring to be as close to seamless as possible in the virtual setting. Thanks to the industrious activities of all the members of the Division, records of research productivity, collaboration, external engagement, service, and training remained strong. We continue to accomplish our mission by conducting innovative etiologic and interventional studies from preconception through adulthood, while working to translate our discoveries into clinical practice and public policy to maximize health and eliminate health disparities. While these aims are ambitious, we readily embrace the undertaking by working in trans-disciplinary research teams across Branches and with extramural partners to achieve the Division's overarching goal of ensuring the health vulnerable populations, e.g., pregnant women, infants, and children. The scientists in the

Division distinguish themselves by actively mentoring a variety of fellows at varying professional stages (i.e., post-baccalaureate through post-doctoral) and by generously providing their expertise throughout the NICHD and the NIH, to professional societies, and to other governmental agencies and research entities.

Our 2020 Annual Report reinforces the commitment of the scientists in the Division to providing evidence-based guidance and highlights recent discoveries on key topics such as helping couples conceive and have a healthy infant born at term; identifying behaviors, lifestyles and environmental factors associated with healthy pregnancies and optimal fetal growth; developing guidance for healthy eating commencing in childhood; making advances in identifying the onset and timing of risky adolescent behaviors that may continue into early adulthood; and elucidating the developmental and social determinants of mental health and health disparities. Among the noteworthy findings from research published last year are the following:

- Opioid use among women trying to conceive is associated with a lower chance of pregnancy and a greater chance of pregnancy loss (Flannagan *et al.*, 2020).
- Maternal immune activity during pregnancy can affect developmental disparities in attention, emotion, and behavior regulation of the offspring (Yu *et al.*, 2020).
- Postpartum depression can persist for an extended period: about 1 in 4 women experienced high levels of symptoms at some point in the three years after giving birth (Putnick *et al.*, 2020).



Jagteshwar (Una) Grewal,
Ph.D., M.P.H.,
Acting Division Director

▼▼▼ Office of the Director

- Vegetarian diets during pregnancy are associated with low birth weight, but not a higher risk of preterm birth or other medical complications (Yisahak *et al.*, 2020)
- Youth who engaged in regular, more frequent driving practice sessions during the learner period had a 39% lower crash risk in the first year after receiving their permanent licenses, compared to youth who practiced less frequently (Ehsani *et al.*, 2020).

Both the DIPHR and NICHD strategic plans reference the importance of research having practical impacts. In keeping with these directives, a signature achievement is the translation of the findings from the NICHD Fetal Growth Studies - Singletons and Twins into online calculators that estimate [fetal growth](#) and [fetal growth velocity](#) percentiles, taking into account racial and ethnic variations to provide more accurate estimates than conventional growth charts. Finally, the Division emphasizes reproducible research and was an early pioneer in building interfaces for sharing data from studies with the public. We encourage the broader scientific community, from students to established professionals, to capitalize on the information resources made available via the online data-sharing platforms of DIPHR ([BRADS](#)) and the NICHD ([DASH](#)).

In reflecting on the last year, I am honored to have the opportunity to be the Acting Division Director and steer DIPHR through a significant period of transition and crisis. I am proud and appreciative of all my colleagues for their extraordinary work in meeting the mission and supporting me and one another during these challenging times. We are also grateful to the NICHD Director Dr. Bianchi and the Acting Scientific Director Dr. Mary Dasso for everything they do to foster the accomplishments of the Division. Looking forward to 2021 and beyond, our steadfast goal is to be good stewards and contribute to maximizing health across the lifespan of the populations we serve.

Please visit DIPHR's [website](#) for information about our research, collaborations, service, training, and career opportunities. [Comments](#) or [questions](#) about the Division are welcome!

Sincerely,

Una Grewal, Ph.D., M.P.H.
Acting Director, DIPHR, NICHD

The Division of Intramural Population Health Research (DIPHR) comprises the Office of the Director, which provides administrative oversight and support for its three intramural research branches - Biostatistics and Bioinformatics Branch, Epidemiology Branch, and Social and Behavioral Sciences Branch - and the Contraceptive Development Program.



In February 2020, the NICHD Director Dr. Diana Bianchi, appointed **Dr. Una Grewal** as the Acting Division Director after Dr. Constantine Stratakis stepped down from the position. In this role, Dr. Grewal provides managerial leadership and scientific administration in cross-cutting areas such as personnel, budgets, contracting, facilities, and professional development – spanning standard practices to crisis response. As a perinatal epidemiologist, Dr. Grewal has been at the forefront of multiple novel, large-scale research initiatives as a Co-Investigator for the [NICHD Fetal Growth Studies](#) (and *Principal Investigator for the Dietary Patterns during Pregnancy* component) and a Co-Principal Investigator for the [Consortium on Safe Labor](#). Findings from the NICHD Fetal Growth Studies revealed differences in fetal growth and individual fetal parameters by self-reported maternal race/ethnicity as early as 10-16 weeks gestation (PMCID: [PMC4584427](#)). These findings indicate that assessment of fetal growth by ultrasound should be evaluated using racial/ethnic-specific standards to bolster early detection of potential abnormalities, minimize misclassification of minority fetuses, and avoid unnecessary interventions. Meanwhile, central findings from the Dietary Patterns during Pregnancy show that most pregnant women in this contemporary cohort reported dietary intakes that, on average, did not meet US Dietary Guidelines for nonpregnant individuals. Moreover, diet differed across racial/ethnic groups, with non-Hispanic Black women having the lowest overall dietary quality in all trimesters (PMCID: [PMC7846139](#)).

At present, Dr. Grewal serves as collaborator for two significant ongoing research initiatives: (1) The [NICHD Fetal Growth 3D Study](#) which relies on ultrasound images collected as a part of the NICHD Fetal Growth Studies to establish standards for fetal body composition and organ volumes, and (2) The [Genetic Epidemiology of Early Growth and Cardiometabolic Diseases](#) which uses the genome-wide data generated from biospecimens collected by the NICHD Fetal Growth Studies to investigate genetic mechanisms in longitudinal fetal growth variations and the contribution of genetic ancestry for fetal growth differences among populations.



Dr. Jennifer Weck is a Scientific Program Specialist who received her Ph.D. in molecular physiology. She oversees the Division's biospecimen collection and assay protocols to support scientific projects. Dr. Weck is the Chair of the [Division's Biospecimen Repository Access and Data Sharing \(BRADS\)](#) program, which provides access to the Division's data and biospecimens for secondary research. Additionally, Dr. Weck serves as the Contracting Officer's Representative for the Division's support laboratories and for the NICHD Biospecimen Repository. Dr. Weck is an active member of the NIH IRB and a core committee member of the NICHD Data and Specimen Hub (DASH).

STAFF

Jagteshwar (Una) Grewal,
Ph.D., M.P.H.,
Acting Division Director

Adrienne Lonaberger,
Program Analyst

Jennifer Weck, Ph.D.,
Laboratory Health Specialist

FELLOWS

Samrawit Yisahak, Ph.D.,
Postdoctoral Fellow

The mission of the Biostatistics and Bioinformatics Branch (BBB) is to:
1) conduct original biostatistical and bioinformatics and collaborative public health research pursuant to the mission of the Division and Institute; 2) recruit, mentor and provide training to Division fellows at various career stages to position them for professional research careers; and 3) provide service to the Division, Institute, NIH, and other professional and government organizations to advance the scientific discipline of biostatistics and the goals of the Institute.

The collaborative research component of the BBB's requires intimate understanding of the scientific issues and state-of-the-art statistical methodology relevant to the scientific problem. Therefore, investigators within BBB play a key role in all aspects of the study. The independent biostatistical and bioinformatics research of BBB is often born from the design and analytic challenges faced in these collaborations. An important component of our collective methodological research is the translation of our novel methodology back to the NICHD scientific constituents through the development of software using free-ware (e.g., R package) and in presenting our work at major scientific meetings.

In 2020, BBB made contributions in traditional areas of biostatistics, such as Bayesian methods, longitudinal data analysis, survival analysis and methods for biomarker data, and expanded the research scope into emerging areas of biostatistics and computational statistics. For example, deep learning and other machine learning methods were developed and applied to gynecology and obstetrics. This methodology was specifically developed to characterize risk for prolonged second stage of labor using over 70 features. Inexpensive, group testing strategy was developed to estimate diagnostic accuracy of biomarkers, such as breath volatile organic compounds, for infectious diseases such as COVID19, reducing assay costs and dramatically reducing the number of specimens to be assayed. Also, a Bayesian methodology was

developed by our staff to evaluate mediation effects of multiple exposures on time to pregnancy.

The BBB also began the process of expansion by recruiting Dr. Peddada as the Chief and transferring Dr. Perkins, a staff scientist, from the Epidemiology Branch and in doing so added expertise in constrained statistical inference, statistical methods in microbiome and genomics and in the areas of pooling designs, missing value and measurement errors and biomarker research, respectively. The BBB is in the process of recruiting additional staff during the next few years in modern and emerging areas of biostatistics and bioinformatics, such as genomics, microbiome, causal inference, analysis of high dimensional data.

BBB investigators are involved in all aspects of the study from its earliest concept, including study design, implementation, ongoing quality control, and analysis. We are also involved in collaborations with Division of Intramural Research (DIR) investigators as well as with extramural staff in and outside NICHD. Further, we serve on important NIH and external committees such as the NICHD's Institutional Review Board, the NIH Biometry and Epidemiology Tenure Advisory Panel, and numerous Data and Safety Monitoring Boards for the NIH. BBB investigators serve as associate editors on a number of the top biostatistics' journals. BBB investigators also serve as editorial board members of leading substantive journals including Clinical Trials and Fertility and Sterility.



Shyamal Peddada, Ph.D.,
Branch Chief

STAFF

Shyamal Peddada, Ph.D.,
Senior Investigator and Chief

Aiyi Liu, Ph.D.,
Senior Investigator

Rajeshwari Sundaram, Ph.D.,
Senior Investigator

Zhen Chen, Ph.D.,
Senior Investigator

Neil J. Perkins, Ph.D.,
Staff Scientist

FELLOWS

Soutik Ghosal, Ph.D.,
Postdoctoral Fellow

Ruijin Lu, Ph.D.,
Postdoctoral Fellow

Abhisek Saha, Ph.D.,
Postdoctoral Fellow

Shyamal Peddada, Ph.D.

Since joining the branch in July 2020, Dr. Peddada's research focused on developing general novel statistical methods for analyzing complex biomedical data generated by researchers at NICHD. Some areas of his research include methods for nonlinear associations between exposures and hormonal changes during fetal development, methods for detecting synergy between two or more treatments (also called the "Bliss independence"), methods for compositional data with applications, human microbiome, and CRISPRi. Using the general statistical framework developed in his recent publication Lin and Peddada (2020, Nature Communications), he is developing methodology for describing nonlinear relationships among microbes in a microbiome data.

Increasingly, researchers are discovering that the microbiome plays a critical role in human health and disease, such as obesity, cardiovascular disease, metabolic syndrome, HIV, depression, anxiety, and so on. This is not entirely surprising because humans have at least 10 times more microbial cells than human cells and from 100 to 1 million times more microbial genes than human genes. Thus, together with genetics, external environment, epigenetics, the human microbiome is associated with our health and disease. Ongoing research includes assessment of effects of maternal diet during pregnancy on the maternal gut microbiome at delivery, effects of antibiotics and mode of delivery on infant gut microbiome over time, and effect of some environmental chemicals on oral microbiome.



Shyamal Peddada, Ph.D.,
Senior Investigator and Chief

STAFF

Neil J. Perkins, Ph.D.,
Staff Scientist

KEY PUBLICATIONS

Lin H and **Peddada, SD**. Analysis of compositions of microbiomes with bias correction. *Nature Communications*, 2020;11(1), 3514. PMID: 32665548.

Iszatt N, Janssen S, Lenters V, Dahl C, Stigum H, Knight R, Mandal S, ... **Peddada SD**, & Eggesbø M. Environmental toxicants in breast milk of Norwegian mothers and gut bacteria composition and metabolites in their infants at 1 month. *Microbiome*. 2019;7(1), 34. PMID: 30813950. PMCID: PMC6393990.

Aiyi Liu, Ph.D.

Dr. Liu's research in 2020 focused on developing innovative group testing methodologies for assessment of the diagnostic accuracy of biomarkers used for diagnostic or prediction of an infectious disease such as the COVID-19 virus, and methods for designing and analysis of dietary intervention studies for episodically consumed foods such as fruits, vegetable, and whole grains. An example of each is listed below.

To effectively combat the spreading of an infectious disease during a pandemic such as the current one with COVID-19, it

"In screening for an infectious disease, group testing methods not only drastically save cost and time, but also can substantially improve statistical precision."

is critical that individuals who are infected be identified and treated as quickly as possible. Cost-effective and time-efficient methods include using group testing strategy for laboratory-based tests and using convenient biomarkers

such as volatile organic compounds (VOC) from exhaled breath to identify infected individuals. A novel nonparametric statistical method was developed to efficiently evaluate the diagnostic accuracy of a biomarker for virus infection which is being tested using group testing strategy. When the virus infection rate in a population is relatively low, using group testing strategy not only drastically reduces the cost and time for testing for the virus, but could also substantially improves statistical precision for estimation of the biomarker's diagnostic accuracy, in terms of its receiver operating characteristic (ROC) curve and their area (AUC) under the curve.

Design and analysis of dietary intervention studies for episodically consumed foods

Dietary intervention studies often target episodically consumed foods such as fruits, vegetable, and whole grains. These studies often generate data concerning the amount of consumption of such foods are often semicontinuous, characterized by a sizable number of zeros due to non-consumption. These zeros need to be properly accounted for when calculating sample sizes to ensure that the study is adequately powered to detect a meaningful intervention effect size. Nonetheless, methods that are common for continuous outcomes are typically used to compute the sample sizes, resulting in a substantially under- or overpowered study. Sample size formulae are derived for detecting the mean difference in the amount of intake of an episodically consumed food between an intervention and a control group for dietary intervention studies that target episodically consumed foods. The formulae are appropriate for estimating the sample sizes needed to achieve the desired power for the study.



Aiyi Liu, Ph.D.
Senior Investigator

KEY PUBLICATIONS

Zhang W, **Liu A**, Li Q, Albert PS. Nonparametric estimation of distributions and diagnostic accuracy based on group-tested results with differential misclassification. *Biometrics*. 2020;76:1147-1156. PMID: 32083733.

Zhang W, **Liu A**, Zhang Z, Nansel T, Halabi S. Best (but oft-forgotten) practices: sample size and power calculation for a dietary intervention trial with episodically consumed foods. *American Journal of Clinical Nutrition*. 2020;112:920-925. PMID: 32644103.

Rajeshwari Sundaram, Ph.D., M.Stat.

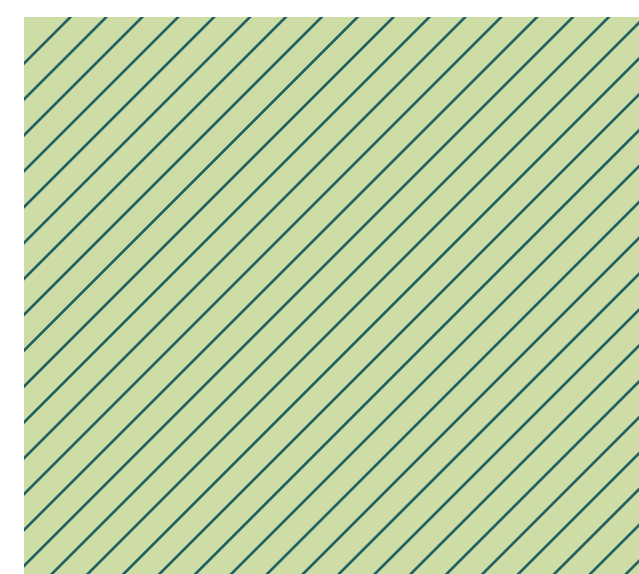
In 2019, Dr. Chen continued his methodological research in diagnostic accuracy, causal inference, and latent class modeling. In diagnostic accuracy, Dr. Chen worked on developing receiver operating characteristic regression techniques in the placement-value framework; in causal inference, Dr. Chen and his collaborators developed a regularized mediation approach to intergenerational association studies; in latent class modeling, Dr. Chen initiated an extended hidden Markov modeling approach for dyads that allows for varying perceptions between members of the dyads. In total, Dr. Chen published 7 statistical methodological papers in top statistical journals including Biometrics and Statistics in Medicine. In addition to his methodology work, Dr. Chen also had a productive year in collaborative research, including 6 publications on subject-specific journals including Journal of the American Medical Association and American Journal of Epidemiology. Two examples of Dr. Chen's 2019 work are listed below.

Modeling placement values in the analysis of receiver operating characteristic curves

Recent advances in receiver operating characteristic (ROC) curve analyses advocate modeling of placement value (PV), a quantity that measures the position of diseased test scores relative to the healthy population. Compared to traditional approaches, this PV-based alternative works directly with ROC curves and is attractive when assessing covariate effects on, or incorporating a priori constraints of, ROC curves. Several distributions can be used to model the PV, yet little guidelines exist in the literature on which to use. Through extensive simulation studies, we investigate several parametric models for PV when data are generated from a variety of mechanisms. We discuss the pros and cons of each of these models and illustrate their applications with data from a study of prenatal ultrasound examinations and large-for-gestational age birth.

Bayesian regularized mediation analysis with multiple exposures

Mediation analysis assesses the effect of study exposures on an outcome both through and around specific mediators. While mediation analysis involving multiple mediators has been addressed in recent literature, the case of multiple exposures has received little attention. With the presence of multiple exposures, we consider regularizations that allow simultaneous effect selection and estimation while stabilizing model fit and accounting for model selection uncertainty. In the framework of linear structural-equation models, we analytically show that a two-stage approach regularizing regression coefficients does not guarantee a unimodal posterior distribution and that a product-of-coefficient approach regularizing direct and indirect effects tends to penalize excessively. We propose a regularized difference-of-coefficient approach that bypasses these limitations. Using the connection between regularizations and Bayesian hierarchical models with Laplace prior, we develop an efficient Markov chain Monte Carlo algorithm for posterior estimation and inference. Through simulations, we show that the proposed approach has better empirical performances compared to some alternatives. The methodology is illustrated using data from two epidemiological studies in human reproduction.



Rajeshwari Sundaram,
Ph.D., M.Stat.,
Senior Investigator

STAFF
Abhisek Saha, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS
Mills JL, Reische EC, Kannan K, Gao C, Shaw GM, **Sundaram R**, Newborn Iodine Status Is Not Related to Congenital Hypothyroidism, *The Journal of Nutrition*. 2020 Sep 1;150(9):2429-2434. PMID: 32633779. doi: 10.1093/jn/nxaa178. PMID: 32633779.

Trinh M, **Sundaram R**, Robinson SL, et al. Association of Trajectory and Covariates of Children's Screen Media Time. *JAMA Pediatrics*. 2020;174(1):71-78. PMID: 31764966.

Zhen Chen, Ph.D.

In 2020, Dr. Chen continued his methodological research in diagnostic accuracy, causal inference, and latent class modeling. In diagnostic accuracy, Dr. Chen worked on developing receiver operating characteristic regression techniques in the placement-value framework; in causal inference, Dr. Chen and his collaborators developed a regularized mediation approach intergenerational association studies; in latent class modeling, Dr. Chen extended hidden Markov modeling approach for dyads that allows for varying perceptions between members of the dyads. In total, Dr. Chen published 2 statistical methodological papers on statistical. In addition to his methodology work, Dr. Chen also had a productive year in collaborative research, including 7 publications on subject-specific journals. Two examples of Dr. Chen's 2020 work are listed below.

A note on modeling placement values in the analysis of receiver operating characteristics curves

Recent advances in receiver operating characteristic (ROC) curve analyses advocate modeling of placement value (PV), a quantity that measures the position of diseased test scores relative to the healthy population. Compared to traditional approaches, this PV-based alternative works directly with ROC curves and is attractive when assessing covariate effects on, or incorporating a priori constraints of, ROC curves. Several distributions can be used to model the PV, yet little guidelines exist in the literature on which to use. Through extensive simulation studies, we investigate several parametric models for PV when data are generated from a variety of mechanisms. We discuss the pros and cons of each of these models and illustrate their applications with data from a study of prenatal ultrasound examinations and large-for-gestational age birth.

Intergenerational associations between maternal diet and childhood adiposity: A Bayesian regularized mediation analysis

Growing evidence supports a positive association between childhood obesity and chronic diseases in later life. It is also suggested that childhood obesity is more prevalent for children born from pregnancies complicated by metabolic disorders such as gestational diabetes and can be related to maternal dietary factors during gestation. Extending conventional analyses that report only the marginal associations within non-causal-mediation frameworks, we present mediation analysis in the case of multiple exposures and multiple mediators using a regularized two-stage approach. By placing shrinkage priors on each parameter relating to direct and indirect effects, a parsimonious model can be obtained, and consequently, the most relevant pathways will be selected to inform the development of efficient prevention programs. We apply this method to data from the Danish site of the Diabetes & Women's Health Study, Danish National Birth Cohort (DNBC) and find 6 significant maternal risk factors either directly or indirectly affecting childhood body mass index z score at age 7. Simulations with data generating mechanisms similar to the DNBC data demonstrate good performance of the proposed model.



Zhen Chen, Ph.D.,
Senior Investigator

STAFF
Soutik Ghosal, Ph.D.,
Postdoctoral Fellow

Ruijin Lu, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS
Wang YB, Zhang CL, **Chen Z.**
Intergenerational associations between
maternal diet and childhood adiposity:
A Bayesian regularized mediation analysis.
Statistics in Biosciences, in press.

Chen Z, Ghosal S. A note on modeling
placement values in the analysis of
receiver operating characteristics curves.
Biostatistics and Epidemiology. 2020.
DOI: 10.1080/24709360.2020.1737794.

▼ Epidemiology Branch ▼ ▼ ▼

In 2020, the Epidemiology Branch of the Division of Intramural Population Health Research continued to pursue its threefold mission: 1) to plan and conduct investigator-initiated original epidemiologic research focusing on reproductive, pregnancy, and infant and child health endpoints to identify etiologic mechanisms, at-risk subgroups, and interventions aimed at maximizing health and preventing, diagnosing, and/or treating disease; 2) to provide service to the Division, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Department of Health and Human Services, and the profession via consultation, collaboration, and assistance to advance the scientific discipline of epidemiology and the goals of the Institute; and 3) to recruit highly qualified students at various stages of their professional careers for training in reproductive, perinatal, pediatric, and methodological epidemiologic research.

The Branch is organized around key life course areas of epidemiologic research, from reproductive health, to pregnancy, infant and child health, in addition to research in epidemiologic methods. The Branch conducts team science and is committed to using trans-disciplinary, cutting-edge techniques to address critical data gaps in these areas while advancing the Division and Institute's mission. Current Epidemiology Branch initiatives are furthering our understanding of health challenges in several areas. In reproductive health, the Epidemiology Branch is focused on clinical trials designed to evaluate inexpensive interventions to improve reproductive health and fertility in men and women, including recent completion of the largest clinical trial focused on male fertility. The Branch also investigates the effects of diet and lifestyle on male and female reproductive health, representing another area for major potential public health impact for couples seeking pregnancy. Moreover, in the field of pregnancy and fetal development, the Branch studies the genetic and environmental determinants, etiology, and health consequences of adverse outcomes including gestational

diabetes, alterations in fetal growth of both singletons and twins in relation to obesity and pregnancy complications, and the impact of air pollution on pregnant women and their offspring. To advance understanding of infant and child health, Branch investigators also focus on the genetic and lifestyle determinants of birth defects through strategic collaborations, and the impacts of conception using assisted reproductive technologies on subsequent child growth, development, and cardiovascular health. In addition, Branch investigators continue to lead research efforts on life course epidemiology to investigate the long-term health implications of common obstetric and gynecologic complications, such as gestational diabetes and preeclampsia, on women's health over life span and to identify determinants to improve women's health. Collectively, the Branch is improving public health through providing evidence to help inform clinical guidance and public policy regarding care of individuals and couples intending to reproduce, pregnant women and their fetuses, and infants and children.



Enrique F. Schisterman,
Ph.D., M.A.,
Branch Chief

STAFF

Elizabeth DeVilbiss, Ph.D.,
M.P.H., M.S., *Research Fellow*

Katherine Laughon Grantz,
M.D., M.S., *Investigator*

Stefanie N. Hinkle, Ph.D.,
Staff Scientist

Keewan Kim, Ph.D., M.P.H.,
Research Fellow

Pauline Mendola, Ph.D., M.S.,
Senior Investigator
(departed 2020)

James L. Mills, M.D., M.S.,
Senior Investigator

Sunni L. Mumford, Ph.D., M.S.,
Earl Stadtman Investigator

Epidemiology Branch (cont.)

High quality scientific investigation in these various domains across the life course has yielded many awards recognizing the hard work of Epidemiology Branch team members. During 2020 alone, five Branch fellows received or were finalists for awards and honors from within NIH as well as international societies in their respective fields, highlighting the top-notch training program and mentoring conducted in the Branch. In addition, Branch investigators received several awards including numerous NICHD awards, and awards from the American Society for Reproductive Medicine and the American Statistical Association, among others. The excellence found within the Branch paired with the freedom and opportunity that comes with having large and unique data sets available makes the Branch uniquely positioned to pursue trans-disciplinary, high-risk research in novel and emerging areas of reproductive, perinatal, pediatric, and methodologic epidemiology.

Carrie J. Nobles, Ph.D., M.P.H., <i>Research Fellow (departed 2020)</i>	Kristen Pollinski, Ph.D., <i>Postdoctoral Fellow</i>
Neil J. Perkins, Ph.D., M.S., <i>Staff Scientist (departed 2020)</i>	Alexandra Purdue-Smith, Ph.D., <i>Postdoctoral Fellow</i>
Diane L. Putnick, Ph.D., M.S., <i>Staff Scientist</i>	Elijah Reische, B.S., <i>Postbaccalaureate Fellow</i>
Lindsey A. Sjaarda, Ph.D., M.S., <i>Staff Scientist</i>	Sonia Robinson, Ph.D., <i>Postdoctoral Fellow</i>
Fasil Tekola-Ayele, Ph.D., M.P.H., <i>Earl Stadtman Investigator</i>	Matthew CH Rohn, B.S., <i>MRSP Fellow</i>
Edwina H. Yeung, Ph.D., Sc.M., <i>Senior Investigator</i>	Danielle Stevens, Ph.D., <i>Postdoctoral Fellow</i>
Cuilin Zhang, M.D., Ph.D., M.P.H., <i>Senior Investigator</i>	Yassamann Vafai, Ph.D., M.P.H., <i>Postdoctoral Fellow (departed 2020)</i>
FELLOWS	Sifang Kathy Zhao, Ph.D., <i>Postdoctoral Fellow</i>
Suvo Chatterjee, Ph.D., <i>Postdoctoral Fellow</i>	Jessica Zolton, D.O., <i>Clinical Fellow (departed 2020)</i>
Kerry Flannagan, Ph.D., <i>Postdoctoral Fellow</i>	
Joshua Freeman, M.S., <i>Predoctoral Fellow</i>	
Jessica Gleason, Ph.D., <i>Postdoctoral Fellow</i>	
Anisa Holloman, B.S., <i>Postbaccalaureate Fellow (departed 2020)</i>	
Jenna Kanner, B.A. <i>Postbaccalaureate Fellow (departed 2020)</i>	
Mengying Li, Ph.D., M.S.P.H., <i>(departed 2020)</i>	
Bryttany McClendon-Weary, B.S., <i>Postbaccalaureate Fellow (departed 2020)</i>	
Marion Ouidir, Ph.D., <i>Visiting Fellow</i>	
Georgia Pitsava, M.D., <i>Postdoctoral Fellow</i>	

Enrique F. Schisterman, Ph.D., M.A.

The field of reproductive epidemiology focuses on factors that affect human reproduction, including conception delay, pregnancy loss, anovulation, and semen quality in relation to environmental, lifestyle, and genetic factors, among others. Resulting from his multidisciplinary training in statistics and epidemiology, Dr. Schisterman's work focuses on developing methodological approaches for study design and analysis in reproductive epidemiology and implementing these tools towards answering the pressing etiologic questions facing couples trying to conceive and their clinicians. In particular, he prioritizes identifying low-cost interventions to improve reproductive health of populations through randomized clinical trials. Dr. Schisterman's recent work conveys from the completion of two such trials: 1) the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, examining the effects of low-cost, low-dose aspirin therapy on fertility outcomes, and 2) the Folic Acid and Zinc Supplementation Trial (FASZT), examining the effects of folate/zinc supplementation in men on semen quality and couples' fertility outcomes.



The EAGeR Trial: The team extended prior work on the effects of preconception-initiated low-dose

aspirin therapy finding that low-dose aspirin was not associated with mode of delivery (PMID: [33075844](#)) or menstrual cycle characteristics (PMCID: [PMC7722096](#)). Further, per-protocol effects of treatment were estimated accounting for non-adherence which suggested that preconception use of low-dose aspirin at least 4 days per week may improve reproductive outcomes (PMID: [33493011](#)). The team also identified that exposure to opioids (PMCID: [PMC7725439](#); PMID: [33001215](#)), cannabis (PMID: [33421071](#)), and selective serotonin reuptake inhibitors (PMCID: [PMC8094179](#)) was associated with reduced fecundability.



FASZT enrolled 2,370 couples, representing the largest ever clinical trial focused on male fertility (PMID: [31712803](#)). The team identified that folic acid and zinc supplementation in men did not improve semen quality parameters (e.g. sperm count, motility) and it modestly increased sperm DNA damage. Most importantly, the supplement did not improve couples' live birth rates. These results indicated for the first time that despite the rapidly growing supplement industry marketing such supplements for improving male fertility based on limited evidence, caution is warranted with use of specialized supplements for male fertility containing folic acid and zinc (PMCID: [PMC6990807](#)).

"Folic acid and zinc supplementation in men did not improve couples' birth rates, emphasizing the importance of proving efficacy prior to broad use."

Methodologic work by Dr. Schisterman's team in 2020 featured several key developments. The team demonstrated a method for visualizing sensitivity analysis for loss to follow-up in clinical trials (PMCID: [PMC7300145](#)), as well as for defining and identifying per-protocol effects in randomized trials (PMCID: [PMC7400733](#)), which tie directly to his etiologic research. Similarly, his work on prediction of pregnancy loss (PMCID: [PMC7994016](#) and [PMC7994023](#)) and a simulation study of the impact of sporadic anovulation on time to pregnancy (PMCID: [PMC7854799](#)), have both etiologic and clinical implications. Dr. Schisterman collaborated on a latent variable-based framework to handle concentrations below the limit of detection to evaluate effects of persistent environmental pollutants on fecundity (PMCID: [PMC7561047](#)). The team also furthered their work discussing study design and analytic challenges in population-based studies of multigenerational associations (PMCID: [PMC7822644](#)).



Enrique F. Schisterman, Ph.D., M.A., *Branch Chief*

STAFF

Neil Perkins, Ph.D., M.S., *Staff Scientist (departed 2020)*

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Elizabeth DeVilbiss, Ph.D., M.P.H., M.S., *Research Fellow*

Kerry Flannagan, Ph.D., *Postdoctoral Fellow*

Sonia Grandi, Ph.D., *Postdoctoral Fellow*

Carrie Nobles, Ph.D., M.P.H., *Postdoctoral Fellow share with Dr. Mendola (departed 2020)*

Jessica Zolton, D.O., *Clinical Fellow (departed 2020)*

KEY PUBLICATIONS

Schisterman EF, Sjaarda LA, Clemons T, et al. Effect of folic acid and zinc supplementation in men on semen quality and live birth among couples undergoing infertility treatment: a randomized clinical trial. *JAMA* 2020;323:35-48. PMID: 31910279.

Naimi AI, Perkins NJ, Sjaarda LA, Mumford SL, Platt RW, Silver RM, **Schisterman EF**. The effect of preconception-initiated low-dose aspirin on human chorionic gonadotropin-detected pregnancy, pregnancy loss, and live birth: per protocol analysis of a randomized trial. *Annals of Internal Medicine* 2021;174(5):595-601. PMID: 33493011.

James L. Mills, M.D., M.S.

We are investigating the effect of iodine deficiency on multiple pregnancy outcomes. Iodine deficiency is common in pregnancy both in Europe and in the US where almost half of pregnant women are deficient. Because severe iodine deficiency can cause congenital hypothyroidism (CH) with devastating neurological damage to the baby, it is important to determine if iodine concentrations at birth in US babies

“Although many pregnant women in the US are iodine deficient, it is reassuring that the deficiency is not severe enough to cause congenital hypothyroidism in their offspring.”

are causing CH.

We conducted a nested case-control study in a cohort of ~2.5 million births in California to determine whether iodine status is related to CH in a

US population. Dried blood spots from 907 newborns with CH identified by newborn screening and 909 unaffected controls matched by month of birth were obtained from the California Newborn Screening Program to measure whole-blood iodine concentration. Iodine status was compared between cases and controls. Iodine status was also compared between cases and controls among infants treated in a neonatal intensive care unit (NICU) because CH has been reported in infants exposed to high levels of iodine in the NICU. Blood iodine concentrations did not differ significantly between cases (median: 20.0 ng/mL; IQR: 12.1-29.8 ng/mL) and controls (median: 20.3 ng/mL; IQR: 12.5-30.9 ng/mL; $P = 0.59$). Neither extremely high nor extremely low blood iodine concentrations (1st, 5th, 95th, and 99th percentiles of the distribution) were more common in cases. Among infants treated in NICUs, however, cases had significantly ($P = 0.01$) higher iodine (median: 22.7 ng/mL; IQR: 16.4-32.1 ng/mL) compared with controls (median: 17.3 ng/mL; IQR: 8.3-26.6 ng/mL). In conclusion, CH cases did not have

significantly higher or lower iodine in this population, which is reassuring given that maternal iodine deficiency is common in the United States. Among newborns in the NICU, CH cases had higher blood iodine concentrations compared with controls, suggesting that excess iodine exposure in the NICU could be causing CH. It may be beneficial to monitor iodine exposure from surgical procedures, imaging, and iodine-containing disinfectants and to consider non-iodine alternatives (PMID: [32633779](#))

Carney complex (CNC) is an autosomal dominant multiple neoplasia and lentiginosis syndrome. Cardiac myxomas is the predominant cause of death in CNC patients but little is known regarding risk factors or recurrence rates. Of the 319 patients studied, 136 (42.6%) developed myxomas. The mean age at diagnosis was 28.7 ± 16.6 years in females and 25.0 ± 16.4 years in males. By age 30, 35% of females and 45% of males had at least one myxoma. The CNC-related lesions, lentigines, cutaneous, mucosal, or breast myxomas, thyroid nodules, pituitary adenoma, and schwannoma were significantly more frequent (all $p < 0.05$) among patients with myxomas. Forty-four percent of patients had recurrences; nearly all within the first 8 and 16 years for males and females, respectively. Recurrences were more common in females. This is the largest study to date and provides the first time risk estimates by age and gender for cardiac myxomas in CNC patients. In summary, cardiac myxomas are common by age 30 and often recur, especially in women, but the risk drops in 10 to 20 years. These findings may guide patient counseling, screening intervals, and surgical approaches (PMID: [32893266](#)).



James L. Mills, M.D., M.S.
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Elijah Reische, B.A.,
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KEY PUBLICATIONS

Mills JL, Reische EC, Kannan K, Gao C, Shaw GM, **Sundaram R**. Newborn Iodine Status Is Not Related to Congenital Hypothyroidism. *The Journal of Nutrition*. 2020 Sep 1;150(9):2429-2434. PMID: 32633779. doi: 10.1093/jn/nxaa178. PMID: 32633779.

Pitsava G, Zhu C, Sundaram R, **Mills JL**, Stratakis CA. Predicting the risk of cardiac myxoma in Carney complex. *Genetics in Medicine*. 2021 Jan;23(1):80-85. doi: 10.1038/s41436-020-00956-3. Epub 2020 Sep 7. PMID: 32893266.

Pauline Mendola, Ph.D.

Dr. Mendola leads the [Air Quality and Reproductive Health](#) study which added air pollution and ambient temperature data to the Consortium on Safe Labor, the LIFE Study, and the NICHD Consecutive Pregnancy Study. In 2020, a key discovery was a replication of our earlier findings that stillbirth was associated with minor variation in acute ambient temperature in a low-risk population (PMID: [32980027](#)).



Residential zip code data for the [NICHD Fetal Growth Studies](#) Singleton and Twin cohorts were added to the clinical data in order to better estimate ambient environmental

exposures. Air pollution and temperature will be assessed in relation to acute changes in placental vascular resistance and maternal blood pressure as well as chronic exposure in relation to fetal growth and organ volumes. A paper on uterine artery doppler indicators of vascular resistance is under review and work on hypertensive

"The reproductive risks associated with ambient environmental exposures are often small but have large population-level impact. Everyone breathes, we are all exposed. These exposures are modifiable and addressing them can prevent adverse pregnancy outcomes."

disorders of pregnancy associated with ambient temperature will be presented at the Society for Epidemiologic Research (SER) annual meeting.



The [B-WELL-Mom Study](#) (Mendola/Chen, PI), which aims to increase understanding of factors that predict poor asthma

control during pregnancy as well as add to our knowledge of the basic immunology of pregnancy was completed in

August 2019 but laboratory analyses have been delayed due to the impact of COVID-19. Even without the biospecimen results needed for the primary hypotheses, we are making great progress with papers in 2020 including highlighting air pollution measurement variation using various strategies such as personal monitoring (PMID: [32645870](#)), and assessing gestational weight gain among women with and without asthma (PMID: [33169142](#)). Another paper under review considers the role of maternal body composition in asthma control given that obesity is associated with asthma. Contrary to traditional assumptions, we did not find similar proportions of women with asthma getting better, same, or worse over the course of pregnancy. Instead, in a paper using machine learning and other techniques to assess asthma control, Dr. Stevens found that most women stayed the same and about 40% got worse. That paper was a finalist for the SER postdoctoral student prize paper award in 2020. Work on placental biomarkers and maternal stress, led by Dr. Williams at the University of North Dakota, will be presented at the Society for Pediatric and Perinatal Epidemiologic Research meeting as well as work on infant size and adiposity led by Dr. Stevens. We look forward to receiving biologic data on maternal allergy with detailed IgE for common allergens (trees, grasses, molds, animal antigens, etc.) as well as total IgE, a global indicator. Allergic asthma is estimated to be about half of all cases, so we will determine if asthma control during pregnancy is predicted by allergy status. With the departure of Dr. Mendola in October 2020, Dr. Zhen Chen has assumed the PI role for B-WELL-Mom. Dr. Mendola will continue to support the study goals under an IPA with NICHD which is currently pending.

B-WELL-Mom website: www.b-well-mom.org



Pauline Mendola, Ph.D.,
Senior Investigator

STAFF

Carrie Nobles, Ph.D.,
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Danielle Stevens, Ph.D.,
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Jenna Kanner, B.S.,
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Matthew CH Rohn, B.S.,
Medical Research Scholar
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KEY PUBLICATIONS

Kanner J, Williams AD, Nobles C, Ha S, Ouidir M, Sherman S, Grantz KL, **Mendola P**. Ambient temperature and stillbirth: Risks associated with chronic extreme temperature and acute temperature change. *Environmental Research* 2020;189:109958. PMID: 32980027.

Stevens D, Grobman W, Kumar R, Lipsky LM, Hinkle SN, Chen Z, Williams A, Rohn MCH, Kanner J, Sherman S, **Mendola P**. Gestational and postpartum weight trajectories among women with and without asthma. *American Journal of Epidemiology* 2020, Nov 10:kwaa248. doi: 10.1093/aje/kwaa248. Online ahead of print. PMID: 33169142.

Edwina Yeung, Ph.D., Sc.M.



In her pursuit to understand the developmental origins of health and disease (DOHaD), Dr. Yeung leads the Upstate KIDS Study which included two phases of follow-up (2008-2014 and 2014-2019). Upstate KIDS was designed to determine whether infertility treatments adversely affect the growth and development of children. Over 6,000 newborns were enrolled between 2008 and 2010, with almost one third conceived by infertility treatments. In 2020, Dr. Yeung's team investigated whether infertility was related to children's risk of autism, using data collected from a screening instrument when the children were 24 and 36 months old. No associations with risk were identified with mode of conception, whether by assisted reproductive technologies or ovulation induction (PMID: [32163552](#)). In a separate investigation using data at older age, maternal obesity was associated with increased childhood risk

"About a quarter of women had elevated depression symptoms sometime in the 3 years postpartum."

of inattentive or hyperactivity problems (PMID: [PMID: 33109744](#)). Recognizing the interconnectedness of a child's development to maternal mental health, Dr. Yeung's team investigated maternal depression from 4 months to 3 years, identifying four depression symptom trajectories (PMID: [33109744](#)). About a quarter of women had elevated depression symptoms sometime in the 3 years postpartum and two trajectory groups containing over 12% of women had elevated depressive symptoms past 6 months postpartum. Findings had clinical implications for depression screening because current guidelines only recommend screening through 6 months postpartum.

An epigenetic mechanism which may explain developmental programming was also scrutinized. Using microarray data measured on DNA methylation in cord blood of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, Dr. Yeung's team found that fatty acid concentrations prior to pregnancy rather than in early pregnancy, were associated with differences at selected CpG sites (PMID: [PMC7049533](#)). Thus, results emphasize the importance of preconception nutrition. Separately, Dr. Yeung determined that maternal inflammation as measured by c-reactive protein (CRP) was associated with differences in newborn DNA methylation only when it was measured at the time of delivery, rather than circulating levels measured in early or mid-pregnancy (PMID: [PMC7193358](#)). Leveraging on international data from the Pregnancy And Childhood Epigenetics (PACE) consortium, a meta-analysis of CRP levels from other pregnancy cohorts confirmed the findings.

After the completion of the Upstate KIDS CVD Follow-Up Study in 2019, laboratory measurements of DNA methylation using follow-up samples at age 8-10 years of age began. Assays were also underway for cardio-metabolic biomarkers to complement information collected at the clinical visits which were aimed to capture childhood cardio-metabolic outcomes (i.e., obesity, high blood pressure, metabolism).



Dr. Yeung also began establishing the SPAN cohort to investigate paternal contributions to the developmental origins of health and disease. While much research has been devoted to maternal exposures, information on paternal factors is greatly lacking despite evidence of potential epigenetic pathways.



Edwina Yeung, Ph.D., Sc.M.,
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Sifang (Kathy) Zhao, Ph.D.,
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Bryttany McClendon-Weary, B.S.,
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KEY PUBLICATIONS

Yeung EH, Guan W, Zeng X, Salas LA, Mumford SL, Prado Bert P, van Meel ER, Malmberg A, Sunyer J, Duijts L, Felix JF, Czamara D, Hämäläinen E, Binder EB, Räikkönen K, Lahti J, London S, Silver RM, Schisterman EF. Cord blood DNA methylation reflects cord blood c-reactive protein levels but not maternal levels: a longitudinal study and meta-analysis. *Clinical Epigenetics* 2020 Apr 30;12(1):60. doi: 10.1186/s13148-020-00852-2. PMID: 32354366. PMCID: PMC7193358.

Putnick DL, Sundaram RS, Bell EB, Ghassabian A, Goldstein RB, Robinson SL, Vafai Y, Gilman SE, Yeung E. Trajectories of Maternal Postpartum Depressive Symptoms. *Pediatrics* 2020 Nov;146(5):e20200857. doi: 10.1542/peds.2020-0857 PMID: 33109744. PMCID: PMC7772818. {Featured on NPR, Oct 27, 2020}

Cuilin Zhang, M.D., Ph.D., M.P.H.

Dr. Cuilin Zhang's research program focuses on determinants and health consequences of gestational diabetes, and developmental origins of cardio-metabolic diseases. Her research endeavors have been motivated by the escalating epidemic of diabetes and obesity worldwide and the considerable comorbidities that individuals experience by the time type 2 diabetes is diagnosed. It is pivotal to identify individuals at high risk for early prevention and for disrupting the 'diabetes begetting diabetes' vicious cycle. Her research is conceptualized within a life course epidemiological paradigm, so that pregnancy complications may be understood in the context of pre- and peri-conceptional factors and linked with later onset diseases and the health implications for "exposed" offspring.

The [Diabetes & Women's Health Study](#) was a retrospective cohort study of more than 4,000 women from the U.S. and Denmark who had diabetes in pregnancy. The overarching goal was to set up a research framework for investigating long-

"Efforts to mitigate fetal overgrowth related to gestational diabetes should be initiated earlier than 24-28 gestational weeks, when gestational diabetes is typically screened for in the US."

further evidence supporting public health efforts to encourage a healthful diet to prevent type 2 diabetes among this high-risk population (PMCID: [PMC7039588](#)). Dr. Zhang also led her team in their continued efforts to identify potentially modifiable

avenues including lactation duration (PMCID: [PMC7594200](#); [PMC7085808](#)) and dietary factors (PMID: [31959496](#)) for the prevention of type 2 diabetes and other comorbidities such as poor renal function.



Using data from the [NICDH Fetal Growth Studies](#) and a comprehensive panel of biomarkers based on system biology approach, Dr. Zhang's team identified targeted and non-targeted metabolomics implicated in [glucose homeostasis](#) and fetal growth. It was discovered that circulating levels of prolactin (PMCID: [PMC7058109](#)), sex hormone binding protein (PMID: [PMC7357819](#)), and novel adipokines (PMCID: [PMC7398109](#)) in early to mid-pregnancy may serve as markers for the identification of women at high risk for developing gestational diabetes. Notably, the team also discovered that the excess body fat seen in infants born to women with gestational diabetes is associated with higher maternal glucose levels as early as the 10th week of pregnancy (PMCID [PMC7676113](#)).



Lastly, analyses in 2020 (PMCID: [PMC7042706](#)) demonstrated the success of the linkage for the [Collaborative Perinatal Project Mortality Linkage Study](#), which aims to investigate long-term associations of overall and cause-specific mortality with a spectrum of pregnancy-related complications.



Cuilin Zhang,
M.D., Ph.D., M.P.H.
Senior investigator

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Sifang Kathy Zhao, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Li M, Hinkle SN, Grantz KL, Kim S, Grewal J, Grobman WA, Skupski DW, Newman RB, Chien EK, Sciscione A, Zork N, Wing DA, Nageotte M, Tekola-Ayele F, Buck Louis GM, Albert PS, **Zhang C**. Glycaemic status during pregnancy and longitudinal measures of fetal growth in a multi-racial US population: a prospective cohort study. *Lancet Diabetes and Endocrinology*. 2020;8(4):292-300.

Li M, Rahman ML, Wu J, Ding M, Chavarro JE, Lin Y, Ley SH, Bao W, Grunnet LG, Hinkle SN, Thuesen ACB, Yeung E, Gore-Langton RE, Sherman S, Hjort L, Kampmann FB, Bjerregaard AA, Damm P, Tekola-Ayele F, Liu A, Mills JL, Vaag A, Olsen SF, Hu FB, **Zhang C**. Genetic factors and risk of type 2 diabetes among women with a history of gestational diabetes: findings from two independent populations. *BMJ Open Diabetes Research Care*. 2020;8(1).

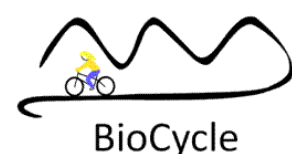
Sunni L. Mumford, Ph.D., M.S.

As the incidence of infertility and pregnancy complications has been rising worldwide, low-cost modifiable risk factors, such as preconception nutrition, have the potential to play a pivotal role in changing the landscape of fertility and pregnancy

"Preconception nutrition has the potential to play a pivotal role in changing the landscape of fertility and pregnancy health to set the foundations for lifelong wellness."

health to set the foundations for lifelong wellness. To that end, Dr. Mumford's research focuses on modifiable dietary and lifestyle factors across the life course that affect reproduction among women, men, and couples. Dr. Mumford has led multiple data collection efforts and innovative analyses to expand

scientific understanding of the roles of diet and lifestyle on many complementary reproductive health endpoints. These interdisciplinary efforts integrate information from different populations, which is critical for informing personalized, and evidence-based guidance. Importantly, this work has resulted in novel discoveries linking dietary factors to multiple aspects of reproductive health.



BioCycle provides rich data to look at dietary and lifestyle factors in relation with reproductive hormones and premenstrual syndrome in healthy women. Dr. Mumford's team found that markers of vitamin D metabolism (PMID: [33864070](#)), and oxidative stress but not antioxidants (PMCID: [PMC7851915](#)), were associated with select symptoms of premenstrual syndrome. Further, low intake of vegetable protein (PMID: [33735390](#)) was associated with hormone levels and a higher risk of anovulation, highlighting the potential role of dietary factors to influence ovulatory function in reproductive-aged women.



EAGeR has resulted in findings that have emphasized the importance of preconception nutritional and lifestyle factors and how they relate to time to pregnancy and reproductive health. Specifically, Dr. Mumford's team has demonstrated the role of preconception leptin levels for healthy pregnancy outcomes (PMCID: [PMC7156817](#)), and that higher physical activity levels were associated with early pregnancy losses (PMCID: [PMC7994027](#)). Dr. Mumford's team also found that preconception cannabis use was associated with reduced fecundability (PMID: [33421071](#)). In addition, maternal caffeine and vitamin use during pregnancy may be associated with ovarian reserve in adult offspring, highlighting the potential importance of pregnancy lifestyle on the reproductive health of daughters (PMCID: [PMC7736224](#)).



FAZST is the largest clinical trial focused on male fertility (PMID: [31712803](#)). The team recently found that folic acid and zinc supplementation in men did not improve live birth rates, nor did it improve semen quality parameters such as sperm count and motility, though was associated with an increase in sperm DNA damage (PMCID: [PMC6990807](#)). These results provide crucial evidence to guide recommendations regarding supplement use for male fertility.



IDEAL is Dr. Mumford's most recent large prospective cohort study, that extends prior work to facilitate a couples-based approach to understanding associations between diet, exercise, and lifestyle on infertility treatment outcomes. Innovative data collection methods, including wrist worn activity trackers, daily diaries, and DXA scans provide novel data to evaluate associations with fertility and reproductive health (PMCID: [PMC7604525](#)).



Sunni L. Mumford, Ph.D., M.S.,
Earl Stadtman Investigator

STAFF

Keewan Kim, Ph.D., M.P.H.,
Research Fellow

Alexandra Purdue-Smith, Ph.D.,
Postdoctoral Fellow share with Dr. Mills

Joshua Freeman, M.S.,
Predoctoral Fellow

KEY PUBLICATIONS

Mumford SL, Johnstone E, Kim K, Ahmad M, Salmon S, Summers K, Chaney K, Ryan G, Hotaling JM, Purdue-Smith AC, Chen Z, Clemons T. A Prospective Cohort Study to Evaluate the Impact of Diet, Exercise, and Lifestyle on Fertility: Design and Baseline Characteristics. *American Journal of Epidemiology*. 2020;189(11):1254-1265. PMID: 32472141. PMCID: PMC7604525.

Schisterman EF, Sjaarda LA, Clemons T, Carrell DT, Perkins NJ, Johnstone E, Lamb D, Chaney K, Van Voorhis BJ, Ryan G, Summers K, Hotaling J, Robins J, Mills JL, Mendola P, Chen Z, DeVilbiss EA, Peterson CM, **Mumford SL**. Effect of Folic Acid and Zinc Supplementation in Men on Semen Quality and Live Birth Among Couples Undergoing Infertility Treatment: A Randomized Clinical Trial. *JAMA*. 2020;323(1):35-48. PMID 31910279. PMCID: PMC6990807.

Katherine Laughon Grantz, M.D., M.S.

Empirical evidence is lacking on many key aspects of pregnancy management. Dr. Grantz's research focuses on fetal growth and labor and delivery management with a particular interest on when to deliver a high-risk pregnancy. The field of obstetrics is in particular need of evidence to help guide the creation of clinical guidelines and her research portfolio identifies critical data gaps and strategies to translate research findings into clinical practice.



Research in the area of fetal growth aims to investigate what happens to normal or expected velocity and fetal growth patterns with medical and obstetrical complications,

to distinguish pathologic fetal growth and birth weight from constitutionally small or large fetuses, and to identify risk factors associated with abnormal fetal growth and birth weight. The primary [NICHD Fetal Growth Studies](#) singleton study demonstrated that racial/ethnic-specific differences in fetal growth can be detected as early as 10-16 weeks, suggesting that racial/ethnic specific fetal growth charts are needed to reduce misclassification of minority fetuses as too small or too big. (PMCID: [PMC4584427](#) PMID: [26410205](#); PMID: [25258202](#)) Her group demonstrated that racial and ethnic differences in neonatal anthropometry in the NICHD study were not explained by differences in individual socioeconomic factors. (PMCID: PMC7579630) From these novel data, Dr. Grantz has led work to develop two publicly available online calculators: an [EFW percentile calculator](#) and an [EFW fetal growth velocity calculator](#).

Defining abnormal fetal growth in twins is more complicated than for singletons given that growth restriction can affect one or both twins and can also be defined in terms of discordance. While birthweight discordance is well studied, few studies have assessed differences in inter-twin estimated fetal weight longitudinally, and the definitive cut-point for defining discordance is not established. The primary [NICHD Fetal Growth Studies](#) twin study discovered that, compared with singleton fetuses, the mean abdominal circumference and estimated

fetal weight trajectories of dichorionic twin fetuses diverged significantly beginning at 32 weeks. (PMCID: [PMC4967402](#)). Dr. Grantz's team followed up this work and found that dichorionic inter-twin estimated weight differences increased across gestation, with a larger percentage of pregnancies exceeding a fixed percent discordance cut-off as gestation advanced, suggesting that a percentile cut-point (e.g., 90th) may be more clinically useful than a fixed cut-point (e.g. 20% difference) for defining discordance. (PMCID: [PMC7535857](#)) Additional work demonstrated that the percent difference in estimated fetal weight (i.e. discordance) increased across gestation in dichorionic twins. However, inter-twin weight differences were stable among women with obesity or IVF conception for reasons that are unknown. Persistence of increasing percent difference in EFW within low-risk groups suggests that some of this progressive increase may be physiologic. (PMID: [31478227](#))



Building on work in 2D ultrasound, she completed the [Fetal 3D Study](#) to establish standards for fetal body composition and organ volumes by race/ethnicity and examine the relationship between pregnancy complications and longitudinal changes in fetal body composition and organ volumes. Technology is advancing and findings from the Fetal 3D Study will establish whether this ultrasound technology can improve clinical practice.



Dr. Grantz also started a trial in [SPAN](#) to determine the optimal timing of delivery for gestational diabetes mellitus complicated pregnancies. Much attention has focused on preterm delivery but less is known about delivery timing in pregnancies with complications, an important data gap highlighted by a 2011 joint NICHD workshop.

Collectively, her research is providing critical empirical data to guide clinical management of pregnancy.



Katherine Laughon Grantz, M.D., M.S., Investigator

STAFF

Jessica Gleason, Ph.D.,
Postdoctoral Fellow

Yassaman Vafai, Ph.D.,
Postdoctoral Fellow
(departed 2020)

KEY PUBLICATIONS

Amyx MM, Albert PS, Bever AM, Hinkle SN, Owen J, Grobman WA, Newman RB, Chien EK, Gore-Langton RE, Buck Louis GM, **Grantz KL**. Intrauterine growth discordance across gestation and birthweight discordance in dichorionic twins. *American Journal of Obstetrics and Gynecology*. 2020;222(2):174.e1-174.e10. PMID: 31454510. PMCID: PMC7535857.

Lambert C, Gleason JL, Pugh SJ, Liu A, Bever A, Grobman WA, Newman RB, Wing D, Gerlanc NM, Tekola-Ayele F, **Grantz KL**. Maternal Socioeconomic Factors and Racial/Ethnic Differences in Neonatal Anthropometry. *International Journal of Environmental Research and Public Health*. 2020;17(19):1-12. PMID: 33036433. PMCID: PMC7579630.

Fasil Tekola-Ayele, Ph.D.

Many cardiometabolic diseases in later life have links with early life growth. Advances in understanding the mechanism of early growth variation will provide early intervention opportunities for cardiometabolic outcomes. Dr. Tekola-Ayele's research aims to determine genetic mechanisms in early growth variations and links between early growth and cardiometabolic diseases/disparities in diverse ancestral populations. To achieve this goal, his group focuses on two overarching complementary research themes at the maternal-placental-fetal interface – genetics of fetal growth and placental epigenome/transcriptome.

The goal of the first research theme is to determine genetic influences on longitudinal fetal growth trajectories, the contribution of genetic ancestry to fetal growth differences, and the shared genetic architectures of fetal growth and cardiometabolic outcomes. Genome-wide single nucleotide polymorphism data have been generated from the NICHD Fetal Growth Studies, complemented by datasets obtained from consortia-based genetic databases and the NIH Database of Genotypes and Phenotypes. This project yielded the following key insights: (1) identified novel maternal genetic loci that influence fetal weight at specific in-utero time periods (PMCID: [PMC7252673](#)), elucidated that fetal genetic influences on fetal growth differ based on gestational age (PMCID: [PMC5940684](#)) and ancestry (PMCID: [PMC5967042](#)), and (2) built evidence that genetic mechanisms partly explain the links between maternal cardiometabolic risk, fetal growth, and future risk for cardiometabolic diseases (PMCID: [PMC6411883](#), [PMC6449964](#), [PMC6753636](#), [PMC6592626](#), [PMC6885118](#), [PMC6224338](#)).

Further, a recently completed pilot study examined the potential to obtain usable DNA for genotyping banked serum samples from the Collaborative Perinatal Project (CPP). By providing proof-of-principle, the pilot paves the way for linking genetic data with the detailed phenotypic records of the CPP to

address high impact long-standing biological questions in early growth, childhood adiposity and subsequent cardiometabolic health.

The goal of the second research theme is to investigate the role of placental genetic/epigenetic/transcriptomic mechanisms and the aging “clock” of the placenta in fetal growth and related maternal cardiometabolic factors. Key findings of this project include the following: (1) demonstrated that epigenetic aging of the placenta has sexually dimorphic relationships with fetal growth ((PMCID: [PMC6710059](#)) and significant associations with maternal cardiometabolic factors and genetic ancestry (PMCID: [PMC6691987](#)), and (2) identified novel placental DNA methylation and transcriptomic signatures for birthweight and maternal cardiometabolic factors, including loci that suggest placental DNA methylation changes as early mechanisms underlying subsequent cardiometabolic disease risk (PMCID: [PMC7261634](#), [PMC7122078](#), [PMC7466909](#), [PMC7268466](#), [PMC7371466](#)).



Dr. Tekola-Ayele has initiated a new genetic study within [SPAN](#): 1) to identify fetal genetic factors that regulate fetal growth and the aging clock of the placenta and through discovery in African Americans followed by trans-ethnic meta-analysis, and 2) to investigate genetic, epigenetic and transcriptomic mechanisms in placental regulation of fetal growth.



Fasil Tekola-Ayele, Ph.D.,
Earl Stadtman Investigator

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Postdoctoral fellow

Marion Ouidir, Ph.D.,
Postdoctoral fellow

KEY PUBLICATIONS

Tekola-Ayele F, Zhang C, Wu J, Grantz KL, Rahman ML, Shrestha D, Ouidir M, Workalemahu T, Tsai MY. Trans-ethnic meta-analysis of genome-wide association studies identifies maternal ITPR1 as a novel locus influencing fetal growth during sensitive periods in pregnancy. *PLoS Genet.* 2020;16(5):e1008747. PMID: 32407400; PMCID: PMC7252673.

Workalemahu T, Ouidir M, Shrestha D, Wu J, Grantz KL, **Tekola-Ayele F**. Differential DNA Methylation in Placenta Associated With Maternal Blood Pressure During Pregnancy. *Hypertension.* 2020;75(4):1117-1124. PMID: 32078381. PMCID: PMC7122078.

2020 impacted all of us in deeply personal ways. The importance of personal connections became even more important upon departing our offices in March, 2020, and remaining out over a year later. Our branch strove to preserve the rich intellectual climate of our academic life, fulfill our training and mentoring mission, and maintain momentum on our active studies in the face of COVID restrictions. I am profoundly moved by the perseverance of our branch members to make our disconnected work life as connected as possible, and greatly appreciate all of them for always being there to help, for cheering each other up and on, for sharing their challenges, and for always being supportive despite often needing support. I am also grateful to our DIPHR leadership team for their unending willingness to creatively engage in solutions and to zoom within a moment's notice: to Dr. Una Grewal, who led us through an unprecedented time with humor and grace; to Dr. Shyamal Peddada, who joined our leadership team remotely but was always present; and to Dr. Cuilin Zhang, who stepped up to, and did not back down from, a full plate of challenges.

-Stephen Gilman, May 2021

The mission of the Social and Behavioral Sciences Branch is to conduct research to understand the social and behavioral determinants of health and health-related behaviors; to develop and test educational, behavioral, and environmental strategies for improving health and health-related behaviors; and to conduct research on the problem of disparities in health, the developmental mechanisms underlying health disparities over the life course, and modifiable intervention targets to reduce disparities. SBSB also recruits, trains, and mentors highly qualified students and trainees for professional careers in the social and behavioral sciences.

Our research integrates approaches from diverse disciplines including psychology (community, clinical, and developmental), nutrition, health education, and epidemiology (social, psychiatric, and developmental). Collaborations with other Division researchers and throughout the NIH's Intramural

Research Program further enhance the trans-disciplinary nature of our work. Our research addresses key contributors to population health including obesity, pre- and perinatal maternal health, early child development, and mental illness. Its developmental focus strives to identify and intervene early in life on pathways to disease for maximal impact on population health.

The Branch's research programs are organized along axes of substantive research domains and key developmental stages. SBSB research on the social determinants of mental health and health disparities takes a life course approach, from the prenatal period through childhood and adolescence, and investigates developmental mechanisms that reach into and beyond middle adulthood.

SBSB research on eating behaviors in children and families uses experimental and observational methods to investigate



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*Senior Investigator and
Branch Chief*

STAFF

Tonja Nansel, Ph.D.,
Senior Investigator

Risë B. Goldstein, Ph.D.,
Staff Scientist (departed 2020)

Denise Haynie, Ph.D.,
Staff Scientist

Jing Yu, Ph.D.,
Research Fellow

influences on, and interventions to improve, eating behaviors leading to optimal growth and development in clinical and general populations. This work is of substantial public health importance because the poor diet quality of the U.S. population, characterized by excessive intake of total energy, added sugar, fat and sodium, and inadequate intake of fruits, vegetables and whole grains is well-documented. Poor diet (not including malnutrition) is now the largest contributor to early death globally, and is associated with numerous adverse health outcomes independent of obesity.

Our risk behavior research centers on adolescence and young adulthood. Adolescence is a critical period for the development of behavior patterns associated with subsequent morbidity and mortality, including diet, physical activity, sleep, substance use, and suicidal behaviors. Influences on these behaviors encompass personal and environmental factors, including social influences and physical contexts (e.g., place of residence, local programs, policies, and resources).

FELLOWS

Mahad Gudal, B.S.,
Postbaccalaureate Fellow
(departed 2020)

Theemeshni Govender, B.A.,
Postbaccalaureate Fellow

Katherine Maultsby, B.A.,
Postbaccalaureate Fellow
(departed 2020)

Reeya Patel, M.S.,
Postbaccalaureate Fellow

Pablo Vidal-Ribas Belil, Ph.D.,
Visiting Fellow

Stephen E. Gilman, Sc.D.

COVID-19 has amplified pre-existing health disparities. The long-term ramifications of the pandemic for children's development and for long-term health and well-being are not yet known, though current disparities in morbidity and mortality brought on by the social, economic, and health impacts of COVID-19 likely reflect a small portion of the underlying vulnerability that will become manifest in the upcoming years.

The pandemic has added urgency to our work, which seeks a better understanding of the environments that have both positive and negative influences on development from the prenatal period onward, and seeks to generate new insights into mechanisms that underlie the early life origins of health disparities, identify developmentally sensitive periods for the emergence of disparities, and uncover opportunities for reducing disparities at the population level.

The pandemic has also posed a shock to both our personal and professional lives. I am profoundly grateful to a wonderful team not only for their perseverance but for their dedication to our work on the social determinants of early child development. Just a few of their many accomplishments are highlighted below.

Ms. Theemeshni Govender joined our team this year as a post-bac fellow, moving cross-country to NICHD only to

work remotely. We are incredibly proud of her work on the infant development assessments in the ENRICHED study, her poster presentation on risks for suicidal behaviors among young adults in the NEXT Generation Health Study, and her ongoing contributions to our lab. Ms. Reeya Patel led a study demonstrating that socioeconomic disadvantage during childhood disproportionately impacts racial/ethnic minorities, compounding racial/ethnic disparities in premature mortality in middle adulthood. And she was admitted to graduate school at UCLA, where she will earn her doctoral degree in public health - congratulations!

Dr. Pablo Vidal-Ribas Belil led our team's research on developmental vulnerability to suicide mortality, conducting both a systematic review as well as empirical work on prenatal risk factors for offspring suicide - mastering new statistical methods along the way. Dr. Jing Yu led a study on maternal immune activity and socioeconomic disparities in children's self-regulation that was published in *Brain, Behavior, and Immunity* (see the findings in the Figure, from [PMC7544646](https://pubmed.ncbi.nlm.nih.gov/3544646/)). Dr. Belil's and Dr. Yu's research accomplishments were as impactful, but ultimately not as important as, their parenting accomplishments during a year with new challenges that occurred by the week.

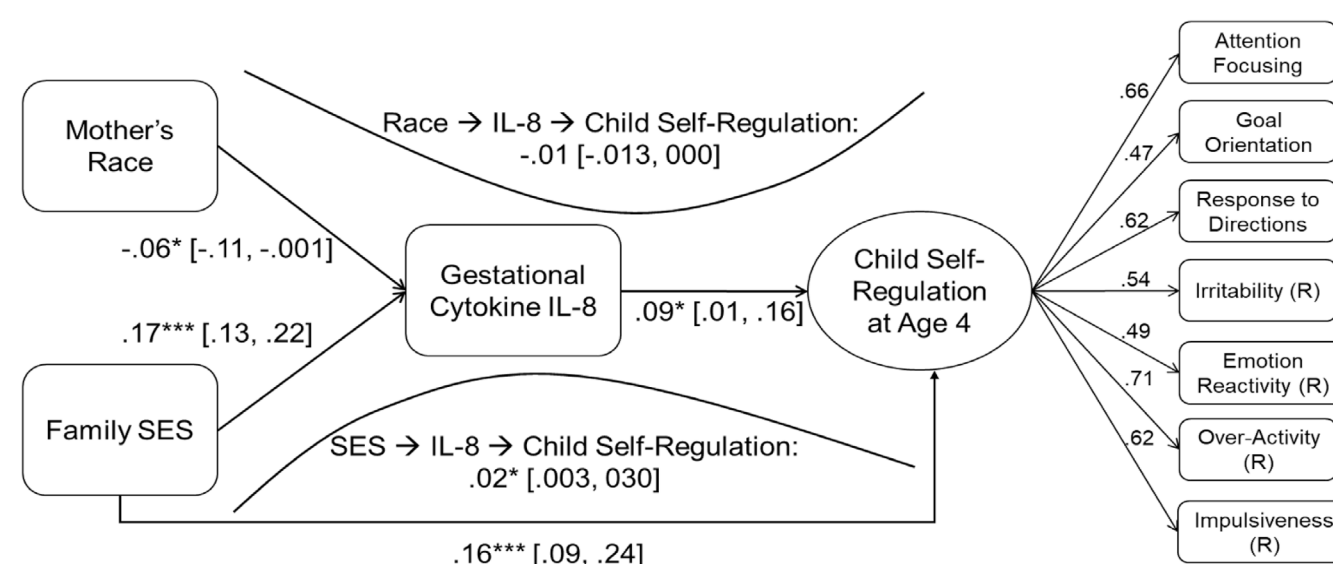


Fig. 1. Family SES, maternal race, gestational IL-8 during pregnancy, and child self-regulation. *Note:* Standardized path coefficients [and their 95% confidence intervals in the bracket] are presented. R = Reverse-coded. * $p < .05$. *** $p < .001$.



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Postbaccalaureate Fellow

Denise Haynie, Ph.D.,
Staff Scientist

Katherine Maultsby, B.A.,
Postbaccalaureate Fellow
(departed 2020)

Reeya Patel, M.S.,
Postbaccalaureate Fellow

Pablo Vidal-Ribas Belil, Ph.D.,
Visiting Fellow

Jing Yu, Ph.D.,
Research Fellow

Social and Behavioral Sciences Branch (cont.)



Our team is indebted to Dr. Denise Haynie for her leadership on the ENRICHED study, which in 2020 was redesigned in the face of pandemic restrictions on in-person data collection and was expanded to incorporate measures of COVID-related impacts on the early origins of disparities. Dr. Haynie continued to direct the NEXT Generation Health Study, to provide mentorship to fellows, service to the NICHD, and valued advice and support to all of SBSB.

Finally, two of our former fellows left NICHD in 2020 to begin the next stage in their careers: Ms. Katherine Maultsby to graduate school in clinical psychology, and Mr. Mahad Gudal to further pre-med training. We wish you well!

KEY PUBLICATIONS

Fairman BJ, Goldstein RB, Simons-Morton BG, Haynie DL, Liu D, Hingson RW, **Gilman SE**. Neighbourhood context and binge drinking from adolescence into early adulthood in a US national cohort. *International Journal of Epidemiology*. 2020;49(1):103-12. Epub 2019/07/03. doi: 10.1093/ije/dyz133. PMID: 31263877. PMCID: PMC7124510.

Yu J, Ghassabian A, Chen Z, Goldstein RB, Hornig M, Buka SL, Goldstein JM, **Gilman SE**. Maternal Immune activity during pregnancy and socioeconomic disparities in children's self-regulation. *Brain, Behavior, and Immunity*. 2020;90:346-52. Epub 2020/09/13. doi: 10.1016/j.bbi.2020.09.003. PubMed PMID: 32919039. PMCID: PMC7544646.

Tonja Nansel, Ph.D.

Poor diet quality, characterized by excessive intake of discretionary foods (i.e., nutrient-poor foods high in energy, added sugar, fat, and sodium) and inadequate intake of fruits, vegetables, and whole grains, is the leading cause of global premature mortality. Insufficient evidence exists to inform approaches to achieve sustainable improvements in diet quality. The goal of this research program is to address this critical knowledge gap by investigating neurobehavioral influences on eating behaviors in children and families and developing novel intervention targets to facilitate dietary change. Current projects include Pregnancy Eating Attributes Study (PEAS) and Sprouts: Development of Eating Behaviors in Early Childhood.



PEAS was an observational prospective cohort study investigating relationships of

reward-related eating, self-regulation, and the home food environment with dietary intake and weight change during pregnancy and postpartum. Participants were enrolled before 12 weeks gestation and followed, with their infants, until 1 year postpartum. The study included data on dietary intake, anthropometrics, biospecimens, medical records, self-reported eating and other health-related behaviors, infant feeding, functional magnetic resonance imaging, focus groups, and a laboratory feeding substudy assessing overeating. Manuscripts published last year addressing the primary aims (PMID: [32958906](#)) reported that there was little support for the hypothesis that self-reported reward-related eating is associated with weight outcomes in pregnancy and postpartum, but postpartum weight change was associated with greater delay of gratification and obesogenic home food environment. Conversely, better prenatal diet quality was associated with lower reward-related eating, greater self-control, and a less obesogenic home food environment (PMID: [33228724](#)).

Postpartum diet quality was also inversely related to an obesogenic home food environment, but not with any measure of reward-related eating or self-control (PMID: [33228724](#)). Additional papers examined the relationship of sleep with gestational weight gain and fat gain (PMID: [32945728](#)), and reported on data from the laboratory feeding substudy (PMID: [33109504](#), [33158801](#)) and the focus group substudy (PMID: [31813756](#)).



Sprouts, a follow-up study of PEAS participants, is an observational prospective cohort study that will examine associations of neurobehavioral factors, parent feeding practices, and early life food exposures on dietary intake and growth during early childhood (ages 3-7 years). Dietary intake, anthropometrics, biospecimens, laboratory-assessed behavioral data, and parent-reported feeding/eating behaviors will be collected from PEAS mothers, children and co-parents. Data collection began in 2019 and is ongoing. In-person data collection was halted in March due to the COVID-19 pandemic, and web-based data collection was initiated for the survey measures. In-person data collection will resume as conditions allow.



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Dr. Leah M. Lipsky, Ph.D.,
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Carolina Schwedhelm, Ph.D.,
Postdoctoral Fellow

Chelsie Temmen, Ph.D.,
Postdoctoral Fellow

Jenna Cummings, Ph.D.,
Postdoctoral Fellow

Evelyn Liu, B.A.,
Postbaccalaureate Fellow

Grace Betts, B.S.,
Postbaccalaureate Fellow

Ndeah Terry, B.S.,
Postbaccalaureate Fellow (50% time)

KEY PUBLICATIONS

Nansel TR, Lipsky LM, Burger K, Faith M, Nicholson W, Stuebe A, Liu A, Siega-Riz AM. Reward-related eating, self-regulation, and weight change in pregnancy and postpartum: the Pregnancy Eating Attributes Study (PEAS). *International Journal of Obesity (Lond)*. 2020 Dec;44(12):2444-2454. doi: 10.1038/s41366-020-00685-2. PMID: 32958906.

Nansel TR, Lipsky LM, Faith M, Liu A, Siega-Riz AM. The accelerator, the brake, and the terrain: associations of reward-related eating, self-regulation, and the home food environment with diet quality during pregnancy and postpartum in the pregnancy eating attributes study (PEAS) cohort. *International Journal of Behavior Nutrition and Physical Activity*. 2020 Nov 23;17(1):149. doi: 10.1186/s12966-020-01047-x. PMID: 33228724.

The mission of the Contraceptive Development Program is to conduct innovative research to develop new safe and effective methods of contraception for men and women.

NICHD is the lead Federal agency for conducting research on contraception. The Contraceptive Development Program (CDP) in DIPHR has the mission to advance clinical development of novel contraceptive methods for men and women. CDP scientists utilize R&D contracts to translate discoveries into IND-enabled products to address unmet contraceptive needs, coordinating and integrating the Program's preclinical and clinical components to perform pioneering research. CDP employs technology transfer agreements with collaborative partners to advance products through development with a goal of product approval. Each product in CDP's developmental pipeline fills a gap or provides greater safety to vulnerable populations at risk of unintended pregnancy. In accordance with NICHD's new Strategic Plan, development of novel methods can assist with efforts to optimize lives, reduce health disparities, improve reproductive health and increase options for people with disabilities or chronic conditions needing effective contraception.

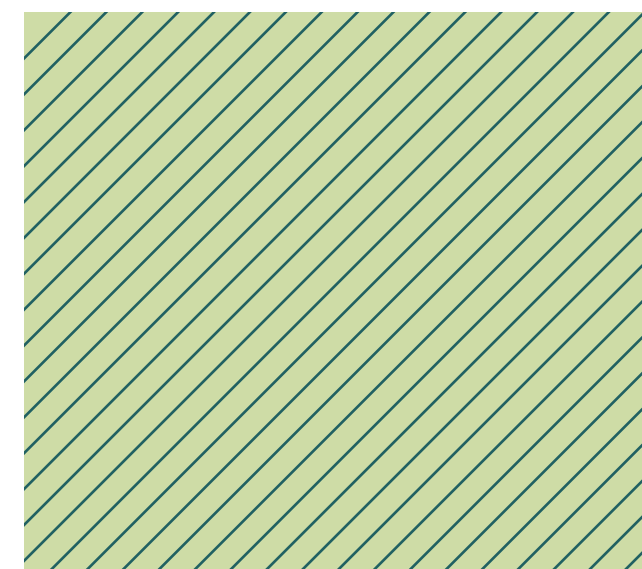
CDP conducts pre-clinical and clinical development of novel products in the pipeline. CDP staff oversee a contracted Chemical Synthesis Facility to synthesize drugs (not commercially available) under current Good Manufacturing Practices (cGMP) as required by FDA, and a Biological Testing Facility to perform preclinical evaluation, toxicology and clinical batch formulation required for first-in-human studies and later Phase clinical trials. IND-enabling preclinical studies of potential new drugs and devices are performed under Good Laboratory Practices (GLP) meeting regulatory standards. Formulation of agents for evaluation in humans are conducted under cGMP with stability studies covering duration of the trials.

The Contraceptive Clinical Trials Network (CCTN)

CDP's CCTN evaluates safety and efficacy of new contraceptive drugs and devices for women and men. Results from clinical trials on new entities form the basis for advancing candidate drugs and devices through development toward FDA regulatory approval. The CCTN comprises top clinical investigators at qualified institutions, both domestic and international, with expertise to conduct all phases of contraceptive evaluation, from first-in-human through Phase III. Clinical sites serve as a training ground for the next generation of investigators in the field.

Pipeline of New Contraceptive Methods for Women and Men

Product development is challenging and has a low success rate with drugs for disease conditions. Once a candidate drug is identified, ~10% pass pre-clinical testing to enter clinical testing; only 12% of those products complete Phase III. Contraceptives are used by healthy people for long durations; thus, long-term safety is essential. CDP has a pipeline of products in clinical evaluation, including hormonal or non-hormonal options for women, and novel hormonal methods for men. Products may enter the pipeline from internal NICHD R&D contracts or from collaborations with partnering organizations. In 2020, seven CDP clinical trials were active, conducting safety and contraceptive evaluation of new drugs or devices in the pipeline. Each new product fills an unmet need or provides greater safety to vulnerable populations at risk of unintended pregnancy. New methods for women include a novel estradiol/progestin vaginal ring that can be used for three months, a long-acting injectable progestin, and a method that protects against HIV infection as well as pregnancy. A trial to evaluate a novel transdermal hormonal male contraceptive method in couples seeking to prevent pregnancy is underway in seven US sites and six international sites.



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Dr. Blithe and CDP collaborators develop new methods for men and women to address unmet needs for safe, effective contraception.

INCREASING CONTRACEPTIVE OPTIONS FOR WOMEN

In the USA, 45% of pregnancies are unintended. One-third of reproductive age women are obese, which increases the risk of diabetes, hypertension and venous thromboembolism (VTE), conditions for which most hormonal methods are contraindicated; yet women face higher risks in pregnancy and need effective contraception.

Contraceptive Vaginal Rings (CVR)

Nestorone®/17β Estradiol CVR is under clinical evaluation for effectiveness over one year of use. Nestorone® blocks follicular development; 17-β estradiol supports bone health without increasing VTE risk. Each ring provides effective contraception for three months. Women can use the product either continuously or cyclically (short ring-out period each cycle) to optimize her individual bleeding pattern.

Long-Acting Reversible Contraceptives (LARCs)

LARCs are effective, highly acceptable methods. The Copper IUD is a safe option for women with health risks to avoid pregnancy. Increased bleeding and cramping associated with Copper IUDs may deter use in nulliparous women, especially adolescents. In collaboration with Gates Foundation and FHI-360, CDP is evaluating a Mini-Copper IUD to determine effectiveness, bleeding characteristics and pain.

Progestin-only Injectable Contraception

LNG-Butanoate (LB) is a novel injectable method with no increase in VTE risk. Injections of long-acting LB improves compliance over progestin-only pills (need intake at same time each day). A subcutaneous route of injection may be self-

administered. Duration of ovulation inhibition is under clinical evaluation.

Multipurpose Prevention Technologies (MPT)

MPTs protect against pregnancy and infection from pathogens.

A Dapivirine/Levonorgestrel (LNG) Vaginal Ring may provide protection from both HIV infection and pregnancy. Safety, drug pharmacokinetics and pharmacodynamics are under clinical evaluation.

Woman's Condom pivotal trial demonstrated acceptability and effectiveness of a novel female condom to prevent pregnancy and transmission of infection. A report to support regulatory approval is in preparation.

DEVELOPMENT OF CONTRACEPTIVE METHODS FOR MEN

The only reversible male method is condoms, which have high failure rates and low acceptability. High testosterone (T) in testes supports spermatogenesis; lower T levels in serum maintain other androgen-dependent functions. Reversible contraception is achieved with exogenous progestins to suppress secretion of gonadotropins responsible for high T production, stopping sperm production in the testes. T replacement in serum is needed to maintain all other androgen-dependent functions.

Nestorone®/Testosterone (Nes/Tes) Gel

Dr. Blithe's CCTN team demonstrated that Nestorone® (a potent progestin) and T gel caused gonadotropin suppression and inhibited sperm production, which recovered after treatment ended; thus, the regimen may be an effective reversible male contraceptive. A Nes/Tes Gel trial is underway to evaluate effectiveness in couples for pregnancy prevention. After a suppression phase to reduce sperm counts, couples use the investigational product for one year of contraception,



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Frances Fernando, M.P.H.,
Postbaccalaureate Fellow

KEY PUBLICATIONS

Chen MJ, Creinin MD, Turok DK, Archer DF, Barnhart KT, Westhoff CL, Thomas MA, Jensen JT, Variano B, Sitruk-Ware R, Shanker A, Long J, Blithe DL. Dose-finding study of a 90-day contraceptive vaginal ring releasing estradiol and segesterone acetate. *Contraception*. 2020;102(3):168-173. PMID: 32416145.

Yuen F, Thirumalai A, Pham C, Swerdloff RS, Anawalt BD, Liu PY, Amory JK, Bremner WJ, Dart C, Wu H, Hull L, Blithe DL, Long J, Wang C, Page ST. Daily Oral Administration of the Novel Androgen 11β-MNTDC Markedly Suppresses Serum Gonadotropins in Healthy Men. *J Clinical Endocrinology and Metabolism*. 2020;105(3):e835-47. PMID: 31976519.



Contraceptive Development Program

then recovery to normal sperm production is followed. Enrollment is ongoing in CCTN sites in the USA, UK, Sweden, Italy, Chile and Kenya.

Novel Progestogenic Androgens for Male Contraception

Dimethandrolone (DMA) and 11 β -Methyl Nortestosterone (MNT) are novel agents with androgenic and progestogenic activities, suppressing gonadotropins while maintaining androgen-dependent functions. CDP is evaluating two pro-drugs (DMA-Undecanoate and MNT-Dodecylcarbonate) administered orally or by injection.

Novel Database to Facilitate Contraceptive Target Discovery

Dr. Lee led development of a new tool for contraceptive and infertility research. This searchable, downloadable [Contraceptive Infertility Target DataBase](#) provides investigators a portal to mine existing transcriptomic and proteomic resources to identify high quality contraceptive/infertility targets in male and female reproductive tissues.

▼▼▼▼ 2020 Key Publications

1. Amyx MM, Albert PS, Bever AM, Hinkle SN, Owen J, Grobman WA, Newman RB, Chien EK, Gore-Langton RE, Buck Louis GM, **Grantz KL**. Intrauterine growth discordance across gestation and birthweight discordance in dichorionic twins. *American Journal of Obstetrics and Gynecology*. 2020;222(2):174.e1-174.e10. PMID: 31454510. PMCID: PMC7535857.
2. **Chen Z**, Ghosal S. A note on modeling placement values in the analysis of receiver operating characteristics curves. *Biostatistics and Epidemiology*. 2020. DOI: 10.1080/24709360.2020.1737794.
3. Chen MJ, Creinin MD, Turok DK, Archer DF, Barnhart KT, Westhoff CL, Thomas MA, Jensen JT, Variano B, Sitruk-Ware R, Shanker A, Long J, Blithe DL. Dose-finding study of a 90-day contraceptive vaginal ring releasing estradiol and segestosterone acetate. *Contraception*. 2020;102(3):168-173. PMID: 32416145.
4. Fairman BJ, Goldstein RB, Simons-Morton BG, Haynie DL, Liu D, Hingson RW, **Gilman SE**. Neighbourhood context and binge drinking from adolescence into early adulthood in a US national cohort. *International Journal of Epidemiology*. 2020;49(1):103-12. Epub 2019/07/03. doi: 10.1093/ije/dyz133. PMID: 31263877. PMCID: PMC7124510.
5. Iszatt N, Janssen S, Lenters V, Dahl C, Stigum H, Knight R, Mandal S, ... **Peddada SD**, & Eggesbø M. Environmental toxicants in breast milk of Norwegian mothers and gut bacteria composition and metabolites in their infants at 1 month. *Microbiome*. 2019;7(1), 34. PMID: 30813950. PMCID: PMC6393990.
6. Kanner J, Williams AD, Nobles C, Ha S, Ouidir M, Sherman S, Grantz KL, **Mendola P**. Ambient temperature and stillbirth: Risks associated with chronic extreme temperature and acute temperature change. *Environmental Research* 2020;189:109958. PMID: 32980027.
7. Lambert C, Gleason JL, Pugh SJ, Liu A, Bever A, Grobman WA, Newman RB, Wing D, Gerlanc NM, Tekola-Ayele F, **Grantz KL**. Maternal Socioeconomic Factors and Racial/Ethnic Differences in Neonatal Anthropometry. *International Journal of Environmental Research and Public Health*. 2020;17(19):1-12. PMID: 33036433. PMCID: PMC7579630.
8. Li M, Hinkle SN, Grantz KL, Kim S, Grewal J, Grobman WA, Skupski DW, Newman RB, Chien EK, Sciscione A, Zork N, Wing DA, Nageotte M, Tekola-Ayele F, Buck Louis GM, Albert PS, **Zhang C**. Glycaemic status during pregnancy and longitudinal measures of fetal growth in a multi-racial US population: a prospective cohort study. *Lancet Diabetes and Endocrinology*. 2020;8(4):292-300.
9. Li M, Rahman ML, Wu J, Ding M, Chavarro JE, Lin Y, Ley SH, Bao W, Grunnet LG, Hinkle SN, Thuesen ACB, Yeung E, Gore-Langton RE, Sherman S, Hjort L, Kampmann FB, Bjerregaard AA, Damm P, Tekola-Ayele F, Liu A, Mills JL, Vaag A, Olsen SF, Hu FB, **Zhang C**. Genetic factors and risk of type 2 diabetes among women with a history of gestational diabetes: findings from two independent populations. *BMJ Open Diabetes Research Care*. 2020;8(1).
10. Lin H and **Peddada, SD**. Analysis of compositions of microbiomes with bias correction. *Nature Communications*, 2020;11(1), 3514. PMID: 32665548.
11. Zhang W, **Liu A**, Li Q, Albert PS. Nonparametric estimation of distributions and diagnostic accuracy based on group-tested results with differential misclassification. *Biometrics*. 2020;76:1147-1156. PMID: 32083733.
12. **Mills JL**, Reische EC, Kannan K, Gao C, Shaw GM, **Sundaram R**. Newborn Iodine Status Is Not Related to Congenital Hypothyroidism, *The Journal of Nutrition*. 2020 Sep 1;150(9):2429-2434. PMID: 32633779. doi: 10.1093/jn/nxaa178. PMID: 32633779.
13. **Mumford SL**, Johnstone E, Kim K, Ahmad M, Salmon S, Summers K, Chaney K, Ryan G, Hotaling JM, Purdue-Smithe AC, Chen Z, Clemons T. A Prospective Cohort Study to Evaluate the Impact of Diet, Exercise, and Lifestyle on Fertility: Design and Baseline Characteristics. *American Journal of Epidemiology*. 2020;189(11):1254-1265. PMID: 32472141. PMCID: PMC7604525.
14. Naimi AI, Perkins NJ, Sjaarda LA, Mumford SL, Platt RW, Silver RM, **Schisterman EF**. The effect of preconception-initiated low-dose aspirin on human chorionic gonadotropin-detected pregnancy, pregnancy loss, and live birth: per protocol analysis of a randomized trial. *Annals of Internal Medicine* 2021;174(5):595-601. PMID: 33493011.
15. **Nansel TR**, Lipsky LM, Burger K, Faith M, Nicholson W, Stuebe A, Liu A, Siega-Riz AM. Reward-related eating, self-regulation, and weight change in pregnancy and postpartum: the Pregnancy Eating Attributes Study (PEAS). *International Journal of Obesity (Lond)*. 2020 Dec;44(12):2444-2454. doi: 10.1038/s41366-020-00685-2. PMID: 32958906.
16. **Nansel TR**, Lipsky LM, Faith M, Liu A, Siega-Riz AM. The accelerator, the brake, and the terrain: associations of reward-related eating, self-regulation, and the home food environment with diet quality during pregnancy and postpartum in the pregnancy eating attributes study (PEAS) cohort. *International Journal of Behavior Nutrition and Physical Activity*. 2020 Nov 23;17(1):149. doi: 10.1186/s12966-020-01047-x. PMID: 33228724.
17. Pitsava G, Zhu C, Sundaram R, **Mills JL**, Stratakis CA. Predicting the risk of cardiac myxoma in Carney complex. *Genetics in Medicine*. 2021 Jan;23(1):80-85. doi: 10.1038/s41436-020-00956-3. Epub 2020 Sep 7. PMID: 32893266.
18. Putnick DL, Sundaram RS, Bell EB, Ghassabian A, Goldstein RB, Robinson SL, Vafai Y, Gilman SE, **Yeung E**. Trajectories of Maternal Postpartum Depressive Symptoms. *Pediatrics* 2020 Nov;146(5):e20200857. doi: 10.1542/peds.2020-0857 PMID: 33109744. PMCID: PMC7772818. {Featured on [NPR](#), Oct 27, 2020}
19. **Schisterman EF**, Sjaarda LA, Clemons T, et al. Effect of folic acid and zinc supplementation in men on semen quality and live birth among couples undergoing infertility treatment: a randomized clinical trial. *JAMA* 2020;323:35-48. PMID: 31910279.
20. Schisterman EF, Sjaarda LA, Clemons T, Carrell DT, Perkins NJ, Johnstone E, Lamb D, Chaney K, Van Voorhis BJ, Ryan G, Summers K, Hotaling J, Robins J, Mills JL, Mendola P, Chen Z, DeVilbiss EA, Peterson CM, **Mumford SL**. Effect of Folic Acid and Zinc Supplementation in Men on Semen Quality and Live Birth Among Couples Undergoing Infertility Treatment: A Randomized Clinical Trial. *JAMA*. 2020;323(1):35-48. PMID 31910279. PMCID: PMC6990807.
21. Stevens D, Grobman W, Kumar R, Lipsky LM, Hinkle SN, Chen Z, Williams A, Rohn MCH, Kanner J, Sherman S, **Mendola P**. Gestational and postpartum weight trajectories among women with and without asthma. *American Journal of Epidemiology* 2020, Nov 10:kwaa248. doi: 10.1093/aje/kwaa248. Online ahead of print. PMID: 33169142.
22. **Tekola-Ayele F**, Zhang C, Wu J, Grantz KL, Rahman ML, Shrestha D, Ouidir M, Workalemahu T, Tsai MY. Trans-ethnic meta-analysis of genome-wide association studies identifies maternal ITPR1 as a novel locus influencing fetal growth during sensitive periods in pregnancy. *PLoS Genet*. 2020;16(5):e1008747. PMID: 32407400; PMCID: PMC7252673.
23. Trinh M, **Sundaram R**, Robinson SL, et al. Association of Trajectory and Covariates of Children's Screen Media Time. *JAMA Pediatrics*. 2020;174(1):71-78. PMID: 31764966.
24. Wang YB, Zhang CL, **Chen Z**. Intergenerational associations between maternal diet and childhood adiposity: A Bayesian regularized mediation analysis. *Statistics in Biosciences*, in press.
25. Workalemahu T, Ouidir M, Shrestha D, Wu J, Grantz KL, **Tekola-Ayele F**. Differential DNA Methylation in Placenta Associated With Maternal Blood Pressure During Pregnancy. *Hypertension*. 2020;75(4):1117-1124. PMID: 32078381. PMCID: PMC7122078.
26. **Yeung EH**, Guan W, Zeng X, Salas LA, Mumford SL, Prado Bert P, van Meel ER, Malmberg A, Sunyer J, Duijts L, Felix JF, Czamara D, Hämäläinen E, Binder EB, Räikkönen K, Lahti J, London S, Silver RM, Schisterman EF. Cord blood DNA methylation reflects cord blood c-reactive protein levels but not maternal levels: a longitudinal study and meta-analysis. *Clinical Epigenetics* 2020 Apr 30;12(1):60. doi: 10.1186/s13148-020-00852-2. PMID: 32354366. PMCID: PMC7193358.
27. Yu J, Ghassabian A, Chen Z, Goldstein RB, Hornig M, Buka SL, Goldstein JM, **Gilman SE**. Maternal Immune activity during pregnancy and socioeconomic disparities in children's self-regulation. *Brain, Behavior, and Immunity*. 2020;90:346-52. Epub 2020/09/13. doi: 10.1016/j.bbi.2020.09.003. PubMed PMID: 32919039. PMCID: PMC7544646.
28. Yuen F, Thirumalai A, Pham C, Swerdlow RS, Anawalt BD, Liu PY, Amory JK, Bremner WJ, Dart C, Wu H, Hull L, Blithe DL, Long J, Wang C, Page ST. Daily Oral Administration of the Novel Androgen 11β-MNTDC Markedly Suppresses Serum Gonadotropins in Healthy Men. *J Clinical Endocrinology and Metabolism*. 2020;105(3):e835-47. PMID: 31976519.
29. Zhang W, **Liu A**, Zhang Z, Nansel T, Halabi S. Best (but oft-forgotten) practices: sample size and power calculation for a dietary intervention trial with episodically consumed foods. *American Journal of Clinical Nutrition*. 2020;112:920-925. PMID: 32644103.



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