NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

DIPHR

2021 ANNUAL REPORT

Division of Population Health Research, DIR, NICHD

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MESSAGE FROM THE DIRECTOR

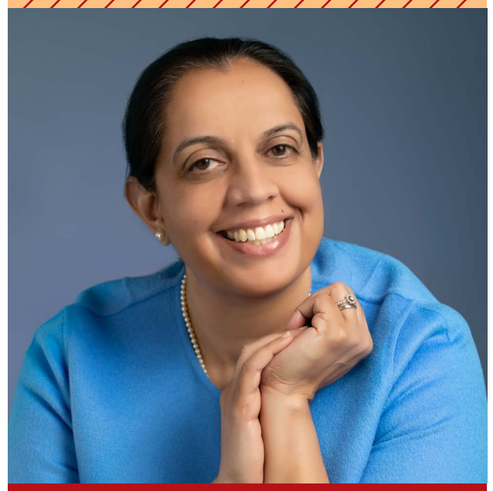
The mission of the Division of Population Health Research (DiPHR) is to conduct research leading to the promotion of population health and well-being.

Thanks to the industrious activities of all the members of DiPHR, records of research productivity, collaboration, external engagement, service, and training remained strong in 2021 despite the unparalleled restrictions on in-person interaction and the overwhelming impact on our daily lives of the global COVID-19 pandemic. The Division has demonstrated resilience in adapting to the disruptions and learning how to remain effective while working in the virtual setting.

DiPHR continues to accomplish its mission by undertaking innovative etiologic and interventional studies from preconception through adulthood and translating discoveries into clinical practice and public policy to improve health outcomes and eliminate health disparities among vulnerable populations, namely pregnant women as well as infants and children. We readily embrace these ambitious aims by partnering in trans-disciplinary research teams across Branches and with extramural partners. The scientists in the Division distinguish themselves by generously providing their expertise throughout the NICHD and the NIH, to professional societies, and to other governmental agencies and research entities and by actively mentoring fellows at the post-baccalaureate through post-doctoral levels.

Our 2021 Annual Report reinforces the Division's commitment 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; discerning maternal and lifestyle factors associated with healthy pregnancies and optimal fetal growth; elucidating the developmental and social determinants of mental health and health disparities; and identifying the onset and timing of behaviors that may extend into childhood. Among the noteworthy findings from research published last year are the following:

- Low-dose aspirin therapy before conception and during early pregnancy increase the likelihood of pregnancy and live births among women who have experienced one or two prior miscarriages (Naimi, et al., 2021)
- Pregnant women with disabilities have a much higher risk for severe pregnancy- and birth-related complications and death than other pregnant women (Gleason, et al., 2021)
- A healthy diet around the time of conception through the second trimester reduces the risk of several common pregnancy complications, including gestational diabetes, hypertension, preeclampsia and preterm delivery (Zhang, et al., 2021)
- Social factors (e.g., low parental education, parental manual occupation) before birth and pregnancy complications are independently related to increased risk of suicide death in offspring, suggesting that vulnerability emerges early in development (Vidal-Ribas, et al., 2021)
- Patterns of screen time indicate that media habits are established early and persist into middle childhood (Trinh, et al., 2021).



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

OFFICE OF THE DIRECTOR

DiPHR emphasizes reproducible research and remains committed to fostering the availability and utilization of original data and biospecimens generated from our population-based studies. The Division was an early pioneer in building interfaces for sharing data from studies with the public. We encourage the broader scientific community, ranging 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).

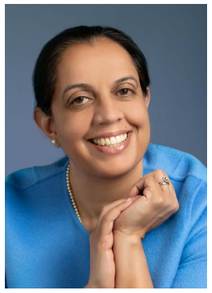
In reflecting on the last year, I am honored to have the opportunity to lead DiPHR through a significant period of transition and unprecedented challenges. On December 5, 2021, I was appointed the Director of DiPHR by Dr. Diana Bianchi, the NICHD Director, after serving as Acting Director since February 2020. I am proud and appreciative of all my colleagues for their extraordinary work in meeting the missions of the Division and the Institute and for supporting me and one another. We are also grateful to the NICHD Director Dr. Bianchi and the Acting Scientific Directors, Drs. Mary Dasso (Feb 2020 – June 2021) and Chris McBain (June 2021 – present) for everything they do to facilitate the work and accomplishments of the Division. Looking forward to 2022 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 and questions about the Division are welcome!

Sincerely,

Una Grewal, Ph.D., M.P.H.
Director, DiPHR, DIR, NICHD

THE DIVISION OF 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.



On December 5, 2021, **Dr. Grewal** was appointed the Director of DiPHR by Dr. Diana Bianchi, the NICHD Director, after serving as Acting Director since February 2020. 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 (PMID: 26410205). 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 (PMID: 33553996. 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 and conducted basic research in molecular endocrinology. 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 DiPHR's data and biospecimens for secondary research, and a core committee member of the NICHD Data and Specimen Hub (DASH). Additionally, Dr. Weck serves as the Contracting Officer's Representative for the Division's biomarker assay laboratory and for the NICHD Biospecimen Repository.

STAFF

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

Adrienne Lonaberger,
Program Analyst

Jennifer Weck, Ph.D.,
Laboratory Health Specialist

FELLOWS

Samrawit Yisahak, Ph.D.,
Postdoctoral Fellow (departed 2021)

BIOSTATISTICS AND BIOINFORMATICS BRANCH

The mission of the Biostatistics and Bioinformatics Branch (BBB) is to (a) conduct methodological research relevant for and motivated by the Intramural Research Program, (b) conduct collaborative research with the researchers in the Intramural Research Program of NICHD, and (c) train the next generation of biostatisticians and bioinformaticians with emphasis on inter-disciplinary sciences.

Motivated by the research conducted in the Division and the Institute, members of BBB develop broadly applicable cutting-edge statistical methodologies that have applications in biomedical, clinical, and population health research. Some areas of expertise within BBB include Bayesian methods, methods for biomarkers and diagnostic accuracy for risk prediction, constrained statistical inference, dynamic risk predictions, genomics, methods for longitudinal data, microbiome, and time to event data, multiple testing, and statistical genetics. Methodological research conducted in BBB often results in freely downloadable, user-friendly software and code available on the BBB webpage. As collaborators, BBB staff are engaged in the entire scientific process of formulating research questions, study design, aims and hypotheses, data analyses and writing manuscripts. An important part of BBB's collaborative mission is to foster Division of Population Health Research (DiPHR) science by maintaining and managing the Statistical Support contract utilized by all DiPHR staff.

In 2021, 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. Novel variable selection-based methods were developed and used to identify important drivers of pregnancy loss in a mixture of environmental toxicants. Specifically, based on exposure to a mixture of 66 persistent endocrine disrupting chemicals (EDCs), females' preconception concentrations of polybrominated diphenyl ether 28 and cadmium were discovered to be positively associated with the incident hCG pregnancy loss in a cohort of couples from the general population trying for pregnancy.

Predictive biomarkers play an important role in precision medicine to identify patients who are more likely to respond to specific therapies. These biomarkers are usually discovered through retrospective analysis from large, randomized trials. A challenge in evaluating predictive biomarkers is that they are usually measured with error, and this would have an adverse impact on the power of a stratified biomarker clinical trial. Members of BBB developed a novel framework for trial designs and an analysis for the stratified biomarker design with time-to-event endpoints, adjusting for biomarker misclassification. They further developed a novel method, making use of a group testing strategy, which involves physically pooling specimens across subjects and assaying pooled samples for the presence of a molecular alteration of interest to improve cost-efficiency beyond the conventional random sampling designs. Also, a Bayesian methodology was developed by BBB staff to evaluate mediation effects of multiple exposures on time to pregnancy.

The members of BBB also developed a novel Bayesian approach for estimating multiple ordered ROC curves for evaluating fetal growth and proposed an innovative extension of a hidden Markov model to understand parent-child relationships in families with youth who have type 1 diabetes.

A pressing research question is whether some people are

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

STAFF

Zhen Chen, Ph.D.,
Senior Investigator

Aiyi Liu, Ph.D.,
Senior Investigator

Rajeshwari Sundaram, Ph.D.,
Senior Investigator

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

FELLOWS

Soutik Ghosal, Ph.D.,
Research Fellow

Ruijin Lu, Ph.D.,
Postdoctoral Fellow

Abhisek Saha, Ph.D.,
Postdoctoral Fellow

Jin Yang, Ph.D.,
Postdoctoral Fellow

Huang Lin, Ph.D.,
Postdoctoral Fellow

BIOSTATISTICS AND BIOINFORMATICS BRANCH

more pre-disposed to a disease than others when exposed to an infection. The BBB researchers have explored answers to this question by identifying microbiota that are differentially abundant among men months before they developed HIV infection, and years before they developed AIDS. This discovery makes one speculate whether similar phenomenon may be true for other diseases including COVID.

BBB investigators collaborated extensively with researchers in the DiPHR in all aspects of their studies including study concept, design, implementation, and analysis. In addition to strengthening existing collaborations with DiPHR researchers, members of the branch have expanded collaborations with researchers in the Division of Intramural Research (DIR), such as new partnerships with the members of Bioinformatics and Scientific Programming Core (BSPC, DIR) and Perinatology Research Branch (DIR), among others. Furthermore, BBB staff serve on important NIH and external committees such as the NICHD's Institutional Review Board, the Women Scientists Advisors (WSA), and numerous Data and Safety Monitoring Boards for the NIH. BBB investigators serve as associate editors of the journals, Statistical Methods in Medical Research, Statistics in Biosciences, Clinical Trials, and Nutrients.

The branch successfully recruited Dr. James Morton as a tenure track investigator who has expertise in computational biology, with a focus on high dimensional microbiome and metabolomics data.

Shyamal Peddada, Ph.D.

Statistical methods under constraints with applications

Dr. Peddada's research focus is on developing broadly applicable statistical methods for analyzing complex biomedical data generated by researchers at NICHD. Some areas of his research include constrained statistical inference with applications, methods for nonlinear associations between exposures and outcomes, methods for compositional data with applications, the human microbiome, and other omics 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, and anxiety. This is not 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, and epigenetics, the human microbiome is associated with our health and disease. Ongoing research includes assessment of factors associated with 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. In a recent publication, Dr. Peddada and his team explored the question of whether some people are more pre-disposed to a disease than other when exposed to an infection. To address this question, the research team worked on identifying microbiota that are differentially abundant among men months before they developed HIV infection, and years before they developed AIDS. This discovery makes one to speculate whether similar phenomenon may be true for other diseases including COVID.

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

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

Huang Lin, PhD.,
Postdoctoral Fellow

KEY PUBLICATIONS

Chen Y, Lin H, Cole M, Morris A, Martinson J, Mckay H, Mimiaga M, Margolick J, Fitch A, Methe B, Srinivas V, **Peddada SD**, Rinaldo CR. Signature changes in gut microbiome are associated with increased susceptibility to HIV-1 infection in MSM. *Microbiome*. 2021 Dec;9(1). PMID: 34879869. PMCID: PMC8656045

Adibi JJ, Xun X, Zhao Y, Yin Q, LeWinn K, Bush NR, Panigrahy A, **Peddada SD**, Alfthan H, Stenman U, Tylavsky F, Koistinen H. Second-Trimester Placental and Thyroid Hormones Are Associated With Cognitive Development From Ages 1 to 3 Years. *J. Endocrinol*. 2021 Feb 23;5(5). PMID: 33928202. PMCID: PMC8064052

Yin Q, Xun X, **Peddada SD**, Adibi JJ. Shape Detection Using Semi-Parametric Shape-Restricted Mixed Effects Regression Spline with Applications. *Sankhya B*. 2021 Feb 24;83(S1):65–85. PMID: 35392640. PMCID: PMC8986130.

Aiyi Liu, Ph.D.

Methods for predictive biomarkers and clinical trials with applications

Dr. Liu's research in 2021 focused on developing innovative methodologies for assessment of predictive biomarkers for precision medicine. Predictive biomarkers play an important role in precision medicine to identify patients who are more likely to respond to specific therapies or behavioral intervention. These biomarkers are usually discovered through retrospective analysis from large, randomized trials. Subject to cost constraints, the level of evidence can be attained by assaying all or a random sample of specimens collected at baseline. A challenge in evaluating predictive biomarkers is that they are usually measured with error, and this would have an adverse impact on the power of a stratified biomarker clinical trial or other designs for evaluation of predictive biomarkers. To further reduce cost and improve efficiency beyond the traditional designs, group testing strategy, which involves physically pooling specimens across subjects and assaying pooled samples for the presence of a molecular alteration of interest, can be employed.

Aiyi Liu, Ph.D.
Senior Investigator

STAFF
Jin Yang, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Zhang W, Zhang Z, Krushkal J, **Liu A**. Group testing can improve the cost-efficiency of prospective-retrospective biomarker studies. *BMC Med Res Methodol*. 2021 Mar 19;21(1):55. doi: 10.1186/s12874-021-01239-4. PMID: 33740890. PMCID: PMC7977501.

Halabi S, Lin CY, **Liu A**. On the design and the analysis of stratified biomarker trials in the presence of measurement error. *Stat Med*. 2021 May 30;40(12):2783-2799. doi: 10.1002/sim.8928. Epub 2021 Mar 16. PMID: 33724513. PMCID: PMC8113124.

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

Statistical methods for time-to-event data with application to reproductive, obstetric, and environmental sciences

Many studies in DiPHR are interested in the characterization of time to an event, recurrent events, and multistage models. In many studies, correlated event-times are measured, for example, repeated time-to pregnancy, gestation at birth in consecutive pregnancies, progression of labor in pregnant women, and recurrent crashes or near crashes by teenage drivers. Furthermore, there is also interest in focusing on identifying time-varying exposures, environmental toxicants or behavioral factors that influence these durations. There are many new analytic challenges for analyzing such data. For example, progression of labor can be classified as multistage data consisting of various stages of labor, intermittent examinations, and unobserved start time. Time to pregnancy and other outcomes related to maternal and child health pose new analytic challenges since, unlike with traditional survival analysis, time-to-pregnancy analysis must account for the fact that there is no risk of pregnancy without intercourse during a particular window in time. Environmental toxicants in the context of mixtures provide high-dimensional longitudinal survival outcomes. The focus of Dr. Sundaram's research program is to develop appropriate statistical methods to address the above data in the presence of non-standard missingness, as well as accounting for the underlying (biological/behavioral) structure of the event of interest. These methods have been developed with a view towards individualized risk predictions. Dr. Sundaram is also interested in studying joint modeling of longitudinal processes with time-to-event for risk prediction. For building better prediction models, an objective of her research program is to develop methods that borrow information across various studies.

Dr. Sundaram is also developing statistical methods to assess associations among environmental pollutants and various biomarkers of reproductive outcomes. To better assess mixtures of chemicals in the context of assessing exposome, she develops novel methods that account for highly skewed and correlated distributions of exposures and issues of limit of detection.

Dr. Sundaram serves as the DiPHR representative and executive committee member of the Women Scientists Advisors (WSA). She is also one of its two representatives on the Working Group for Women in Biomedical Career (WgWBC). In these multiple committees involving women scientists, Dr. Sundaram has focused on the retention of women scientists at various levels, strategizing to protect the tenure track scientists from the long-term impact of the pandemic on their careers, and advancing senior women scientists in leadership positions. She was also the Chair of the DiPHR professional development committee where she engaged to train fellows in grant writing and organized various webinars on career opportunities, building resumes, and effective stress management.

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

STAFF
Abhisek Saha, Ph.D., *Postdoctoral Fellow*

KEY PUBLICATIONS

Smarr MM, Mirzaei Salehabadi S, Boyd Barr D, Buck Louis GM, **Sundaram R**. A multi-pollutant assessment of preconception persistent endocrine disrupting chemicals and incident pregnancy loss. *Environ Int*. 2021 Dec; 157:106788. Epub 2021 Jul 28. PMID: 34332300.

Yeung EH, Saha A, Zhu C, Trinh MH, Hinkle SN, Pollack AZ, Grantz KL, Mills JL, Mumford SL, Zhang C, Robinson SL, Gillman MW, Zhang J, Mendola P, **Sundaram R**. Placental characteristics and risks of maternal mortality 50 years after delivery. *Placenta*. 2022 Jan;117:194-199. Epub 2021 Dec 15. PMID: 34929460. PMCID: PMC8938897.

Zhen Chen, Ph.D.

In 2021, Dr. Chen worked on 7 methodological papers and 23 collaborative manuscripts. Dr. Chen presented his research work in the seminar series of Mount Sinai. He also actively participated in professional services, including serving as an ad-hoc reviewer for the NIEHS BSC site visit, on the NICHD Data Safety Monitoring Committee, in the NICHD BRADS Committee, as BBB Staff Scientist Search Committee chair, as BBB Seminars Committee chair, and as an Associate Editor for the journal, Statistics in Biosciences. Dr. Chen mentored two postdoctoral fellows (Ghosal and Lu). Of special note, Dr. Chen stepped in to serve as PI of the NICHD B-Well-Mom study after its original PI departed. This is in addition to a similar responsibility Dr. Chen shouldered as part of the NICHD ENDO study. Two examples of Dr. Chen's 2021 work are listed below.

Estimation of multiple ordered ROC curves using placement values

In many diagnostic accuracy studies, ***a priori*** orders may be available on multiple receiver operating characteristics (ROC) curves. For example, being closer to delivery, fetal ultrasound measures in the third trimester should be no less accurate than those in the second trimester in predicting small-for-gestational-age births. Such an ***a priori*** order should be incorporated in estimating ROC curves and associated summary accuracy statistics, as it can potentially improve statistical efficiency of these estimates. Earlier work in the literature has mainly taken an indirect approach to this task and has induced the desired ***a priori*** order through modeling test score distributions. Rather than this indirect approach, an order among ROC curves was modeled directly in the estimation. This was achieved by exploiting the link between placement value (the relative position of a diseased test score in the healthy score distribution), the cumulative distribution function of placement value, and ROC curve, and by building stochastically ordered random variables through mixture distributions. A Bayesian semiparametric approach was taken in using Dirichlet process mixture models so that the placement values can be flexibly modeled. The methodology was evaluated using synthetic data and was applied to several datasets from obstetrics and women's health studies.

A perception-augmented hidden Markov model for family management of diabetes

In youth with Type 1 diabetes, adherence to medical treatment regimens requires the involvement of both parent and child. A clinic-integrated behavioral intervention in the Family Management of Diabetes (FMOD) trial was shown to be effective in controlling deterioration in glycemic level; yet the mechanism remains unknown. It is possible that the effectiveness is through improved parent-child relationships. To investigate whether the intervention improves parent-child relationships, a novel methodology was developed that allows differential perceptions of parent and child toward the unobserved parent-child relationship. Leveraging manifesto data collected from both parent and child in the FMOD trial, the proposed approach extended a standard hidden Markov model by inserting a layer of parent- and child-specific hidden states. A Bayesian estimation procedure was developed that was computationally efficient to sample from the joint posterior distribution. Extensive simulations were conducted to demonstrate the performance of the proposed modeling framework. Application to the FMOD trial data revealed that families in the intervention arm were more likely to stay in the Harmonious parent-child relationship state and less likely to transition from a Harmonious to an Indifferent state. Compared to the parent, children tend to have a more heterogeneous perception of the parent-child relationship.

Zhen Chen, Ph.D.,
Senior Investigator

STAFF

Soutik Ghosal, Ph.D.,
Research Fellow

Ruijin Lu, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Ghosal S, Grantz K, **Chen Z**. Estimation of multiple ordered ROC curves using placement values. *Stat Methods Med Res*. 2022; in press.

Lu R, Nansel T, **Chen Z**. A perception-augmented hidden Markov model for family management of diabetes. *Stat Med*. 2022; under review.

EPIDEMIOLOGY BRANCH

In 2021, the Epidemiology Branch (EB) of the Division of 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 researchers at various stages of their professional careers for training in reproductive, perinatal, pediatric, and methodological epidemiologic research.

Research in EB is organized around health during key developmental stages throughout the life course; including reproductive health, pregnancy, infancy, and childhood, in addition to research in epidemiologic methods. The EB is committed to using trans-disciplinary, cutting-edge techniques to address critical data gaps in these areas while advancing the mission of NICHD and DiPHR. Current Epidemiology Branch initiatives are furthering our understanding of health challenges in several areas. In reproductive health, EB is focused on clinical trials evaluating inexpensive interventions to improve reproductive health and fertility in men and women, including the recent completion of the largest clinical trial focused on male fertility. Research within EB also investigates the effects of diet and lifestyle on male and female reproductive health, with critical public health implications for couples seeking pregnancy. Moreover, in the field of pregnancy and fetal development, EB studies the genetic and environmental determinants, etiology, and health consequences of adverse pregnancy 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, EB 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, EB 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 the life span and to identify determinants to improve women's health. Collectively, EB is improving public health by providing evidence to inform clinical guidance and public policy regarding care of individuals and couples intending to reproduce, pregnant women and their fetuses, and infants and children.

Edwina H. Yeung, Ph.D., Sc.M.,
Senior Investigator and Acting Chief

STAFF

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

Jessica L. Gleason, Ph.D., M.P.H.,
Research Fellow

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

Stefanie N. Hinkle, Ph.D.,
Staff Scientist
(departed in 2021)

Keewan Kim, Ph.D., M.P.H.,
Research Fellow
(departed in 2021)

EPIDEMIOLOGY BRANCH (CONT.)

High quality scientific investigation in these various domains across the life course has yielded many awards recognizing the hard work of EB team members. During 2021 alone, four EB postdoctoral 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, EB investigators received several awards from NICHD and from the Society for Birth Defects Research and the American Society of Human Genetics. The excellence found within the EB paired with the freedom and opportunity that comes with having large and unique data sets available makes the EB uniquely positioned to pursue trans-disciplinary, high-risk research in novel and emerging areas of reproductive, perinatal, pediatric, and methodologic epidemiology.

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

Sunni L. Mumford, Ph.D., M.S.,
Stadtman Investigator
(departed in 2021)

Diane L. Putnick, Ph.D., M.S.,
Staff Scientist

Enrique F. Schisterman, Ph.D., M.A., *Senior Investigator and Chief*
(departed in 2021)

Lindsey A. Sjaarda, Ph.D., M.S.,
Staff Scientist
(departed in 2021)

Fasil Tekola-Ayele, Ph.D., M.P.H.,
Stadtman Investigator

Cuilin Zhang, M.D., Ph.D., M.P.H.,
Senior Investigator
(departed in 2021)

FELLOWS

Suvo Chatterjee, Ph.D.,
Postdoctoral Fellow

Kerry Flannagan, Ph.D.,
Postdoctoral Fellow
(departed in 2021)

Joshua Freeman, M.S.,
Predoctoral Fellow
(departed in 2021)

Susanna Mitro, M.P.H., Ph.D.
Postdoctoral Fellow

Marion Ouidir, Ph.D.,
Visiting Fellow

Georgia Pitsava, M.D.,
Visiting Fellow

Kristen Polinski, Ph.D.,
Postdoctoral Fellow

Alexandra Purdue-Smith, Ph.D.,
Postdoctoral Fellow
(departed in 2021)

Sonia Robinson, Ph.D.,
Postdoctoral Fellow
(departed in 2021)

Danielle Stevens, Ph.D.,
Postdoctoral Fellow
(departed in 2021)

Sifang (Kathy) Zhao, Ph.D.,
Postdoctoral Fellow

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

Edwina Yeung, Ph.D., Sc.M., *Senior Investigator and Chief (Acting)*

STAFF

Diane Putnick, Ph.D., *Staff Scientist*

Kristen Polinski, Ph.D., *Postdoctoral Fellow*

Sonia Robinson, Ph.D., *Postdoctoral Fellow* (departed 2021)

Sifang (Kathy) Zhao, Ph.D., *Postdoctoral Fellow*

KEY PUBLICATIONS

Yeung EH, Mendola P, Sundaram R, Zeng X, Guan W, Tsai MY, Robinson SL, Stern JE, Ghassabian A, Lawrence D, O'Connor TG. Conception by fertility treatment and offspring deoxyribonucleic acid methylation. Fertility and Sterility 2021 Aug 1;116(2):493-504. PMID: 33823999. PMCID: PMC8349775

Robinson SL, Sundaram R, Putnick DL, Gleason JL, Ghassabian A, Lin TC, Bell EM, **Yeung EH**. Predictors of Age at Juice Introduction and Associations with Subsequent Beverage Intake in Early and Middle Childhood. The Journal of Nutrition 2021 Nov;151(11):3516-23. PMID: 34486676. PMCID: PMC8564695

Upstate KIDS Follow-up

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. 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 have been completed. Assays are also completed 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).

In 2021, an epigenetic mechanism which may explain developmental programming was scrutinized. Leveraging longitudinal measures of child DNA methylation in the Upstate KIDS cohort, Dr. Yeung investigated differences in DNA methylation by infertility treatment status (assisted reproductive technology (ART) vs. ovulation induction vs. no treatment) at birth and age 9 (PMID: 33823999). Compared to no fertility treatment, ART was associated with different DNA methylation levels at birth in 12 cytosine-guanine (CpG) sites. In addition, nine regions in maternally imprinted genes were hypomethylated among newborns conceived by ART, one of which was replicated at age 9. Ovulation induction was not associated with differences in DNA methylation, suggesting that infertility treatment, and not infertility itself, was the acting factor. Separately, 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 preconception serum caffeine metabolites were not associated with individual CpG sites, but theobromine measured in pregnancy was associated with methylation at a single site (PMID: 34669932). Thus, results suggest few effects of maternal caffeine exposure on neonatal methylation differences in a cohort with low caffeine intake.

Dr. Yeung's team also used the Upstate KIDS cohort to investigate aspects of early child growth and development. In one study, increased gestational age at birth was associated with reduced odds of developmental delay in offspring among singletons and twins regardless of mode of conception (PMID: 32143225). In another study, the age a child was first introduced to juice was associated with higher childhood juice intake, any soda intake, and lower water intake. Early introduction of juice in infancy may serve to "program" a preference for sweet tastes in children (PMID: 34486676).

> "Early introduction of juice in infancy may serve to 'program' a preference for sweet tastes in children."

SPAN Study of Pregnancy & Neonatal Health

Dr. Yeung also began establishing the Study of Pregnancy and Neonatal Health (SPAN) 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.

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.

"Screening for gestational diabetes may start early in the first trimester of pregnancy based on a panel of biomarkers including metabolomics profile."

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-term health consequences of gestational diabetes and their determinants. In 2021, Dr. Zhang's team identified both the amount and type of alcohol consumption significantly associated with type 2 diabetes risk among women with a history of gestational diabetes (PMID: 34499132). Dr. Zhang also led her team in their continued efforts to identify potentially modifiable avenues including lactation duration (PMID: 33115816; 32041900) 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 a 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 acylcarnitines (PMID: 34940643) and lipidomics (PMID: 33674279) in early to mid-pregnancy, and changes in phospholipids fatty acids (PMID: 34632496) were significantly related to the risk for developing gestational diabetes. Notably, the team also discovered that maternal plasma levels of fatty acids and proinflammatory adipokines were significantly associated with birth weight and neonatal anthropometric measures indicating potential intergenerational impacts of nutrition and inflammation (PMID: 34693193; 35276951).

Lastly, analyses in 2021 (PMID: 35136903) demonstrated the significant association of pregnancy loss with long-term mortality in 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,
Branch Chief (Former Acting)

STAFF

Stefanie N. Hinkle, Ph.D.,
Staff Scientist
(departed 2021)

Sifang Kathy Zhao, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Zhang C, Catalano P. Screening for Gestational Diabetes. *JAMA*. 2021 Aug 10;326(6):487-489. PMID: 34374733.

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Hinkle SN, Bao W, Wu J, Sun Y, Ley SH, Tobias DK, Qian F, Rawal S, Zhu Y, Chavarro JE, Hu FB, **Zhang C**. Association of Habitual Alcohol Consumption with Long-term Risk of Type 2 Diabetes Among Women with a History of Gestational Diabetes. *JAMA Netw Open*. 2021 Sep 1;4(9):e2124669. PMID: 34499132. PMCID: PMC8430455.

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

Iodine deficiency is common in pregnancy both in Europe and in the US where almost half of pregnant women are deficient. Prior research suggests that severe iodine deficiency in pregnancy may be associated with stillbirth. However, the relationship between mild to moderate iodine insufficiency and risk of stillbirth is unclear. We examined associations of iodine status and risk of stillbirth in a prospective population-based nested case-control study in Finland, a mild to moderately iodine insufficient population. Stillbirth cases (n = 199) and unaffected controls (n = 249) were randomly selected from among all singleton births in Finland from 2012 to 2013. Serum samples were collected between 10 and 14 weeks gestation and analyzed for iodide, thyroglobulin (Tg) and thyroid-stimulating hormone (TSH). Iodine is essential for normal thyroid function and Tg and TSH are good markers of thyroid function during pregnancy. Odds ratios (ORs) and 95% confidence intervals (CIs) for stillbirth were estimated using logistic regression. After adjusting for maternal age, pre-pregnancy body mass index, socio-economic status and other factors, neither high nor low serum iodide was associated with risk of stillbirth (Q1 vs. Q2-Q3 OR = 0.92, 95% CI = 0.78-1.09; Q4 vs. Q2-Q3 OR = 0.78; 95% CI = 0.45-1.33). Tg and TSH were also not associated with risk of stillbirth in adjusted models. In summary, maternal iodine status was not associated with stillbirth risk in this mildly to moderately iodine-deficient population. Tg and TSH, which reflect functional iodine status, were also not associated with stillbirth risk. The lack of associations observed between serum iodide, TSH and Tg and risk of stillbirth is reassuring, given that iodine deficiency in pregnancy is prevalent in many developed countries.

"Although half of pregnant women in the US are iodine deficient, it is reassuring that the deficiency is not severe enough to cause stillbirths."

Bladder exstrophy (BE) is a rare, lower ventral midline defect with the bladder and part of the urethra exposed. The etiology of BE is unknown but thought to be influenced by genetic variants. We conducted paired-end exome sequencing in 26 child/mother/father trios. Three children had rare (allele frequency ≤ 0.0001 in several public databases) inherited variants in TSPAN4, one with a loss-of-function variant and two with missense variants. Two children had loss-of-function variants in TUBE1. Four children had rare missense or nonsense variants (one per child) in WNT3, CRKL, MYH9, or LZTR1, genes previously associated with BE. We detected 17 de novo missense variants in 13 children and three de novo loss-of-function variants (AKR1C2, PRRX1, PPM1D) in three children (one per child). We also detected rare compound heterozygous loss-of-function variants in PLCH2 and CLEC4M. Variants in two genes identified may implicate disruption in cell migration (TUBE1) and adhesion (TSPAN4) processes, mechanisms proposed for BE, and provide additional evidence for rare variants in the development of this defect.

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

STAFF
Georgia Pitsava, M.D.,
Visiting Fellow

Alexandra Purdue-Smithe, Ph.D.,
Postdoctoral Fellow
(departed 2021)

KEY PUBLICATIONS

Purdue-Smithe AC, Männistö T, Reische E, Kannan K, Kim UJ, Suvanto E, Surcel HM, Gissler M, **Mills JL**. Iodine and thyroid status during pregnancy and risk of stillbirth: A population-based nested case-control study. Matern Child Nutr. 2022 Jan;18(1):e13252. Epub 2021 Aug 4. PMID: 34350728. PMCID: PMC8710109.

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

Obstetrics is in need of evidence to help guide the creation of clinical guidelines. Dr. Grantz's research program focuses on fetal growth and labor and delivery management with a particular interest on when to deliver a high-risk pregnancy. As co-PI of the NICHD Fetal Growth Studies, her research program investigates normal or expected growth velocity and fetal growth patterns, works to distinguish pathologic fetal growth and birth weight from constitutionally small or large fetuses, and identifies risk factors associated with abnormal fetal growth and birth weight. In 2021, Dr. Grantz followed up the original fetal growth standards stratified by race/ethnicity to lead creation of a contemporary, unified, multi-ethnic fetal growth standard (PMID: 34906542). Her team also developed an innovative approach for calculating longitudinal fundal height that, compared to the standard cross-sectional fundal height, improved identification of SGA birthweight, while simultaneously reducing the number of ultrasounds needed (PMID: 33940642). As an essentially free-of-charge screening test, this novel method has potential to decrease costs as well as perinatal morbidity and mortality (through better prediction of SGA). Her team also found that plasma cotinine concentration (from passive smoking exposure) had a variable association with neonatal size that differed by maternal race/ethnicity (PMID: 34793459). These findings indicate that public health campaigns should advocate for reducing pregnancy exposure, particularly for vulnerable populations.

Fetal Growth Study NICHD

In the primary twin study from the NICHD Fetal Growth Studies, the mean estimated fetal weight trajectories of dichorionic twin fetuses diverged significantly from singletons beginning at 32 weeks (PMID: 26410205). However, it was unclear whether this reduced growth was a result of pathologic growth restriction or whether SGA twins are simply constitutionally smaller because of adaptation to a restricted intrauterine environment. Dr. Grantz's team found that using a singleton-based growth reference to define SGA may overestimate SGA in twins, but a singleton reference may be appropriate for twins because it identifies more twins at risk of developmental delay and require outreach services than a twin-based reference (PMID: 34416423).

Fetal 3D Study NICHD

Building on work in 2D ultrasound, her team is beginning work in 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.

SPAN Study of Pregnancy & Neonatal Health

Dr. Grantz also is co-PI on the Study of Pregnancy and Neonatal Health (SPAN), leading the TIMing of dElivery (TIME) trial 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., *Research Fellow*

Susanna Mitro, Ph.D. *Postdoctoral Fellow*

KEY PUBLICATIONS

Gleason JL, Yeung E, Sundaram R, Vafai Y, Robinson SL, Mendola P, Bell E, Putnick D, **Grantz KL**. Exploring developmental outcomes in small for gestational age twins using a singleton versus twin birthweight reference: Upstate KIDS. American Journal of Obstetrics & Gynecology Maternal-Fetal Medicine. 2021; 3(6):100465. PMID: 34416423. PMCID: PMC8630670.

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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. The genetic influence on fetal growth is not well characterized in non-European ancestry populations. By leveraging the mosaic pattern of ancestry among admixed African Americans and Hispanic Americans in the NICHD Fetal Growth Studies cohort, the team identified 13 genetic loci in which the level of African or Amerindigenous ancestry at a given genetic locus (known as local ancestry) is associated with fetal growth. Notably, at the chr2q.23.3-q24.2 African ancestry locus, which is associated with longer long bones, a genetic variant (GALNT13) that explained most of the association has distributions that are starkly different between African and European ancestry populations. The GALNT13 locus overlaps with a transcription factor previously implicated in bone formation in mice. This and other genetic loci identified by the study point to molecular pathways involved in fetal growth regulation and ancestry-related differences. These findings shed light on potential contribution of ancestry in fetal growth differences (PMID: 33590300). In another study, the group revealed an abundance of shared genetic effect (pleiotropy) between childhood obesity and adult cardiometabolic phenotypes, offering novel insights on shared molecular pathways and potential early intervention targets to mitigate future risk for cardiometabolic diseases (PMID: 33420178).

The goal of the second research theme is to investigate placental genetic/epigenetic mechanisms related to fetal growth, placental aging "clock", and cardiometabolic risk factors. Studies on this line of investigation identified placental methylation "footprints" of maternal cardiometabolic factors and maternal depression during pregnancy. The DNA methylation changes associated with maternal depression are implicated in fetal neurodevelopmental outcomes and psychiatric diseases (PMID: 34585950). Epigenetic loci that exhibit high inter-individual variation in methylation levels, known as variably methylated regions (VMRs), can play crucial regulatory roles in development. Dr. Tekola-Ayele's team developed a genome-wide atlas of placenta-specific VMRs and demonstrated that methylation at a striking 82% of VMRs is best explained by interactions of genetic and environmental factors. The placental VMRs are made available as a resource for investigating functionally and clinically relevant epigenetic sites (PMID: 34155504).

Dr. Tekola-Ayele has continued the preparation for recruitment of study participants in a newly initiated genetic study in 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. Successful completion of this study will lay a foundation for etiological insights into pregnancy outcomes and childhood diseases, biomarker discovery, and clinical and public health translations.

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

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Suvo Chatterjee, Ph.D.,
Postdoctoral fellow

Marion Ouidir, Ph.D.,
Postdoctoral fellow

KEY PUBLICATIONS

Tekola-Ayele F, Ouidir M, Shrestha D, Workalemahu T, Rahman ML, Mendola P, Grantz KL, Hinkle SN, Wu J, Zhang C. Admixture mapping identifies African and Amerindigenous local ancestry loci associated with fetal growth. *Hum Genet*. 2021;140(7):985-997. PMID: 33590300. PMCID: PMC8197736.

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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 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, couples, and across generations. 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.

"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."

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 (PMID: 33530988), 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, and exposure to cadmium with endocrine features to a PCOS-phenotype, highlighting the potential role of dietary and environmental factors to influence ovulatory function in reproductive-aged women (PMID: 34022900).

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 that preconception cannabis use was associated with reduced fecundability (PMID: 33421071), but that serum caffeine (PMID: 35030239), telomere length (PMID: 34477845), and hemoglobin A1c levels (PMID: 35386497) were not associated with fecundability. In addition, preconception vitamin D levels were positively associated with the offspring sex ratio, suggesting that vitamin D may mitigate maternal inflammation that would otherwise be detrimental to the implantation or survival of male conceptuses in utero (PMID: 33986298).

FAZST is the largest clinical trial focused on male fertility (PMID: 31712803). The team recently found that folic acid and zinc supplementation in men was not associated with sperm DNA methylation, in line with prior findings that found no relationships with live birth rates or semen quality parameters (PMID: 34656303). 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 (PMID: 32472141).

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

STAFF

Keewan Kim, Ph.D., M.P.H., *Research Fellow* (departed 2021)

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

Alexandra Purdue-Smith, Ph.D., *Postdoctoral Fellow* (departed 2021)

Joshua Freeman, M.S., *Predoctoral Fellow* (departed 2021)

KEY PUBLICATIONS

Jenkins T, Aston K, Carrell D, DeVilbiss E, Sjaarda L, Perkins N, Mills JL, Chen Z, Sparks A, Clemons T, Chaney K, Peterson CM, Emery B, Hotaling J, Johnstone E, Schisterman E, **Mumford SL**. The impact of zinc and folic acid supplementation on sperm DNA methylation: results from the folic acid and zinc supplementation randomized clinical trial (FAZST). *Fertil Steril*. 2022 Jan;117(1):75-85. Epub 2021 Oct 14. PMID: 34656303.

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SOCIAL AND BEHAVIORAL SCIENCES BRANCH

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.

In 2021, SBSB welcomed Dr. Bobby Cheon as a new Stadtman Investigator. Prior to joining SBSB, Dr. Cheon served on the faculty at Nanyang Technological University in Singapore.

Research within SBSB integrates approaches from diverse disciplines including psychology (community, clinical, and developmental), nutrition, health education, and epidemiology (social, psychiatric, and developmental). Collaborations with other DiPHR 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. The developmental focus strives to identify and intervene early in life on pathways to disease for maximal impact on population health.

The SBSB research programs are organized along axes of substantive 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 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 due to 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. 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.

An area of investigation initiated in the past year creates a bridge between our work on health disparities and eating behaviors by investigating how perceptions of stigma and economic insecurity may represent a mechanism through which dipartites in socioeconomic status may translate into overeating and risks for obesity.

Stephen E. Gilman, Sc.D.,
Senior Investigator and Branch Chief

STAFF

Bobby Cheon, Ph.D.,
Stadtman Investigator

Denise Haynie, Ph.D., M.P.H.
Staff Scientist

Leah Lipsky, Ph.D., M.H.S
Staff Scientist

Tonja Nansel, Ph.D.,
Senior Investigator

Jing Yu, Ph.D.,
Research Fellow

SOCIAL AND BEHAVIORAL SCIENCES BRANCH (CONT.)

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

Diana Augustin, B.A., *NIH Academy Enrichment Program Postbaccalaureate Fellow*

Jenna Cummings, Ph.D., *Postdoctoral Fellow*

Theemeshni Govender, B.A., *Postbaccalaureate Fellow*

Evelyn Liu, B.S., *Postbaccalaurate Fellow*

Jan Mooney, M.A., *Predoctoral Fellow*

Reeya Patel, M.S., *Postbaccalaureate Fellow* (departed 2021)

Julia Porth, Ph.D., *Postdoctoral Fellow*

Carolina Schwedhelm-Ramirez, Dr.P.H., *Visiting Fellow* (departed 2021)

Meeghan Smith, B.A., *Postbaccalaureate Fellow*

Chelsie Temmen, Ph.D., *Postdoctoral Fellow* (departed 2021)

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

Stephen E. Gilman, Sc.D.

Social determinants of child development and mental healt

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.

Our work seeks a better understanding of how environments influence development from the prenatal period onward, generate new mechanistic insights into early life origins of health disparities, identify developmentally sensitive periods for the emergence of health disparities, and uncover opportunities for reducing disparities at the population level.

Our research focuses on child development, environmental factors at multiple levels of analysis (individual, family, and neighborhood), associated biomarkers of exposure and impact, and long-term outcomes with an emphasis on mental health and mental disorders. Inspired by the "Developmental Origins of Health and Disease" and "Life Course Epidemiology" movements, our work adopts multiple approaches in diverse populations to advance knowledge of the social determinants of health, focusing on developmental mechanisms (e.g., figure 1 from Yu et al., Current Opinion in Psychiatry, 2021). Ongoing studies are described below.

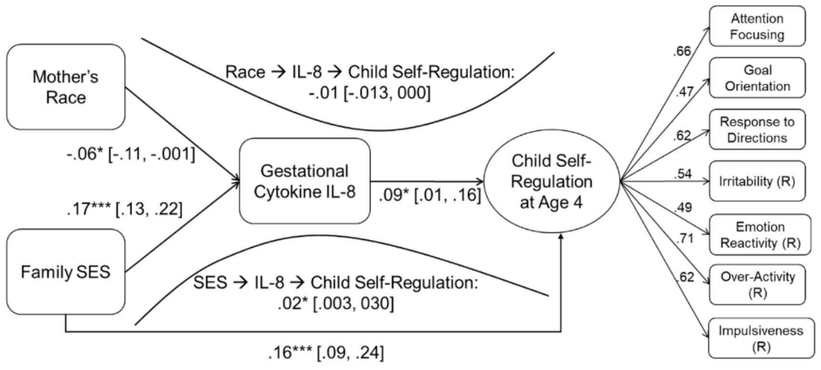
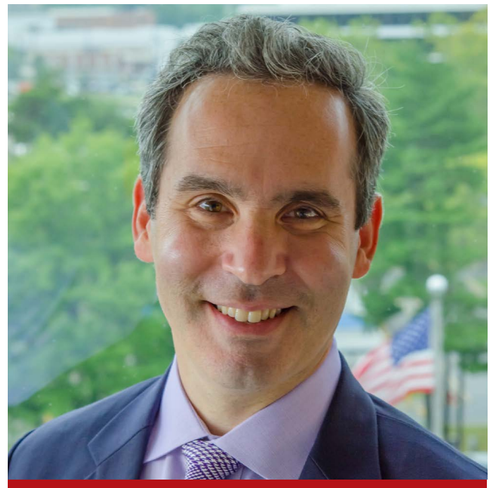


Fig. 1. Family SES, maternal race, gestational IL-8 during pregnancy, and child self-regulation. *Note:* Standardized path coefficients [and their 95% confidence intervals in the bracket] are presented. R = Reverse-coded. * $p < .05$. *** $p < .001$.

The prenatal period and early childhood

Maternal immune activity during pregnancy has been repeatedly linked to neuropsychiatric disorders in offspring. To the extent that maternal inflammation during pregnancy causes deviations from typical neurodevelopmental trajectories in offspring that result in elevated risk of neuropsychiatric disorders such as schizophrenia, autism, and major depressive disorder, it is unlikely that neurocognitive functioning in childhood would remain otherwise intact. However, much less is known regarding the role of immune markers at specific points during gestation in children's neurocognitive development. This is important because impairments in neurocognitive function in the domains of intellectual ability, language, and higher order cognitive processes might serve as early markers of vulnerability to lifetime risk and recurrence of neuropsychiatric disorders. The ENRICHED study seeks to expand our knowledge about disparities in maternal immune activity and inflammation during pregnancy and its relationship with prenatal and childhood development.



Stephen E. Gilman, Sc.D.,
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Denise Haynie, Ph.D., M.P.H.
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Jing Yu, Ph.D.,
Research Fellow

Diana Augustin, B.A.,
NIH Academy Enrichment Program Postbaccalaureate Fellow

Theemeshni Govender, B.A.,
Postbaccalaureate Fellow

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

Adolescence and adulthood

ENRICHED
Rhode Island Children's Health Equity & Development Study

Trajectories established as early as infancy influence mental and physical health in later stages of the life course extending into adolescence and young and middle adulthood. One of our team's focus areas concerns the developmental vulnerability to suicide, a leading cause of death among young people and a major contributor to the disease burden associated with mental illness. Accordingly, we have undertaken a large-scale cohort study of the developmental origins of suicide mortality based on the historic United States Collaborative Perinatal Project. Related work in collaboration with our colleagues on the Next Generation Health Study concerns the social determinants of mental health problems during adolescence (e.g., Yu et al.'s study on depressive symptoms in the Journal of Adolescent Health – see Figure 2; and Luk et al., study on sexual orientation disparities in suicide risk in Pediatrics – see Figure 3). Finally, we continue our work toward understanding the long-term and potentially intergenerational influences of the early environment on health.

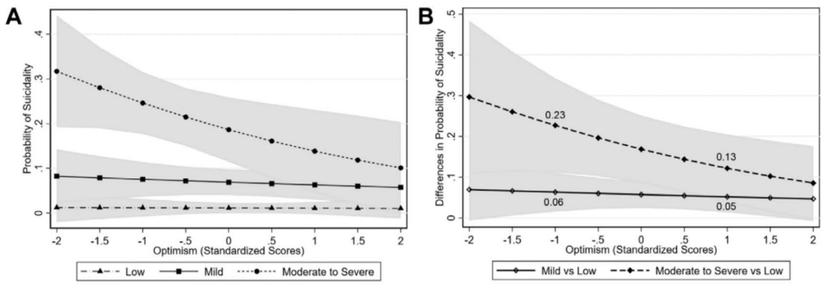

Figure 2. Yu, et al, 2021.

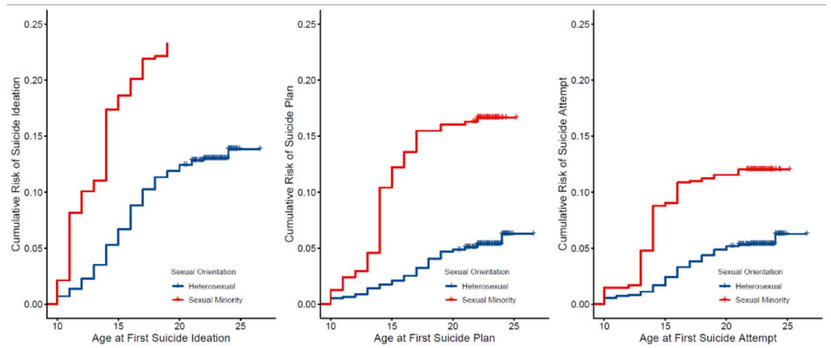

Figure 3. Luk et al., 2021.

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Yu J, Patel RA, **Gilman SE**. Childhood disadvantage, neurocognitive development and neuropsychiatric disorders: Evidence of mechanisms. *Curr Opin Psychiatry*. 2021;34(3):306-23. PMID: 33587493.

Tonja R. 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 to guide the development of future 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 is an observational prospective cohort study investigating relations 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 collected 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 during the past year include findings led by Dr. Leah Lipsky from a laboratory feeding study showing that overall, pregnant women a consumed a similar proportion of highly processed and minimally processed foods following a standardized meal, but their relative intake of each type of food differed, resulting in substantial differences in energy intake (Figure 1) (PMID: 33109504). Further, only their intake of highly processed food was associated with worse diet quality (PMID: 33158801). In work lead by fellows, Ms. Betts' investigation showed that depression, stress, and poor sleep quality were associated with greater reward-related eating (PMID: 33933087), and Ms. Mooney found that while women reported experiencing stronger food cravings in response to increased stress, stress was not associated with overall diet quality (PMID: 33737210). Dr. Schwedhelm's novel application of Gaussian graphical models indicated meal-specific patterns associated with diet quality (PMID: 34301273), and Dr. Temmen's examination of early-life feeding behaviors revealed bidirectional associations of maternal use of feeding to soothe and infant food responsiveness (PMID: 34380499).

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 are collected from PEAS mothers, children, and co-parents. Data collection began in 2019 and is ongoing. In-person data collection was halted in March 2020 due to the COVID-19 pandemic, and web-based data collection was utilized for parent-reported measures until late 2021, when in-person visits resumed.

Eating in the Absence of Hunger of highly and minimally processed foods in pregnant women

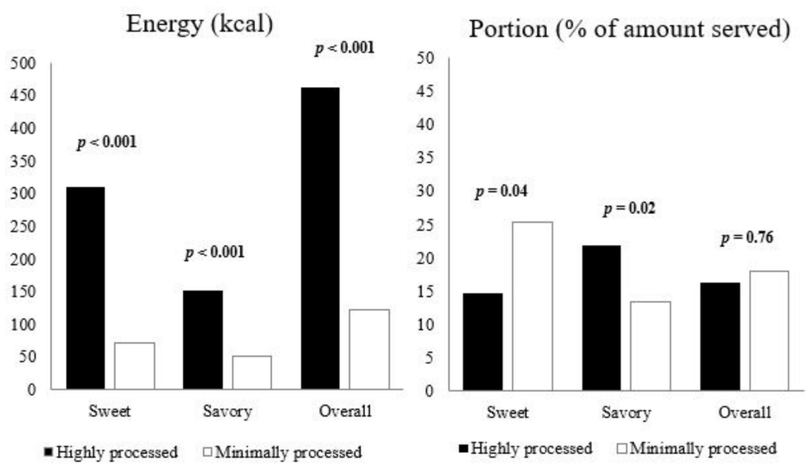

Figure 1. Energy (kcal) and portion (%) of highly and minimally processed food consumed after a standardized meal during a laboratory cross-over feeding study in pregnant women. PMID: 33109504.

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Carolina Schwedhelm-Ramirez, Dr.P.H., *Visiting Fellow* (departed 2021)

Chelsie Temmen, Ph.D., *Postdoctoral Fellow* (departed 2021)

Jan Mooney, M.A., *Pre-doctoral Fellow*

Evelyn Liu, B.A., *Postbaccalaureate Fellow*

KEY PUBLICATIONS

Lipsky LM, Burger KS, Faith MS, Siega-Riz AM, Liu A, Shearrer G, **Nansel TR**. Pregnant women consume a similar proportion of highly versus minimally processed foods in the absence of hunger, leading to large differences in energy intake. *Journal of the American Dietetic Association* 2021; 121(3):446-457. PMID: 33109504. PMCID: PMC8329945

Temmen CD, Lipsky LM, Faith MS, **Nansel TR**. Relations between maternal emotional eating, feeding to soothe, and infant appetitive behaviors. *International Journal of Behavioral Nutrition and Physical Activity 2021*; 18:105. PMID: 34380499. PMCID: PMC8359102.

Bobby Cheon, Ph.D.

Dr. Cheon joined the Social and Behavioral Sciences Branch (SBSB) in August, 2021. His research program focuses on psychosocial influences on appetite and eating behaviors, with emphasis on the contribution of perceived socioeconomic disadvantage to diet quality and excess energy intake. His research has applied experimental approaches to test the unique causal role that perceptions of socioeconomic disadvantage may have on people's relationship with food. This work has demonstrated that perceptions and feelings of inadequate socioeconomic standing may heighten preferences for calorie-dense foods, selection and consumption of larger portion sizes, taste-based perceptual sensitivity to the presence of calories in foods, and circulation of the appetite-stimulating hormone ghrelin. Notably, these results were observed independent of the participants' actual socioeconomic background (e.g., household income or poverty status). This work has revealed that social inequality may have inherently obesogenic properties, which raises the need to understand how disparities are experienced and influence eating behavior throughout development.

"…social inequality may have inherently obesogenic properties, which raises the need to understand how disparities are experienced and influence eating behavior throughout development."

Since joining SBSB, Dr. Cheon's research initiatives have sought to test how social disadvantage is experienced during youth, and how these processes may program one's relationship with food during development. Although socioeconomic status (SES) is one dimension of social status, children's experience of SES may differ from adults. For instance, children may place greater emphasis on other signals of social status beyond SES, such as peer acceptance.

Drawing on NICHD's Children's Growth and Behavior Study (CGBS), Dr. Cheon's team is investigating the interplay of children's and their parents' perceptions of family socioeconomic standing on children's eating behaviors (i.e., hyperphagia and emotional eating). In other studies and cohorts, Dr. Cheon is testing how individual variations in children's emotional reactivity to an experimentally-induced experience of ostracism by peers predicts snacking behavior and future body mass. Finally, Dr. Cheon is examining how expectations of future socioeconomic attainment among adolescents, rather than the current SES of their families, may predict dietary patterns and trajectories of cardiometabolic health. By integrating methods and measures that capture diverse ways that young people experience social status and disadvantage, his team's research seeks to identify mechanisms by which social disparities in diet quality emerge and potential targets for future interventional studies.

Bobby Cheon, Ph.D.
Earl Stadtman Tenure-track Investigator

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KEY PUBLICATIONS

Pink, A., Stylianou, K., Lee, L., Jolliet, O., & **Cheon, B**. The effects of presenting health and environmental impacts of food on consumption intentions. Food Quality and Preference. Available online 2021 [DOI: https://doi.org/10.1016/j.foodqual.2021.104501].

Pink, A., & **Cheon, B**. Development of a simplified portion size selection task. Foods. 2021;10(5):1121. PMID: 34070072. PMCID: PMC8158092.

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 coordinate and integrate the Program's components to produce groundbreaking contraceptive research. CDP scientists utilize technology transfer mechanisms to form collaborative partnerships, translating discoveries and clinical advances into products that address unmet contraceptive needs of women and men.

CDP uses R&D contracts to achieve the goal of new contraceptive method development. The Program evaluates new drugs that are not commercially available and must be synthesized under current Good Manufacturing Practice (cGMP) as recommended by FDA guidance. CDP maintains a contracted Chemical Synthesis Facility to produce novel drugs required for the program. Potential new drugs and devices require toxicology testing to demonstrate safety. IND-enabling preclinical studies must be performed under Good Laboratory Practice (GLP) meeting regulatory standards. Human trials require formulation and release of agents under cGMP, and stability studies covering the duration of the trial. CDP maintains a Biological Testing Facility to perform preclinical evaluation and clinical batch preparation under regulatory requirements needed for first-in-human studies as well as batch preparation and longer toxicology studies for later Phase clinical trials of novel contraceptive drug candidates.

The Contraceptive Clinical Trials Network (CCTN)

CDP's network of qualified clinical sites (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 with the goal of FDA regulatory approval. The CCTN comprises top clinical investigators at qualified institutions, including both domestic and international sites, with expertise to conduct all phases of contraceptive evaluation, from first-in-human through Phase III. The clinical sites serve as the 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 is identified, ~10% pass pre-clinical testing to enter clinical testing; only 12% of those products complete Phase III and FDA submission. Contraceptives are used by healthy people for long durations; so, long-term safety is critical. CDP has a pipeline of products in clinical evaluation, including hormonal or non-hormonal options for women, and novel hormonal methods for men. In 2021, clinical trials were actively recruiting for safety and contraceptive evaluation of new drugs or devices in the CDP pipeline. New methods for women include a novel vaginal ring that can be used for three months, a long-acting injectable that inhibits ovulation for three months, a novel copper IUD that provides contraceptive effectiveness for at least three years or 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 nine US sites and six international sites. Each product in development fills an unmet need or provides greater safety to vulnerable populations at risk of unintended pregnancy.

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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, with increased incidence of diabetes, hypertension and risk of venous thromboembolism (VTE) for which hormonal methods may be 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® is a potent progestin that blocks follicular development; 17-β estradiol supports bone health without increasing VTE risk.

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. The product is being evaluated to assess inhibition of ovulation.

The Woman's Condom pivotal trial demonstrated acceptability and effectiveness of a novel female condom to prevent pregnancy and transmission of infection. A final report will be prepared to allow consideration of approval by the FDA.

Long-Acting Reversible Contraceptives (LARCs)

LARCs are effective, highly acceptable methods. Copper IUD is a safe option for women with health risks or conditions that increase the risk associated with unintended pregnancy. Increased bleeding and cramping associated with the currently marketed Copper IUD may deter use in nulliparous women, especially adolescents. In collaboration with Gates Foundation and FHI-360, CDP is evaluating a Mini-Copper IUD in nulliparous women to determine effectiveness, bleeding characteristics and pain.

Progestin-only Injectable Contraception

LNG-Butanoate (LB) is a novel injectable progestin that does not increase risk of VTE. Injections of long-acting LB improve compliance and efficacy compared with progestin-only pills. A study is underway to optimize LB dose, formulation, route of injection and duration of ovulation inhibition.

DEVELOPMENT OF CONTRACEPTIVE METHODS FOR MEN

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

Nestorone®/Testosterone (Nes/T) Gel is a highly promising product for male contraception. Dr. Blithe and CDP colleagues conducted studies with the CCTN team to determine the most effective dose of Nestorone® (a potent progestin) that caused gonadotropin suppression, inhibiting endogenous testicular T production needed to support sperm production. The team combined Nestorone® (Nes) with T in a single gel formulation delivered in a metered pump. Doses were evaluated to

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KEY PUBLICATIONS

Long JE, Lee MS, **Blithe DL**. Update on Novel Hormonal and Nonhormonal Male Contraceptive Development. *J Clin Endocrinol Metab* 106:e2381-92, 2021; PMID: 33481994. PMCID: PMC8344836.

Chen MJ, Creinin MD, Turok DK, Archer DF, Barnhart KT, Westhoff CL, Thomas MA, Jensen JT, Variano B, Sitruk-Ware R, Shanker A, Long JE, **Blithe DL**. Dose-finding study of a 90-day contraceptive vaginal ring releasing estradiol and segesterone acetate. *Contraception* 102:168-73, 2020; PMID: 32416145. PMCID: PMC7483386.

Nguyen B, Farrant M, Anawalt BD, Yuen F, Thirumalai A, Amory JK, Swerdloff RS, Bremner WJ, Liu PY, **Blithe DL**, Page ST, Wang C. Acceptability of oral dimethandrolone undecanoate in a 28-day placebo-controlled trial of a male hormonal contraceptive prototype. *Contraception* 102:52-7, 2020: PMID: 32298717. PMCID: PMC7287214.

demonstrate that the product can inhibit testicular production of T, thus stopping sperm production while maintaining normal serum T levels to support sexual function. The novel Nes/T Gel is currently being evaluated in couples who wish to use a novel male contraceptive product to prevent pregnancy. When couples complete the 1-year efficacy period, the male partner stops using the product and enters a recovery phase to demonstrate return to normal fertility levels of sperm production. This Phase IIb trial is ongoing to evaluate effectiveness in couples for pregnancy prevention as well as reversibility and acceptability of the method. Enrollment is ongoing in nine CCTN sites in the USA, two sites in the UK, and single sites in Sweden, Italy, Chile and Kenya.

Novel Progestogenic Androgens for Male Contraception

Dimethandrolone (DMA) and 11β-Methylnortestosterone (11β-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 11β-MNT-Dodecylcarbonate) in early clinical trials of safety and dose-finding.

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