Eunice Kennedy Shriver National Institute
of Child Health and Human Development

DPHR

2023 ANNUAL REPORT

Division of Population Health Research, DIR, NICHD

TABLE OF CONTENTS

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.

In reflecting on the last year, I am proud and appreciative of all my colleagues for their demonstrated resilience in adapting to the new hybrid work environment. Thanks to the industrious activities of the members of the Division, records of research productivity, collaboration, external engagement, service, and training remained strong in 2023.

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. Our 2023 Annual Report reinforces the Division's commitment to improving health outcomes and eliminating health disparities among vulnerable populations, namely pregnant people as well as infants and children. We readily embrace these ambitious aims by partnering in trans-disciplinary research teams across Branches and with our 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 postbaccalaureate through postdoctoral levels.

DiPHR emphasizes reproducible research and remains committed to fostering the availability and bolstering the 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 accessible via the online data-sharing platforms of DiPHR (BRADS) and the NICHD (DASH).

We are grateful to the NICHD Director, Dr. Diana Bianchi, and the Scientific Director, Dr. Chris McBain, for everything they do to facilitate the work and accomplishments of the Division. Looking forward to 2024 and beyond, our steadfast goal is to be good stewards of resources 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, NICHD

Una Grewal, Ph.D., M.P.H.,
Director

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.

As Director of DiPHR, 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-Principal Investigator for the NICHD Fetal Growth Studies and Principal Investigator for the *NICHD Fetal Growth Studies: Dietary Patterns during Pregnancy* component. This past year, findings from the NICHD Fetal Growth Studies (PMID: 37934328) indicate that women with twin gestations moderately increased total energy as pregnancy progressed; however, dietary composition and quality remained unchanged. Dr. Grewal serves as collaborator for 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. Currently, her team is examining the association between nutrition during pregnancy and fetal body composition and organ volumes.

In addition, Dr. Grewal is leading two new initiatives in the Division: (1) establishing a Nutrition Core and (2) creating a novel database for climate change research. The aims of the Nutrition Core are to leverage existing DiPHR cohorts and build out the Division's portfolio on nutrition, one of the major cross-cutting themes enumerated in NICHD's 2020 Strategic Plan. Dr. Grewal's ambition is that the integration of data from the different cohorts will permit examination of the contributions of nutrition to health outcomes across the lifespan. Similarly, the climate change project seeks to integrate, harmonize, and standardize data across four pre-conception cohorts in the Division, as well as to incorporate various climate indicators from publicly available datasets compiled by the U.S. Environmental Protection Agency (EPA) and The National Oceanic and Atmospheric Administration (NOAA). The purpose of the resulting database will be to investigate spatiotemporal changes in human fertility, pregnancy, and childbirth in the US associated with climate change.

STAFF

Una Grewal, Ph.D., M.P.H.,
Division Director

Yvette Pittman, Ph.D.,
Deputy Director

Adrienne Lonaberger,
Program Analyst

Jennifer Weck, Ph.D.,
Laboratory Health Specialist

Elizabeth DeVilbiss, Ph.D.,
Staff Scientist

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 interdisciplinary sciences.

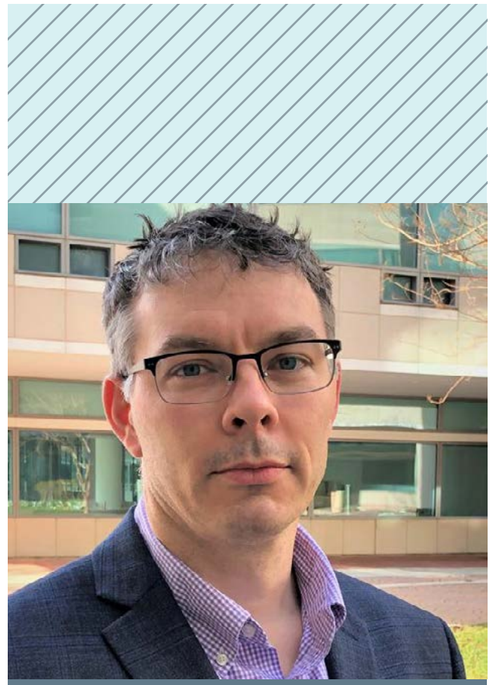
Motivated by the research conducted in the division and the institute, members of BBB develop broadly applicable cutting-edge statistical methodologies that have applications in biomedical, clinical, and population health research.

Some areas of expertise within BBB include Bayesian methods, methods for biomarkers and diagnostic accuracy for risk prediction, innovative clinical trial design and analysis, dynamic risk predictions, genomics, methods for longitudinal data, 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. Our staff are engaged collaborators in the entire scientific process from formulating research questions, formalizing study design, aims and hypotheses, conducting 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 2023, BBB research resulted in contributions to 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 joint modeling methods were developed to further build dynamic risk prediction of time-to-pregnancy based on longitudinal geometric features of reproductive hormones. This contribution extends the capabilities of the time-to-pregnancy risk calculator being developed in the BBB. The calculator will utilize a couples' age, BMI and multiple biological longitudinal processes (ex., menstrual cycle lengths) and behavioral (ex, intercourse pattern) longitudinal processes that can be self-measured as a low cost a first step for identifying infertility risks at home.

BBB staff proposed a perception-augmented hidden Markov modeling approach for family management of diabetes 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. Application to the FMOD trial data reveals that families in the intervention arm are more likely to stay in the Harmonious parent–child relation state and less likely to transition from Harmonious to Indifferent state. These methods also found that compared to the parent, the child tends to have a more heterogeneous perception of the parent–child relation.

BBB staff collaborated extensively with DiPHR researchers on emerging projects being design and proposed, projects in the field, and complete projects through data analysis and manuscript writing. In addition to strengthening collaborations with intramural and extramural researchers, members of the branch have expanded collaborations with researchers in the Division of Intramural Research (DIR), such as new partnerships



STAFF

Neil J. Perkins, Ph.D.,
Acting Branch Chief

Aiyi Liu, Ph.D.,
Senior Investigator

Rajeshwari Sundaram, Ph.D.,
Senior Investigator

Zhen Chen, Ph.D.,
Senior Investigator

James Morton, Ph.D.,
Investigator
(departed in 2023)

BIOSTATISTICS AND BIOINFORMATICS BRANCH

with the members of Bioinformatics and Scientific Programming Core (BSPC, DIR) and Perinatology Research Branch (DIR), among others. BBB is also collaborating with NIEHS investigators on a funded climate change initiative consisting of etiologic and methodologic aims. Furthermore, BBB staff serve on important NIH and external committees such as the NICHD DER Clinical Trials Network initiative, the Women Scientists Advisors (WSA), and numerous Data and Safety Monitoring Boards for the NIH. BBB investigators also serve as associate editors of the journals, Statistical Methods in Medical Research, Statistics in Biosciences, Clinical Trials, and Nutrients.

The year saw the departure of Dr. James Morton and Dr. Neil Perkins fulfilling the role of Acting Chief of BBB for the entirety of 2023 while the search is ongoing.

FELLOWS

Maddy St Ville, Ph.D.,
Postdoctoral Fellow

Abhisek Saha, Ph.D.,
Postdoctoral Fellow

Jin Yang, Ph.D.,
Postdoctoral Fellow

Lars Hunger, Ph.D.,
Postdoctoral Fellow
(departed in 2023)

Aiyi Liu, Ph.D.

Innovative Clinical Trial Design and Analysis

Dr. Liu's research in 2023 focused on development of methods for innovative clinical trial design and analysis. Specifically, optimizing treatment allocation for statistical efficiency in randomized clinical trials by utilizing study subjects' information (e.g., age, biomarker, microbiome) collected prior to randomization. Such information, usually independent of the randomization scheme, enables the construction of more efficient estimators of treatment effect by incorporating pre-randomization information, resulting in better trial designs that could potentially save resources and study cost.

Aiyi Liu, Ph.D.
Senior Investigator

STAFF
Jin Yang, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Zhang W, Zhang Z, Liu A. Optimizing treatment allocation in randomized clinical trials by leveraging baseline covariates. Biometrics 2023; 79:2815-2829. PMID: 37641532; PMCID: PMC10843680

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 in 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. The methods are being 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 toxicant and reproductive outcomes, fetal growth and perinatal outcomes. The statistical challenges encountered in assessing mixtures of chemical toxicants include highly correlated exposures, issues of high percentage of chemical exposures below limit of detection as well as certain class of chemicals binding to lipids. Her focus has been in identifying "important drivers" in the mixtures of chemical toxicants, using the approach of variable selection in high dimensional data.

Dr. Sundaram serves as the DiPHR representative and executive committee member of the Women Scientists Advisors (WSA). She also serves as the Chair of the Subcommittee for the WSA Women Scholars Symposium, as also one of its two representatives on the Working Group for Women in Biomedical Career (WgWBC) and organizing member of the WSA 30th anniversary celebration subcommittee. She is also active in the American Statistical Association (ASA), serving as the Chair of the ASA Jeanne E. Griffith Mentoring Award and is actively involved in the Risk Analysis Section of the ASA.

"We developed a joint modeling framework to study the predictive ability of peak of reproductive hormone for classifying women as infertile or not. This was developed by modeling the geometric features of the longitudinal hormonal profile and the time-to-pregnancy as discrete survival outcome, subject to right censoring. We did detailed analysis of the pre-conception cohort of Oxford Conception Study and found that the value of the peak was the best predictor among various other geometric features in identify the risk for infertility."

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

STAFF
Abhisek Saha, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Saha A., Ma L, Biswas A, Sundaram R. Joint modeling of geometric features of longitudinal data and time-to-event: with application to fecundity studies. *Statistics in Biosciences*, https://doi.org/10.1007/s12561-023-09381-x

Mitro SD, Sundaram R, Louis GMB, Peddada S, Chen Z, Kannan K, Gleason JL, Zhang C, Grantz KL. Associations of pregnancy per- and polyfluoroalkyl substance concentrations and uterine fibroid changes across pregnancy: NICHD Fetal Growth Studies - Singletons cohort. *Environ Health Perspect.* May;131(5):57007, 2023. PMID: 37224071; PMCID: PMC10208432

Zhen Chen, Ph.D.

In 2023, Dr. Chen published 5 methodological papers and 15 collaborative manuscripts. Dr. Chen presented his research work at WNAR. He also actively participated in professional services, continuing serving as a co-Editor for a special volume for the journal *Statistics in Biosciences* and in NICHD DSMC and BRADS Committee. Dr. Chen mentored two postdoctoral fellows (Drs. St. Ville and Yang). Dr. Chen kept serving as PI of the NICHD B-Well-Mom study and the GDM etiology sub-study of the NICHD Fetal Growth Studies. An example of Dr. Chen's 2023 work is listed below.

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 relation. To investigate whether the intervention improves parent–child relations, we proposed a novel approach 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. We took a Bayesian perspective to estimation and developed an efficient computational algorithm 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 reveals that families in the intervention arm are more likely to stay in the Harmonious parent–child relation state and less likely to transition from Harmonious to Indifferent state. Compared to parent, child tends to have a more heterogeneous perception of the parent–child relation.

Zhen Chen, Ph.D.
Senior Investigator

STAFF
Maddy St. Ville, Ph.D.,
Postdoctoral Fellow

Jin Yang, Ph.D.,
Postdoctoral Visiting Fellow

KEY PUBLICATIONS

Lu R, Nansel T, Chen Z. A perception-augmented hidden Markov model for family management of diabetes. *Statistics in Biosciences* 2023; 15:288-308. https://doi.org/10.1007/s12561-022-09360-8

EPIDEMIOLOGY BRANCH

In 2023, 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 pregnancy, infancy, and childhood. 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 the field of pregnancy and fetal development, EB studies the genetic and environmental determinants, etiology, and health consequences of adverse pregnancy outcomes, and alterations in fetal growth of both singletons and twins in relation to obesity and pregnancy complications. 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 pregnant women and their fetuses, and infants and children.

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 2023, EB investigators and fellows received multiple awards from NICHD for career development, collaborative service, and scientific advances. Additionally, EB research has broad public appeal, as demonstrated by high-impact publications and both national and international media attention. 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 perinatal and pediatric epidemiology. Efforts were underway to identify a permanent branch chief.

STAFF

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

Jessica L. Gleason, Ph.D., M.P.H., *Staff Scientist*

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

James L. Mills, M.D., M.S., *Senior Investigator (retired April 2023)*

Diane L. Putnick, Ph.D., M.S., *Statistician*

Fasil Tekola-Ayele, Ph.D., M.P.H., *Senior Investigator (promoted August 2023)*

FELLOWS

Priscilla Clayton, Ph.D., *Postdoctoral Fellow*

Tesfa Habtewold, Ph.D., *Visiting Fellow*

Alexandra Jean-Louis, B.S., *Postbaccalaureate Fellow*

Randy Le, B.S., *Postbaccalaureate Fellow*

Ian Trees, Ph.D., *Postdoctoral Fellow*

Jordan Tyris, M.D., *Pediatric Scientist Development Program Fellow*

Kathryn Wagner, Ph.D., *Postdoctoral Fellow*

Prabhavi Wijesiriwardhana, Ph.D., *Visiting Fellow*

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

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

STAFF
Diane Putnick, Ph.D.,
Statistician

Priscilla Clayton, Ph.D.,
Postdoctoral Fellow

Ian Trees, Ph.D.,
Postdoctoral Fellow

Jordan Tyris, M.D.,
Pediatric Scientist Development Program Fellow

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.

In 2023, Dr. Yeung investigated potential sequalae of infertility treatment, leveraging Upstate KIDS' decade of longitudinal data. Exposure to assisted reproductive technologies (ART) may increase the risk of diseases due to suboptimal environments in a critical window of early embryonic development. Differences in attention deficit/hyperactivity disorder (ADHD) and related behavioral disorders were explored among singleton and twin children aged 8–10 years from New York State based on the mode of conception (i.e., using ART, including both in vitro fertilization and intracytoplasmic sperm injection, or ovulation induction [OI] compared to spontaneous conception). Overall, risk of ADHD was comparable in children conceived using ART or OI and children not conceived by any treatments. However, elevated risks of anxiety and depression, even after accounting for parental history of mood disorders and other factors was observed (PMC10247509). Both ART and OI were associated with increased risk, and there was an indication that it was not related to the specific techniques used in fertility treatment itself but that parents with underlying infertility (as indicated by maternal report of taking more than 12 months to conceive) without using any treatment was also associated increased risk.

In two other studies, Dr. Yeung's team investigated child outcomes in relation to maternal polycystic ovary syndrome (PCOS) and hirsuitism, common causes of infertility in women and associated with metabolic dysfunction. One study investigated offspring newborn DNA methylation (PMC10732621) and the other assessed cardio-metabolic health in middle childhood (PMC10767861). While the team confirmed that women with PCOS diagnosed before pregnancy had suboptimal cardio-metabolic measures 8-9 years after delivery (i.e., elevated HbA1c as a measure of hyperglycemia, and heart rate), their children did not differ in their body mass index, fat mass, arterial stiffness, and other cardio-metabolic factors from children of mothers without PCOS. DNA methylation was also interrogated with respect to exposure to maternal PCOS/hirsuitism in Upstate KIDS and pregnancy testosterone levels from another Divisional study (the Effects of Aspirin in Gestation and Reproduction trial). A few CpG sites were associated with hirsuitism or eleveated testosterone levels suggesting in utero impact of those exposures but these findings require replication in larger samples.

SPAN Study of Pregnancy & Neonatal Health

In addition to her work on Upstate KIDS, Dr. Yeung's Study of Pregnancy and Neonatal Health (SPAN), designed to investigate paternal contributions to the developmental origins of health and disease, is recruiting participants. While much research has been devoted to maternal exposures, information on paternal factors is greatly lacking despite evidence of potential epigenetic pathways.

KEY PUBLICATIONS

Yeung E, Putnick D, Ghassabian A, Sundaram R, Lin T-C, Mirzaei S, Stern J, Bell E. Examining attention deficit/hyperactivity disorder and related behavioral disorders by fertility treatment exposure in a prospective cohort. *Annals of Epidemiology* 2023 Jun; 82:59-65.e1. PMID: 36972758 PMCID: PMC10247509

Polinski KJ, Robinson SL, Putnick DL, Sundaram R, Ghassabian A, Joseph P, Gomez-Lobo V, Bell EM, Yeung EH. Maternal self-reported polycystic ovary syndrome with offspring and maternal cardiometabolic outcomes. *Human Reproduction* 2024 Jan 5;39(1):232-239. PMID: 37935839 PMCID: PMC10767861

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

Dr. Grantz is an Obstetrician and Maternal-Fetal Medicine specialist who leads a research program on clinical management of pregnancy complications, including aberrant fetal growth, when to deliver a high-risk pregnancy, and labor and delivery management. Findings from her research have informed over 28 national and international clinical guidelines with evidence-based practice recommendations.

The NICHD Fetal Growth Studies team was responsible for a multidisciplinary effort that generated fetal growth percentile charts in a diverse U.S population for clinical practice. She led development of a first ever fetal growth velocity calculator for clinical use as well as development of twin fetal growth percentile charts. Her work is addressing the clinical challenge of differentiating constitutionally small-for-gestational-age from fetal growth restriction that is associated with increased morbidity and mortality. In a recent effort, her team performed an in-depth examination of the statistical assumptions of a customized fetal growth that's currently used in clinical practice in various countries. Customized fetal growth references are appealing as they provide a more personalized definition of small-for-gestational-age, in line with a precision medicine approach. Her findings question one of the main assumptions, namely the constant coefficient of variation assumption that the standard deviation, and therefore the customized percentiles, is proportional to the mean birthweight. Therefore, her team created a new customization method that has more flexibility in calculating customized percentiles using a heteroscedastic regression. (PMID: 36928064)

An emerging area uses 3-dimensional (3D) ultrasound that provides more detail than the standard 2D ultrasound in determining fetal fat and lean tissue volumes. In the Fetal 3D Study, Dr. Grantz's group is among the first to have accumulated the largest collection of fetal 3D volumes from a race/ethnically diverse pregnancy cohort with repeat ultrasounds spanning the length of gestation. (PMID: 37946325) Detection of fetal volume and body composition changes in fetuses that are growth restricted or growing excessively has potential to inform clinical management, such as increased antenatal monitoring to prevent stillbirth or changes in maternal nutrition to prevent excess fetal fat accumulation.

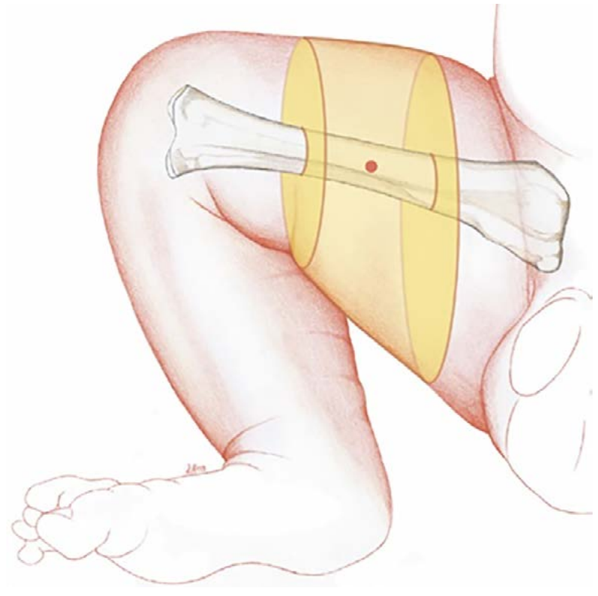


Figure. Fractional limb volume
Fractional limb thigh (TVol) volumes are based on 50% of the femoral diaphysis length. Mid-limb measurement eliminates the need for tracing soft tissue borders near the ends of the bone shaft, where acoustic shadowing is more likely to be encountered. Reprinted with permission from Lee W, Balasubramaniam M, Deter RL, et al. Fractional limb volume--a soft tissue parameter of fetal body composition: validation, technical considerations, and normal ranges during pregnancy. Ultrasound Obstet Gynecol. Apr 2009;33(4):427-40. doi:10.1002/uog.6319

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

STAFF
Jessica Gleason, Ph.D.,
Staff Scientist

Alexandra Jean-Louis, B.S.,
Postbaccalaureate Fellow

Kathryn Wagner, Ph.D.,
Postdoctoral Fellow

Dr. Grantz also is co-PI of Study of Pregnancy and Neonatal Health (SPAN), leading the TIMing of dElivery (TIME) trial to determine the optimal timing of delivery for uncontrolled 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.

Her team is also addressing labor and delivery management to prevent medically unnecessary cesarean deliveries, an issue declared as a national priority as cesarean delivery is a risk factor for severe maternal morbidity and mortality. Collectively, her research is providing critical empirical data to guide clinical management of pregnancy.

KEY PUBLICATIONS

Grantz KL, Lee W, Chen Z, Hinkle S, Mack L, Sanz Cortes M, Goncalves LF, Espinoza J, Gore-Langton R, Sherman S, He D, Zhang C, Grewal J. The NICHD Fetal 3D Study: A Pregnancy Cohort Study of Fetal Body Composition and Volumes. *American Journal of Epidemiology*. 2023 Nov 8. PMID: 37946325. PMCID: in process

Grantz KL, Hinkle SN, He D, Owen J, Skupski D, Zhang C, Roy A. A new method for customized fetal growth reference percentiles. *PLoS One*. 2023;18(3):e0282791. PMID: 36928064. PMCID: PMC10019672

Gleason JL, Grewal J, Chen Z, Cernich A, Grantz KL. Risk of adverse neonatal outcomes among pregnant women with disabilities. *International Journal of Epidemiology*. 2023; 52(1):203-213. PMID: 36172968. PMCID: PMC9908045

Fasil Tekola-Ayele, Ph.D.

Dr. Tekola-Ayele's research aims to determine genetic mechanisms in early growth variations and links between fetal growth and cardiometabolic diseases/disparities in diverse ancestral populations. 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. To achieve this goal, his research group focuses on two complementary research themes at the maternal-placental-fetal interface – genetics of fetal growth and placental epigenome/transcriptome.

Maternal cardiometabolic status during pregnancy influences the success of pregnancy as well as long term child and maternal health outcomes. Genetic and environmental interplays influence the trajectory of maternal cardiometabolic factors such as lipids. Physiological adaptations during pregnancy alter the physiological levels of maternal blood lipid levels, but little is understood about the genetic influence on lipid traits during pregnancy. Using datasets of multi-ancestral pregnant women, we performed a genomic study to identify maternal genetic loci linked to blood levels of lipids including high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides in early gestation. We identified four genetic loci near/in *CELSR2, APOE, CETP,* and *ABCA1* associated with lipid levels, all associations concurring with genetic associations with adult lipids. Evidence of genetic colocalization was found between LDL level in early pregnancy and CELSR2 gene expression in liver and skeletal muscle. In addition, we found that less than 20% of genetic variants associated with lipid levels in adults of European ancestry show transferability to pregnancy lipid levels in multi-ancestral women, suggesting the need for large scale genomic studies for pregnancy lipid studies (PMC9974591).

One of the contributors to maternal metabolic health during pregnancy is social support, an important resilience factor with positive effects on health and well-being as well as on pregnancy and fetal outcomes. Given the role of the placenta in regulating fetal development and its exposure to the maternal physiological environment, the placental epigenome may provide clues to molecular processes relevant to social support and how this may influence offspring health outcomes. In a recent study, we found placental DNA methylation loci associated with social support. The expression of nearby genes in placenta correlated with methylation levels of placental DNA loci associated with social support. Fetal sex-specific methylation changes linked to social support have also been identified. The functions of the genes nearby differentially methylated placental DNA loci overlap with important pathways related to immune response relevant to fetal growth, energy metabolism and neurodevelopment providing insight into the potential molecular mechanisms in the association between maternal social support and offspring health outcomes later in life (PMC9827682).

Dr. Tekola-Ayele is a co-PI in a newly initiated genetic study in SPAN, which has begun recruitment of study participants 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. In another study embedded in the collaborative perinatal project (CPP), he leads a genotyping effort to 1) establish a genomic database for children in the cohort (n= 10800; 5400 African American and 5400 European American), and 2) identify genetic influences on early growth

Fasil Tekola-Ayele, Ph.D., *Senior Investigator*

STAFF

Tesfa Habtewold, Ph.D., *Postdoctoral Fellow*

Prabhavi Wijesiriwardhana, Ph.D., *Postdoctoral Fellow*

Randy Le, B.S., *Postbaccalaureate Fellow*

anthropometry and obesity-related phenotypes at seven longitudinal time points from birth through school age. Successful completion of these studies will lay a foundation for etiological insights into pregnancy outcomes and childhood diseases, biomarker discovery, and clinical and public health translations.

KEY PUBLICATIONS

Tesfaye M, Wu J, Biedrzycki RJ, Grantz KL, Joseph P, Tekola-Ayele F. Prenatal social support in low-risk pregnancy shapes placental epigenome. BMC Med. 2023; 8; 21(1):12. PMID: 36617561; PMCID: PMC9827682

Ouidir M, Chatterjee S, Wu J, Tekola-Ayele F. Genomic study of maternal lipid traits in early pregnancy concurs with four known adult lipid loci. J Clin Lipidol. 2023; 17(1):168-180. PMID: 36443208; PMCID: PMC9974591

SOCIAL AND BEHAVIORAL SCIENCES BRANCH

The mission of the Social and Behavioral Sciences Branch (SBSB) 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. We host academic and professional development activities throughout the year as part of our SBSB education and training (SBSBeat) series.

SBSB's 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 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 domains and key developmental stages. SBSB research on the social determinants of mental healthand 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.

BSB 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 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).

STAFF

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

Bobby Cheon, Ph.D., *Stadtman Investigator*

Denise Haynie, Ph.D., *Staff Scientist*

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

Tonja Nansel, Ph.D., *Senior Investigator*

Jing Yu, Ph.D., *Staff Scientist*

FELLOWS

Aleah Brown, B.S., *Postbaccalaureate Fellow*

Allison Choe, B.S., *Postbaccalaureate Fellow*

Amara Channell Doig, Ph.D., *Postdoctoral Fellow*

Theemeshni Govender, B.A., *Postbaccalaureate Fellow (departed in 2023)*

Mia Kwan, B.A., *Postbaccalaureate Fellow (departed in 2023)*

Julia M.P. Bittner, Ph.D., *Postdoctoral Fellow*

Matt Siroty, B.S., *Postbaccalaureate Fellow*

Meegan Smith, B.A., *Postbaccalaureate Fellow (departed in 2023)*

Andre Tulloch, B.A., *Postbaccalaureate Fellow*

Zoe Chang, B.A., *Postbaccalaureate Fellow*

Stephen E. Gilman, Sc.D.

Social determinants of child development and mental health

Our work 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.

Our research focuses on both healthy and abnormal 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 – and in particular, the developmental mechanisms involved. Ongoing studies are described below.

The prenatal period and early childhood

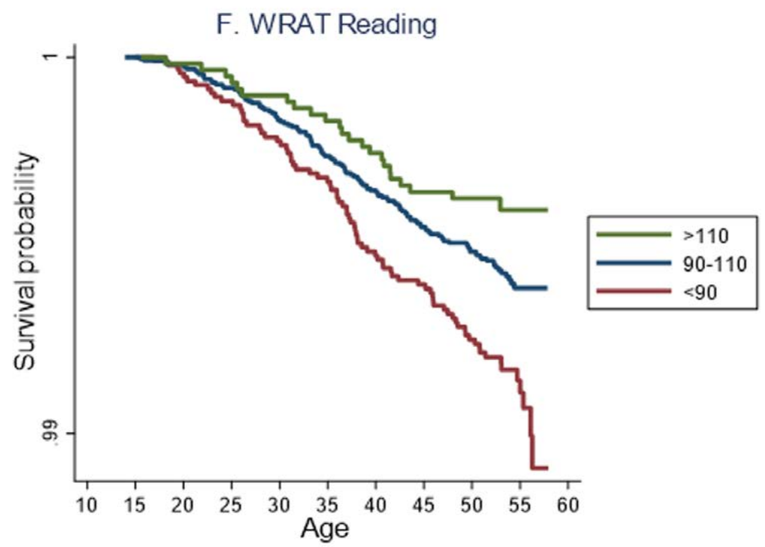
ENRICHED
Rhode Island Children's Health Equity & Development Study

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 the prenatal and childhood mechanisms of health disparities (https://www.nichd.nih.gov/about/org/dir/dph/officebranch/sbsb/social-determinants).

Adolescence and adulthood

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 premature all-cause mortality and suicide mortality based on the historic United States Collaborative Perinatal Project (e.g., see Figure 1, from a study on childhood cognitive

Figure 1.



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

STAFF
Andre Tulloch, B.A.,
Postbaccalaureate Fellow

Denise Haynie, Ph.D.,
Staff Scientist

Jing Yu, Ph.D.,
Staff Scientist

Zoe Chang, B.A.,
Postbaccalaureate Fellow

development and the risk of suicide mortality led by Dr. Pablo Vidal-Ribas demonstrating higher suicide risk among adults with lower scores on the Wide Range Achievement Test of reading at age 7). Related work in collaboration with our colleagues on the Next Generation Health Study concerns the social determinants of mental health problems and substance use during adolescence (e.g., see Figure 2, from a study showing patterns of substance use during high school led by Ms. Theemeshni Govender). Finally, we continue our work toward understanding the long-term and potentially intergenerational influences of the early environment on health.

Figure 2.

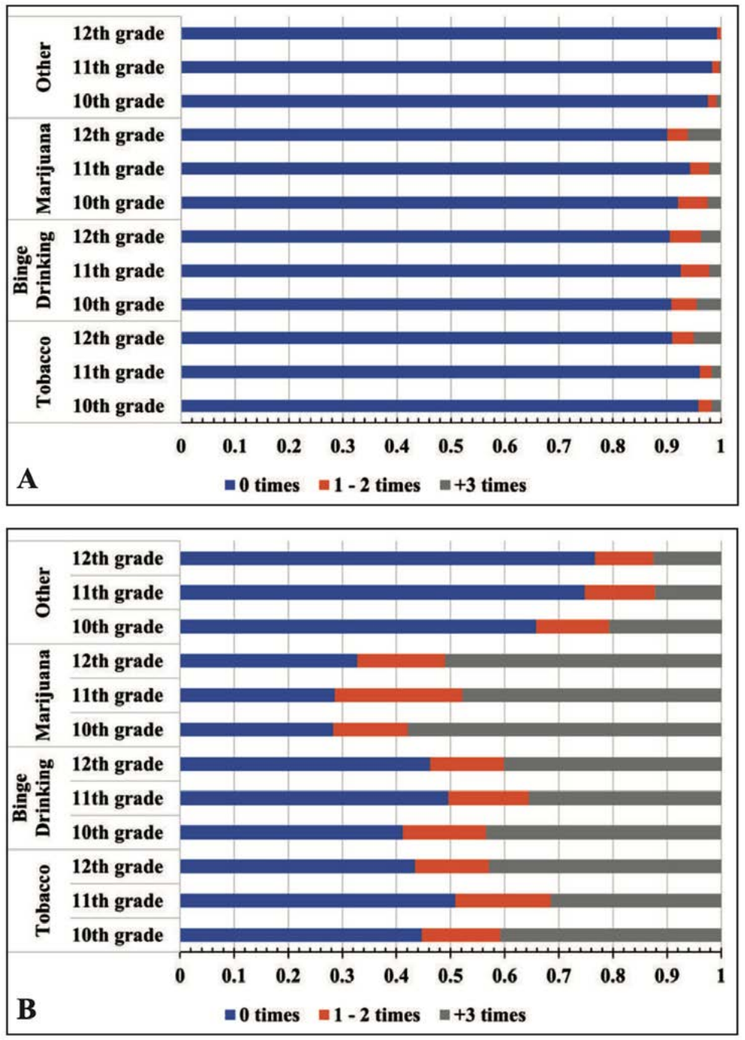


FIGURE 2. Results of latent class analysis of substance use from 10th to 12th grade. *Notes:* Non-/infrequent users (n = 1,976; 2A) include adolescents with a low probability of using tobacco, binge drinking, using marijuana, and using other drugs. Multiple substance users (n = 804; 2B) include adolescents with a higher probability of using all substances, particularly tobacco, alcohol, and marijuana.

KEY PUBLICATIONS

Govender T, Yu J, Vidal-Ribas P, Gilman SE, Haynie DL. Adolescent Substance Use Patterns and Risk for Suicidal Thoughts and Behaviors in Young Adulthood. *J Stud Alcohol Drugs*. 2023;84(6):892-901. PMID: 37589372. PMCID: PMC10765979

Luk JW, Yu J, Haynie DL, Goldstein RB, Simons-Morton BG, Gilman SE. A Nationally Representative Study of Sexual Orientation and High-Risk Drinking From Adolescence to Young Adulthood. *J Adolesc Health*. 2023;72(2):222-9. PMID: 36456451. PMCID: PMC9832524

Vidal-Ribas P, Govender T, Yu J, Sundaram R, Perlis RH, Gilman SE. Children's cognitive performance and suicide risk through middle adulthood. *J Child Psychol Psychiatry*. 2023;64(10):1480-91. PMID: 37263773. PMCID: PMC10524389

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 premature mortality globally. This research program investigates neurobehavioral influences on eating behaviors in children and families to guide the development of future novel approaches 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 determinants of dietary intake and weight change during pregnancy and postpartum. Participants were enrolled at <12 weeks gestation and followed, with their infants, until 1 year postpartum; data include dietary intake, anthropometrics, biospecimens, medical records, self-reported eating and other health-related behaviors, and infant feeding. Findings from 2023 examining anthropometric changes across pregnancy lend support for current Institute of Medicine gestational weight gain guidelines. Participants whose weight gain was within the recommended range had minimal fat gain while avoiding negative anthropometric changes. Those with normal weight who gained within the recommended range showed a small fat gain, while those with overweight or obesity who gained within the recommended range had a small fat loss (Siega-Riz 2023 PMID 38187988). Additionally, maternal pregnancy and postpartum diet were associated with infant weight outcomes. Better pregnancy diet quality was related to lower odds of infant large-for-gestational-age at delivery.

"Infants of mothers whose overall diet quality score was at the 75th percentile had 90% lower odds of being large-for-gestational-age and 0.2 standard deviation lower weight-for-length z-score at age 12 months compared with diet quality at the 25th percentile."

In infants breastfed for at least six months, greater maternal postpartum diet quality was related to lower weight trajectory from birth through age 12 months, whereas relations in infants breastfed for fewer than six months were not statistically significant. Relations of maternal diet quality with infant adiposity were stronger for moderation than adequacy components, indicating the importance of efforts to reduce intake of discretionary foods during pregnancy and postpartum (Lipsky et al 2023 PMID 37731285). Findings that greater perceived stress was associated with lower eating competence, especially in postpartum, suggest the importance of a holistic approach for promoting healthful eating (Pour et al. 2023 PMID 37741977).

Sprouts, a follow-up study of PEAS participants, is an observational prospective cohort study examining associations of neurobehavioral factors, parent feeding practices, and early life food exposures on dietary intake and growth from ages 3-7 years. Dietary intake, anthropometrics, laboratory-assessed behavioral data, and parent-reported feeding/eating behaviors are collected from PEAS parents and children. Data collection began in 2019 and will continue through 2024. Analyses examining appetitive traits from infancy to age 3.5 suggest an influence of early life feeding on the development of appetitive traits, and an influence of appetitive traits on weight. Specifically, parent feeding to soothe at 12 months and permissive feeding at 2 years were associated with greater child emotional overeating, emotional undereating, and desire to drink. Older age at introduction to fruit and younger age at introduction to discretionary sweet foods were associated with greater emotional overeating, while older age at introduction to vegetables and less frequent feeding of fruit were associated with greater food fussiness (Lipsky et al 2023 PMID 36997010). Further, lower infant satiety responsiveness predicted greater child zBMI, while infant zBMI did not predict child appetitive traits (Cummings et al 2023 PMID 37669768).

Tonja R. Nansel, Ph.D.
Senior Investigator

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

Amara Channel-Doig, Ph.D.,
Postdoctoral Fellow

Allison Choe, B.S.,
Postbaccalaureate Fellow

KEY PUBLICATIONS

Lipsky LM, Cummings J, Siega-Riz AM, Nansel T. Relations of pregnancy and postpartum diet quality with offspring birth weight status through 12 months. *Obesity (Silver Spring)* 2023; 31(12):3008-3015. PMID: 37731285 DOI: 10.1002/oby.23891

Cummings JR, Lipsky LM, Faith MS, Nansel TR. Developmental trajectory of appetitive traits and their bidirectional relations with body mass index from infancy to early childhood. *Clinical Obesity* 2023; 14(1):e12620. PMID: 37669768 PMCID: PMC10841422 DOI: 10.1111/cob.12620

Bobby Cheon, Ph.D.

Socioeconomic disparities persist in diet-related chronic health conditions, such as obesity and diabetes. While socioeconomic disadvantage may impose barriers to accessing healthier diets and lifestyles, it may also influence psychological processes that guide food choices and eating behaviors. Dr. Cheon's research investigates how psychological processes associated with socioeconomic disadvantage contribute to disparities in diet quality, excess energy intake, and health. Psychological experiences of socioeconomic disadvantage may be shaped by objective socioeconomic vulnerabilities, such as poverty, but also by relative socioeconomic vulnerabilities, such as rising inequality in income and opportunities for upward social mobility. Dr. Cheon's team applies both experimental and population-health approaches to investigate how these types of socioeconomic vulnerabilities influence food-related preferences, behaviors, and health across development.

In 2023, Dr. Cheon's lab completed multiple studies examining the role of disadvantaged socioeconomic status on children's eating behavior and growth. In collaboration with NICHD's Children's Growth and Behavior Study (CGBS), Dr. Cheon's team identified that socioeconomic stressors may interact with perceived socioeconomic disadvantage to contribute to behaviors associated with overeating and adiposity. Specifically, among children from lower socioeconomic status (SES) households, perception of having relatively disadvantaged socioeconomic standing compared to other families was associated with more severe hyperphagic behaviors (excessive preoccupation with eating) and higher levels of adiposity.

In another study completed this year, Dr. Cheon's lab demonstrated that absolute socioeconomic deprivation (i.e., poverty) and perceived socioeconomic disadvantage experienced during early life may be associated with metabolic health during pregnancy. This research revealed that family poverty during adolescence and perceptions of one's family as being financially worse off than other families when growing up were independently associated with odds of gestational diabetes, but not other pregnancy complications, such as preeclampsia/eclampsia or hypertensive disorders of pregnancy.

Together, these findings suggest that while objective socioeconomic stressors like poverty may contribute to children's obesogenic eating behaviors and adiposity, the internalization of perceptions and feelings of socioeconomic disadvantage may exacerbate these relationships. Notably, objective and perceived socioeconomic disadvantage experienced in early life may also increase odds of metabolic disorders later in life, such as gestational diabetes. This work demonstrates that efforts to address disparities in diet-related and metabolic health outcomes of children and pregnant people should not only focus on objective socioeconomic vulnerabilities, but also experiences of socioeconomic disadvantage that may shape one's relationship with food in obesogenic ways.

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

STAFF

Julia Bittner, Ph.D., M.P.H,
Postdoctoral Fellow

Aleah Brown, B.S.,
Postbaccalaureate Fellow

Matt Siroty, B.S.,
Postbaccalaureate Fellow

KEY PUBLICATIONS

Bittner, J. M. P., Gilman, S. E., Zhang, C., Chen, Z., & Cheon, B. K. (2023). Relationships between early-life family poverty and relative socioeconomic status with gestational diabetes, preeclampsia, and hypertensive disorders of pregnancy later in life. *Annuals of Epidemiology, 86*, 8-15. PMID: 37573949. PMCID: PMC10538385

Smith, M. R., Bittner, J. M. P., Loch, L. K., Haynes, H. E., Bloomer, B. F., Te-Vazquez, J., Bowling, A. I., Brady, S. M., Tanofsky-Kraff, M., Chen, K. Y., Yanovski, J. A., & Cheon, B. K. (2023). Independent and interactive associations of subjective and objective socioeconomic status with body composition and parent-reported hyperphagia among children, *Childhood Obesity.* PMID: 37943608

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 obtaining 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; thus, 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 2023, clinical trials were actively recruiting for safety and contraceptive evaluation of new drugs or devices in the CDP pipeline. Additionally, results from completed trials were being analyzed to prepare manuscripts for publication of findings and to provide clinical study reports to FDA to support advancing promising products to the next stage of development. New

Diana Blithe, Ph.D.,
Senior Scientist and Chief

STAFF

Jeffrey Kroopnick, M.D.,
Medical Officer

Min S. Lee, Ph.D.,
Chemist

Ahnyah Phillips, B.S.,
Postbaccalaureate Fellow

Danielle Gross, B.A.,
Postbaccalaureate Fellow

CONTRACEPTIVE DEVELOPMENT PROGRAM

methods for women include 1) a novel vaginal ring that can be used for three months; 2) a long-acting injectable that inhibits ovulation for three months: 3) a novel copper IUD that provides contraceptive effectiveness for at least three years; 4) a method that protects against HIV infection as well as pregnancy; 5) a non-hormonal vaginal shield. A trial to evaluate a novel transdermal hormonal male contraceptive method in couples seeking to prevent pregnancy is underway in nine US sites and seven international sites. Each product in development in the CDP fills an unmet need or provides greater safety to vulnerable populations at risk of unintended pregnancy.

Diana Blithe, Ph.D.

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 with these conditions 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. The 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. Hormonal approaches to male contraception use a similar endocrine feedback regulatory loop that female methods use. High testosterone (T) synthesized in testes supports spermatogenesis; lower T levels in serum maintain other androgen-dependent functions and normal sexual function. Reversible contraception is achieved with administration of exogenous progestins to suppress secretion of pituitary 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 Testosterone in a single gel formulation delivered in a

KEY PUBLICATIONS

Lee MS, Bunin DI, Furimsky AM, Nguyen D, Parman T, Kim K, Rausch L, Lin MT, Gupta P, Brown JE, Kroopnick JM, Blithe DL. Novel progestogenic androgens for male contraception: design, synthesis, and activity of C7 α-substituted testosterone. *Biol Reprod*. 109:851-863, 2023. PMID: 37669128; PMCID: PMC10724455

Amory JK, Blithe DL, Sitruk-Ware R, Swerdloff RS, Bremner WJ, Dart C, Liu PY, Thirumalai A, Nguyen BT, Anawalt BD, Lee MS, Page ST, Wang C. Design of an international male contraceptive efficacy trial using a self-administered daily transdermal gel containing testosterone and segesterone acetate (Nestorone). *Contraception* 124:110064, 2023. PMID: 37210024; PMID: PMC37210024

metered pump. Doses were evaluated to 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 being evaluated in couples who wish to use a novel male contraceptive product to prevent pregnancy. When couples complete a 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 was completed in 2022 and follow-up is ongoing in nine CCTN sites in the USA, two sites in the UK, and one site in Sweden, Italy, Chile, Kenya and Zimbabwe.

Novel Progestogenic Androgens for Male Contraception

Dimethandrolone (DMA) and 11βMethyl Nortestosterone (MNT) are novel agents with androgenic and progestin activities, suppressing gonadotropins while maintaining androgen-dependent functions. CDP is evaluating two pro-drugs (DMA-Undecanoate and MNT-Dodecylcarbonate) in early clinical trials of safety and dose-finding. Additional novel progestogenic androgens are in development.

KEY PUBLICATIONS

Lue Y, Swerdloff R, Pak Y, Nguyen BT, Yuen F, Liu PY, Blithe DL, Wang C. Male contraception development: monitoring effective spermatogenesis suppression utilizing a user-controlled sperm concentration test compared with standard semen analysis. *Fertil Steril* 119:208-217, 2023. PMID: 36347310; PMCID: PMC9898087

Shapley-Quinn MK, Song M, Chen BA, Devlin B, Luecke E, Brown J, Blithe DL, Achilles SL, van der Straten A. Participant experiences with a multipurpose vaginal ring for HIV and pregnancy prevention during a phase 1 clinical trial: learning from users to improve acceptability. *Front Reprod Health* 5:1147628, 2023. PMID: 37484873; PMCID: PMC10359149

2023 KEY PUBLICATIONS

Amory JK, Blithe DL, Sitruk-Ware R, Swerdloff RS, Bremner WJ, Dart C, Liu PY, Thirumalai A, Nguyen BT, Anawalt BD, Lee MS, Page ST, Wang C. Design of an international male contraceptive efficacy trial using a self-administered daily transdermal gel containing testosterone and segesterone acetate (Nestorone). *Contraception* 124:110064, 2023. PMID: 37210024; PMID: PMC37210024

Bittner, J. M. P., Gilman, S. E., Zhang, C., Chen, Z., & Cheon, B. K. (2023). Relationships between early-life family poverty and relative socioeconomic status with gestational diabetes, preeclampsia, and hypertensive disorders of pregnancy later in life. *Annuals of Epidemiology*, 86, 8-15. PMID: 37573949. PMCID: PMC10538385

Cummings JR, Lipsky LM, Faith MS, Nansel TR. Developmental trajectory of appetitive traits and their bidirectional relations with body mass index from infancy to early childhood. *Clinical Obesity* 2023; 14(1):e12620. PMID: 37669768 PMCID: PMC10841422

Gleason JL, Grewal J, Chen Z, Cernich A, Grantz KL. Risk of adverse neonatal outcomes among pregnant women with disabilities. *International Journal of Epidemiology.* 2023; 52(1):203-213. PMID: 36172968. PMCID: PMC9908045

Govender T, Yu J, Vidal-Ribas P, Gilman SE, Haynie DL. Adolescent Substance Use Patterns and Risk for Suicidal Thoughts and Behaviors in Young Adulthood. *J Stud Alcohol Drugs*. 2023;84(6):892-901. PMID: 37589372. PMCID: PMC10765979

Grantz KL, Hinkle SN, He D, Owen J, Skupski D, Zhang C, Roy A. A new method for customized fetal growth reference percentiles. *PLoS One*. 2023;18(3):e0282791. PMID: 36928064. PMCID: PMC10019672

Grantz KL, Lee W, Chen Z, Hinkle S, Mack L, Sanz Cortes M, Goncalves LF, Espinoza J, Gore-Langton R, Sherman S, He D, Zhang C, Grewal J. The NICHD Fetal 3D Study: A Pregnancy Cohort Study of Fetal Body Composition and Volumes. *American Journal of Epidemiology*. 2023 Nov 8. PMID: 37946325. PMCID: in process

Lee MS, Bunin DI, Furimsky AM, Nguyen D, Parman T, Kim K, Rausch L, Lin MT, Gupta P, Brown JE, Kroopnick JM, Blithe DL. Novel progestogenic androgens for male contraception: design, synthesis, and activity of C7 α-substituted testosterone. *Biol Reprod*. 109:851-863, 2023. PMID: 37669128; PMCID: PMC10724455

Lipsky LM, Cummings J, Siega-Riz AM, Nansel T. Relations of pregnancy and postpartum diet quality with offspring birth weight status through 12 months. *Obesity (Silver Spring)* 2023; 31(12):3008-3015. PMID: 37731285 DOI: 10.1002/oby.23891

Lu R, Nansel T, Chen Z. A perception-augmented hidden Markov model for family management of diabetes. *Statistics in Biosciences* 2023; 15:288-308. https://doi.org/10.1007/s12561-022-09360-8

Lue Y, Swerdloff R, Pak Y, Nguyen BT, Yuen F, Liu PY, Blithe DL, Wang C. Male contraception development: monitoring effective spermatogenesis suppression utilizing a user-controlled sperm concentration test compared with standard semen analysis. *Fertil Steril* 119:208-217, 2023. PMID: 36347310; PMCID: PMC9898087

Luk JW, Yu J, Haynie DL, Goldstein RB, Simons-Morton BG, Gilman SE. A Nationally Representative Study of Sexual Orientation and High-Risk Drinking From Adolescence to Young Adulthood. *J Adolesc Health*. 2023;72(2):222-9. PMID: 36456451. PMCID: PMC9832524

Mitro SD, Sundaram R, Louis GMB, Peddada S, Chen Z, Kannan K, Gleason JL, Zhang C, Grantz KL. Associations of pregnancy per- and polyfluoroalkyl substance concentrations and uterine fibroid changes across pregnancy: NICHD Fetal Growth Studies - Singletons cohort. *Environ Health Perspect*. May;131(5):57007, 2023. PMID: 37224071; PMCID: PMC10208432

Ouidir M, Chatterjee S, Wu J, Tekola-Ayele F. Genomic study of maternal lipid traits in early pregnancy concurs with four known adult lipid loci. *J Clin Lipidol*. 2023; 17(1):168-180. PMID: 36443208; PMCID: PMC9974591

Polinski KJ, Robinson SL, Putnick DL, Sundaram R, Ghassabian A, Joseph P, Gomez-Lobo V, Bell EM, Yeung EH. Maternal self-reported polycystic ovary syndrome with offspring and maternal cardiometabolic outcomes. *Human Reproduction* 2024 Jan 5;39(1):232-239. PMID: 37935839 PMCID: PMC10767861

Saha A., Ma L, Biswas A, Sundaram R. Joint modeling of geometric features of longitudinal data and time-to-event: with application to fecundity studies. *Statistics in Biosciences*, https://doi.org/10.1007/s12561-023-09381-x

Shapley-Quinn MK, Song M, Chen BA, Devlin B, Luecke E, Brown J, Blithe DL, Achilles SL, van der Straten A. Participant experiences with a multipurpose vaginal ring for HIV and pregnancy prevention during a phase 1 clinical trial: learning from users to improve acceptability. *Front Reprod Health* 5:1147628, 2023. PMID: 37484873; PMCID: PMC10359149

Smith, M. R., Bittner, J. M. P., Loch, L. K., Haynes, H. E., Bloomer, B. F., Te-Vazquez, J., Bowling, A. I., Brady, S. M., Tanofsky-Kraff, M., Chen, K. Y., Yanovski, J. A., & Cheon, B. K. (2023). Independent and interactive associations of subjective and objective socioeconomic status with body composition and parent-reported hyperphagia among children. *Childhood Obesity*. PMID: 37943608

Tesfaye M, Wu J, Biedrzycki RJ, Grantz KL, Joseph P, Tekola-Ayele F. Prenatal social support in low-risk pregnancy shapes placental epigenome. *BMC Med*. 2023; 8; 21(1):12. PMID: 36617561; PMCID: PMC9827682

Vidal-Ribas P, Govender T, Yu J, Sundaram R, Perlis RH, Gilman SE. Children's cognitive performance and suicide risk through middle adulthood. *J Child Psychol Psychiatry*. 2023;64(10):1480-91. PMID: 37263773. PMCID: PMC10524389

Yeung E, Putnick D, Ghassabian A, Sundaram R, Lin T-C, Mirzaei S, Stern J, Bell E. Examining attention deficit/hyperactivity disorder and related behavioral disorders by fertility treatment exposure in a prospective cohort. *Annals of Epidemiology* 2023 Jun;82:59-65.e1. PMID: 36972758 PMCID: PMC10247509

Zhang W, Zhang Z, Liu A. Optimizing treatment allocation in randomized clinical trials by leveraging baseline covariates. *Biometrics* 2023; 79:2815-2829. PMID: 37641532; PMCID: PMC10843680