Eunice Kennedy Shriver National Institute
of Child Health and Human Development

DIPHR

2022 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.

In reflecting on the last year, my first full year as Director, I am proud and appreciative of all my colleagues for their extraordinary work in fulfilling the missions of the Division and the Institute. Everyone has 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 2022.

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 2022 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 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 2023 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.

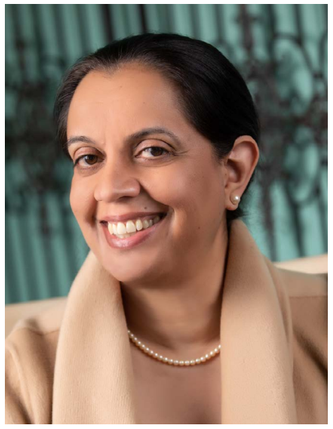
Please visit DIPHR's website for information about our research, collaborations, service, training, and career opportunities. Comments and questions about the Division are welcome!

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. Findings from the NICHD Fetal Growth Studies (PMCID: PMC4584427) indicate that assessment of fetal growth by ultrasound should be evaluated using racial/ethnic-specific standards to bolster early detection of potential abnormalities, minimize misclassification of minority fetuses, and avoid unnecessary interventions. Meanwhile, central findings from the Dietary Patterns during Pregnancy show that most pregnant women in this contemporary cohort reported dietary intakes that, on average, did not meet US Dietary Guidelines for nonpregnant individuals. Moreover, diet differed across racial/ethnic groups, with non-Hispanic Black women having the lowest overall dietary quality in all trimesters (PMCID: PMC7846139). In addition, 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, 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.,
Research Fellow

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 2022, 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 further developed and used to identify important drivers of pregnancy loss in a mixture of environmental toxicants. Members of BBB continue to develop time-to-event tools specifically focusing on identifying time-varying exposures, environmental toxicants or behavioral factors that influence these durations. Building upon time to pregnancy work, methods for progression of labor can be classified as multistage data consisting of various stages of labor, intermittent examinations, and unobserved start time and provide clinicians with real-time tools to predict and hopefully avoid complications.

Biomarker methods for analysis of microbial communities were a focus of BBB staff in 2022. Specifically, new methods were developed to account for the complex nature of microbial biomarkers, enabling the understanding of association with complex diseases by account for compositional constraint, excessive zeros, and high dimensionality. Another complex problem due to compositionality of microbiome data is describing correlations. Furthermore, since microbiota form a complex ecology where the dependencies are not often linear. For all these reasons, standard concepts of association are not valid for microbiome data. Members of the branch have developed a statistically rigorous methodology to describe associations among microbes. Using these methods, for the first time in the literature, they described temporal changes in interactions among the gut microbes in infants during the first year after birth.

BBB staff developed a placement value-based Bayesian regression model with random effects to estimate ROC curves. The use of placement value allows covariate effects directly on the ROC curves, and the adoption of a Bayesian approach accommodates the a *priori* constraint that an ROC curve of

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

STAFF

Aiyi Liu, Ph.D.,
Senior Investigator

Rajeshwari Sundaram, Ph.D.,
Senior Investigator

Zhen Chen, Ph.D.,
Senior Investigator

James Morton, Ph.D.,
Investigator

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

BIOSTATISTICS AND BIOINFORMATICS BRANCH

EFW near delivery should dominate another further away. The proposed methodology is shown to perform better than some alternative approaches in simulations and its application to the Scandinavian Study data suggest that diagnostic accuracy of EFW can improve about 65% from week 17 to 37 of gestation.

Determining whether some people are more pre-disposed to a disease than others when exposed to an infection is of great public health importance. Researchers in BBB pursued 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 could lead to advancements in understanding of potentially similar phenomenon 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 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 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 also serve as associate editors of the journals, *Statistical Methods in Medical Research, Statistics in Biosciences, Clinical Trials,* and *Nutrients*.

The year closed with Dr. Shyamal Peddada transitioning to NIEHS and Dr. Neil Perkins becoming Acting Chief of BBB while a search is conducted in 2023.

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

Lars Hunger, Ph.D.,
Postdoctoral Fellow

Aiyi Liu, Ph.D.

Methods for predictive biomarkers and clinical trials with applications

Dr. Liu's research in 2022 focused on biomarkers, particularly microbial biomarkers, in the diagnosis and treatment of disease. Microbial communities have been shown to be associated with many complex diseases, such as cancers and cardiovascular diseases. The identification of differentially abundant taxa is clinically important. It can help understand the pathology of complex diseases, and potentially provide preventive and therapeutic strategies. Appropriate differential analyses for microbiome data are challenging due to its unique data characteristics including compositional constraint, excessive zeros, and high dimensionality. Most existing approaches either ignore these data characteristics or only account for the compositional constraint by using log-ratio transformations with zero observations replaced by a pseudocount. New methods are needed to account for these data features.

Aiyi Liu, Ph.D.,
Senior Investigator

STAFF
Jin Yang, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Zhang W, Liu A, Zhang Z, Chen G, Li Q. An adaptive direction-assisted test for microbiome compositional data. *Bioinformatics*. 2022 Jul 11; 38(14):3493-3500. doi: 10.1093/bioinformatics/btac361. PMID: 35640978. PMCID: PMC9890306.

Zhang Z, Nie L, Soon G, Liu A. The Use of Covariates and Random Effects in Evaluating Predictive Biomarkers Under a Potential Outcome Framework. *Ann Appl Stat*. 2014 Dec; 8(4):2336-2355. doi: 10.1214/14-AOAS773. Epub 2014 Dec 19. PMID: 26779295. PMCID: PMC4714717.

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.

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

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

KEY PUBLICATIONS

Saha, A. and Sundaram, R., 2023. Variable selection for discrete survival model with frailty in presence of left truncation and right censoring: Studying association of environmental toxicants on time‐to‐pregnancy. *Statistics in Medicine*; 42(2), pp.193-208. PMID: 36457137.

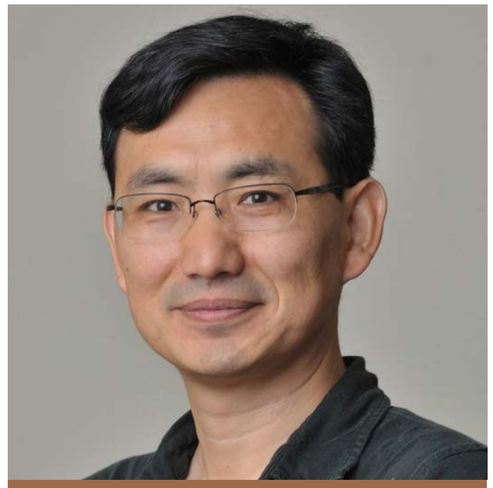
Gleason, J.L., Sundaram, R., Mitro, S.D., Hinkle, S.N., Gilman, S.E., Zhang, C., Newman, R.B., Hunt, K.J., Skupski, D.W., Grobman, W.A. and Nageotte, M., 2022. Association of Maternal Caffeine Consumption During Pregnancy With Child Growth. *JAMA Network Open*; 5(10), pp.e2239609-e2239609. PMID: 36315142. PMCID: PMC9623443.

Zhen Chen, Ph.D.

In 2022, Dr. Chen published 3 methodological papers and 11 collaborative manuscripts. Dr. Chen presented his research work in the seminar series of NIEHS Biostatistics and Computational Biology Branch and at the International Biometric Conference. He also actively participated in professional services, including co-chairing the 2022 NIH Stadtman Search Computational Biology/Bioinformatics/ Biostatistics/Mathematics Committee, serving as a reviewer for Data Analysis and Statistical Programming Support Technical Evaluation, as a co-Editor for a special volume for the journal *Statistics in Biosciences*, and in the Program Committee of 35th New England Statistics Symposium. Dr. Chen mentored two postdoctoral fellows (Drs. Ghosal and Lu), with both started their academic positions in top universities, and have successfully recruited his next postdoc fellow. Of special note, 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 2022 work is listed below.

Discriminatory capacity of prenatal ultrasound measures for large-for-gestational-age birth

Predicting large fetuses at birth is of great interest to obstetricians. Using an NICHD Scandinavian Study that collected longitudinal ultrasound examination data during pregnancy, we estimate diagnostic accuracy parameters of estimated fetal weight (EFW) at various times during pregnancy in predicting large for gestational age. We adopt a placement value-based Bayesian regression model with random effects to estimate ROC curves. The use of placement value allows us to model covariate effects directly on the ROC curves, and the adoption of a Bayesian approach accommodates the a priori constraint that an ROC curve of EFW near delivery should dominate another further away. The proposed methodology is shown to perform better than some alternative approaches in simulations and its application to the Scandinavian Study data suggest that diagnostic accuracy of EFW can improve about 65% from week 17 to 37 of gestation.



Zhen Chen, Ph.D.,
Senior Investigator

STAFF
Soutik Ghosal, Ph.D.,
Research Fellow

Ruijin Lu, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS
Ghosal S, Chen Z. Discriminatory capacity of prenatal ultrasound measures for large-for-gestational-age birth: A Bayesian approach to ROC analysis using placement values. *Statistics in Biosciences*. 2022; 14:1-22. PMID: 35342482. PMCID: PMC8942391.

EPIDEMIOLOGY BRANCH

In 2022, 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 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.

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

STAFF

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

Katherine Grantz, M.D., M.S.,
Senior Investigator (promoted October 2022)

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

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

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

EPIDEMIOLOGY BRANCH (CONT.)

High quality scientific investigation in these various domains across the life course has yielded many awards recognizing the hard work of EB team members. During 2022, EB investigators and fellows received multiple awards from NICHD for mentoring and collaborative service. 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.

FELLOWS

Suvo Chatterjee, Ph.D.,
Postdoctoral Fellow (departed 2022)

Priscilla Clayton, Ph.D.,
Postdoctoral fellow

Tesfa Habtewold, Ph.D.,
Visiting Fellow

Alexandra Jean-Louis, Ph.D.,
Postbaccalaureate fellow

Susanna Mitro, Ph.D.,
Postdoctoral Fellow (departed 2022)

Marion Ouidir, Ph.D.,
Visiting Fellow (departed 2022)

Georgia Pitsava, M.D.,
Postdoctoral Fellow (departed 2022)

Kristen Polinski, Ph.D.,
Postdoctoral Fellow (departed 2022)

Ian Trees, Ph.D.,
Postdoctoral Fellow

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

Kathryn Wagner, Ph.D.,
Postdoctoral Fellow

Sifang (Kathy) Zhao, Ph.D.,
Postdoctoral Fellow (departed 2022)

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

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

STAFF

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

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

Kristen Polinski, Ph.D., *Postdoctoral fellow (departed 2022)*

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

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

Sifang (Kathy) Zhao, Ph.D., *Postdoctoral fellow (departed 2022)*

KEY PUBLICATIONS

Yeung EH, Mendola P, Sundaram R, Lin TC, Broadney MM, Putnick DL, Robinson SL, Polinski KJ, Wactawski-Wende J, Ghassabian A, O'Connor TG, Gore-Langton RE, Stern JE, Bell E. Conception by fertility treatment and cardiometabolic risk in middle childhood. *Fertility and Sterility* 2022 Aug; 118(2):349-359. PMID: 35697532. PMCID: PMC9329264

Polinski KJ, Stevens DR, Mendola P, Lin TC, Sundaram R, Bell E, Yeung EH. Infertility treatment associated with childhood asthma and atopy. *Human Reproduction* 2022 Jun 30; 37(7):1609-1618. PMID: 35446387 PMCID: PMC9247411.

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 2022, 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 cardiometabolic outcomes 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, cardiometabolic clinical measures did not indicate greater cardiometabolic risk in children conceived using ART or OI compared with controls, which is reassuring for those undergoing fertility treatments (PMC9329264). In another study, infertility treatment was associated with child asthma and atopic conditions like wheezing, eczema, and allergies (PMC9247411). Findings showed that the increased risk of persistent wheeze by age 3 years among children conceived with fertility treatment remained even after accounting for parental asthma and atopy. Longer term, asthma and eczema reported at 7-9 years was also increased.

The mechanistic links between in utero exposures and DNA methylation were also explored in a series of investigations among different cohorts. Particularly, these studies explored the impact of maternal stress on cord blood methylation (PMC8882928) and maternal physical activity (PMC9535520) on placental methylation, respectively. Furthermore, Dr. Yeung's team investigated the relationship between epigenetic gestational age compared to clinical gestational age on early childhood development. While higher clinical gestational age is known to be protective of risks of developmental delay, using two separate clocks, epigenetic aging measured using DNA methylation in Upstate KIDS performed similarly well in marking those protective associations. However, accelerated aging (the difference between clinical gestational age and DNA methylation age) was not an important independent factor to identify newborns at risk of delay. The study was strengthened by inclusion of twins and singletons with a wider range of gestational age than previous studies (PMID: 36617164).

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.

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

Ectopic posterior pituitary (EPP) is a rare condition due to defective neuronal migration in which the pituitary stalk is displaced distally and usually located at the third ventricle. It may be associated with an empty pituitary fossa, hypoplasia or absence of the pituitary stalk, and pituitary hormone deficiencies. EPP is virtually always associated with pituitary dysfunction, in particular growth hormone (GH) deficiency. EPP can be identified in 40% to 60% of all patients with isolated GH deficiency or combined pituitary hormone deficiencies. Genetic variants are known to contribute to EPP. Genetic variants, however, have only been identified in less than 5% of EPP cases. It is likely that other genes related to EPP remain to be discovered. Using whole exome sequencing (WES), we sought to identify novel genetic defects associated with EPP in a large cohort of Brazilian patients with this condition. We identified 16 different variants in 12 genes in 15 of the 78 cases (19.2%). Complete anterior pituitary deficiency was twice as common in cases with variants of interest compared to cases without variants. Our study confirmed ROBO1 and HESX1 as relevant associated genes and added important evidence for other NOTCH pathway-related genes being potentially important in pituitary development.

Sacral agenesis (SA) is a rare (0.01–0.05 per 1,000 live births) birth defect characterized by varying degrees of agenesis of the lower spinal column. Respiratory, genitourinary, central nervous system, and gastrointestinal defects have been reported with SA. Few factors, genetic or environmental, have been reported that contribute to the development of SA. Maternal diabetes mellitus during organogenesis is by far the most important. The current study conducted whole exome sequencing on 28 child-parent trios and two child-father duos with non-syndromic SA. This study was designed to add to our limited knowledge of gene variants possibly associated with non-syndromic SA. We identified three children with non-syndromic SA, each inheriting a different rare variant in the ID1 gene. ID1 is a member of a four-protein family (ID1-ID4) of helix-loop-helix (HLH) transcriptional regulatory proteins that play a role in cell growth and differentiation. These genes participate in crucial developmental processes, including neurogenesis, myogenesis, and sex determination. Additional rare variants identified using the established primary and secondary filtering criteria were not identified in more than one child in the study sample. These rare variants may also contribute to SA etiology, but very large sample sizes would be required to replicate these associations. Many children had variants identified in more than one gene. Together, these findings suggest no single, common cause of non-syndromic SA in protein-coding regions. Future sequencing studies for non-syndromic SA require collaboration among multiple study populations to examine both rare variants reported here and additional variants.

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

STAFF
Georgia Pitsava, M.D.,
Postdoctoral Fellow
(departed 2022)

KEY PUBLICATIONS

Silva TS, Faucz FR, Hernández-Ramírez LC, Pankratz N, Lane J, Kay DM, Lyra A, Kochi C, Stratakis CA, Longui CA, Mills JL. Whole Exome Sequencing in Patients With Ectopic Posterior Pituitary. *J Endocr. Soc.* 2022 Aug 11; 6(10):bvac116. doi: 10.1210/jendso/bvac116. eCollection 2022 Oct 1. PMID: 36042976. PMCID: PMC9419495.

Pitsava G, Feldkamp ML, Pankratz N, Lane J, Kay DM, Conway KM, Hobbs C, Shaw GM, Reefhuis J, Jenkins MM, Almli LM, Moore C, Werler M, Browne ML, Cunniff C, Olshan AF, Pangilinan F, Brody LC, Sicko RJ, Finnell RH, Bamshad MJ, McGoldrick D, Nickerson DA, Mullikin JC, Romitti PA, Mills JL; UW Center for Mendelian Genomics, NISC Comparative Sequencing Program and the National Birth Defects Prevention Study. Exome sequencing identifies variants in infants with sacral agenesis. *Birth Defects Res.* 2022 Apr; 114(7):215-227. doi: 10.1002/bdr2.1987. Epub 2022 Mar 10. PMID: 35274497. PMCID: PMC9338687.

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

Obstetrics is need of evidence to help guide the creation of clinical guidelines. Dr. Grantz's research program focuses on pregnancy management and outcomes, fetal growth and development in singleton and twin pregnancies, and is building a program to determine the optimal timing of delivery for pregnancies with complications. Fetal growth is a one of the earliest indicators of health. Restricted growth as well as excessive growth increases perinatal morbidity and mortality and poses health risks for the offspring long-term. However, classifying "optimal" growth to identify individuals at each end of the spectrum for clinical intervention remains a challenge. Dr. Grantz's research addresses this important data gap using several approaches, including generating fetal growth standards for application in clinical practice and investigating the role of fetal growth velocity, or how quickly a fetus grows.

Fetal Growth Study
NICHD

As co-PI of the NICHD Fetal Growth Studies, her major contributions this past year were publications of two new references and clinical calculators for fetal growth and growth velocity that for the first-time account for the diversity of pregnancies in the United States (PMID: 34906542; PMID: 35926648). The new, multiethnic fetal growth reference represents a major improvement over existing references that are retrospective or cross-sectional in design and based on limited and/or nondiverse samples. (Figure) Incorporating knowledge about growth velocity into traditional cross-sectional assessments of estimated fetal weight improves prediction of birthweight. Decreasing error in birthweight prediction has the potential to advance clinical intervention decisions that depend on estimated fetal weight, such as cesarean for suspected fetal macrosomia. Her team is also examining the benefits of customized and individualized fetal growth references.

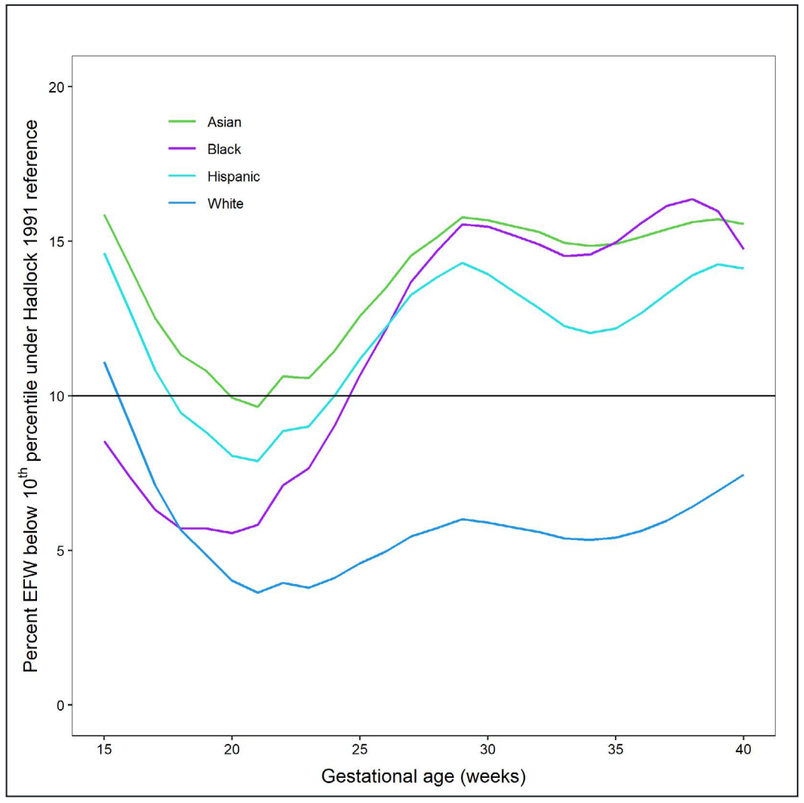


Figure. EFW in the NICHD Fetal Growth Studies versus Hadlock

Percentage of fetuses with an estimated fetal weight (EFW) <10th percentile by racial and ethnic group, Hadlock reference, and gestational age. The difference between racial- and ethnic-specific curves and the 10% referent line reflects the amount of differential classification attributed to using the Hadlock reference that was developed in White pregnant individuals in 1991 and is commonly used in clinical practice in the US. (Adapted from Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991;181: 129–33.)

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

STAFF

Jessica Gleason, Ph.D., *Research Fellow*

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

Susanna Mitro, Ph.D., *Postdoctoral Fellow (departed 2022)*

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

Furthermore, in a follow-up project from the NICHD Fetal Growth Studies, Dr. Grantz's team found that consumption of even small amounts of caffeine during pregnancy were associated with shorter offspring height, first observed at birth (PMID: 33764424), and persisting into childhood (PMID: 36315142).

Fetal 3D Study
NICHD

Building on work in 2D ultrasound, her team has analyses underway in the Fetal 3D Study to establish standards for fetal body composition and organ volumes and to 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 of 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.

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Gleason, J.L., Sundaram, R., Mitro, S.D., Hinkle, S.N., Gilman, S.E., Zhang, C., Newman, R.B., Hunt, K.J., Skupski, D.W., Grobman, W.A. and Nageotte, M., 2022. Association of Maternal Caffeine Consumption During Pregnancy With Child Growth. *JAMA Network Open*; 5(10), pp.e2239609-e2239609. PMID: 36315142. PMCID: PMC9623443.

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Grantz KL, Grewal J, Kim S, Grobman WA, Newman RB, Owen J, Sciscione A, Skupski D, Chien EK, Wing DA, Wapner RJ, Ranzini AC, Nageotte MP, Craigo S, Hinkle SN, D'Alton ME, He D, Tekla-Ayele F, Hediger ML, Buck Louis GM, Zhang C, Albert PS. Unified Standard for Fetal Growth Velocity: the NICHD Fetal Growth Studies. *American Journal of Obstetrics and Gynecology*. 2022 Dec; 227(6):916-922. PMID: 35926648. PMCID: PMC9729377.

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.

Genome wide association studies have identified genetic variants associated with birthweight; however, absence of the placenta in many genomics databases has hindered functional advance. Recently, the group provided mechanistic insight into the causal pathway from a genetic variant to birthweight by integrating placental methylation and gene expression with established genetic loci for birthweight. Enrichments have been identified for cardiometabolic, immune response, and hormonal pathways for loci involved in regulation of placental gene expression and methylation. The integrated work prioritized four causal genes that impact fetal growth via placental epigenetic and transcriptomic mechanisms (*PLEKHA1, FES, CTDNEP1,* and *PRMT7*) (PMC9061712).

Genetic modulation of placental function can also vary by context-specific factors such as fetal sex, which have profound implication in placental function and pregnancy outcomes. Sex-stratified analysis of placental gene expression unraveled novel pathways linked to small-for-gestational age that could have been missed in sex-pooled analysis (PMC9010378). Gene regulatory effects on fetal growth can also be related to genetic variants that alter the maternal cardiometabolic status. The group identified genetic loci linked to early pregnancy maternal plasma lipid levels (PMC9974591). A positive association has been found between maternal genetic risk score for type 2 diabetes and fetal growth starting at mid-second trimester only among European ancestry women independent of maternal blood glucose levels (PMC8914278). Absence of similar associations in non-European ancestry groups urges the need for genetic type 2 diabetes studies in diverse ancestries (PMC8914278).

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 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 pregnan

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

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Marion Ouidir, Ph.D,
Postdoctoral fellow (departed in 2022)

KEY PUBLICATIONS

Tekola-Ayele F, Zeng X, Chatterjee S, Ouidir M, Lesseur C, Hao K, Chen J, Tesfaye M, Marsit CJ, Workalemahu T, Wapner R. Placental multi-omics integration identifies candidate functional genes for birthweight. *Nat Commun*. 2022; 13(1):2384. PMID: 35501330; PMCID: PMC9061712.

Ouidir M, Zeng X, Chatterjee S, Zhang C, Tekola-Ayele F. Ancestry-Matched and Cross-Ancestry Genetic Risk Scores of Type 2 Diabetes in Pregnant Women and Fetal Growth: A Study in an Ancestrally Diverse Cohort. *Diabetes*. 2022; 71(2):340-349. PMID: 34789498; PMCID: PMC8914278.

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.

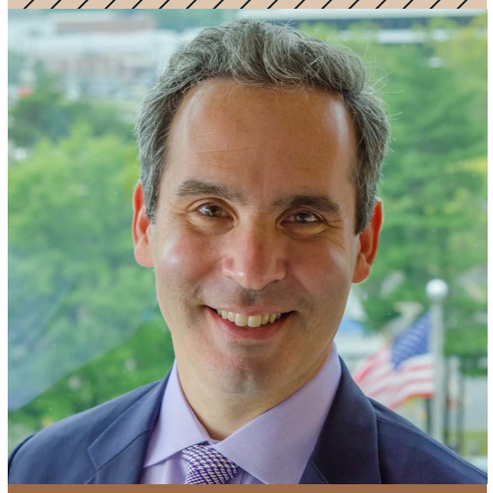
SBSB also recruits, trains, and mentors highly qualified students and trainees for professional careers in the social and behavioral sciences. We host academic and professional development activities throughout the year as part of our SBSB education and training (SBSBeat) series. In 2022, a notable highlight was our Fall Seminar Series, which hosted six outstanding scientists to give presentations to our Division about their cutting edge research and methods related to our Branch's mission. Joining us were: Dr. Byron Reeves (Stanford University), Dr. Christina Roberto (University of Pennsylvania), Dr. Pamela Morris-Perez (New York University), Dr. Fanita Tyrell (University of Maryland), Dr. Dara Mendez (University of Pittsburgh), and Dr. Akihiro Nishi (UCLA). Thanks to SBSB members Diana Augustin, Jenna Cummings, Theemeshni Govender, and Julia Porth for organizing this 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 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 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.



Stephen E. Gilman, Sc.D.,
Branch Chief

STAFF

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

SOCIAL AND BEHAVIORAL SCIENCES BRANCH (CONT.)

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 a mechanism through which dipartites in socioeconomic status may translate into overeating and risks for obesity.

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

FELLOWS

Diana Augustin, B.A.,
Postbaccalaureate Fellow, NICHD Developing Talent Scholar

Jenna Cummings, Ph.D.,
Postdoctoral Fellow (departed in 2022)

Theemeshni Govender, B.A.,
Postbaccalaureate Fellow

Mia Kwan, B.A.,
Postbaccalaureate Fellow

Evelyn Liu, B.S.,
Postbaccalaureate Fellow (departed in 2022)

Jan Mooney, M.A.,
Predoctoral Fellow (departed in 2022)

Julia Porth, Ph.D.,
Postdoctoral Fellow

Meegan Smith, B.A.,
Postbaccalaureate Fellow

Pablo Vidal-Ribas Belil, Ph.D.,
Visiting Fellow (departed in 2022)

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.

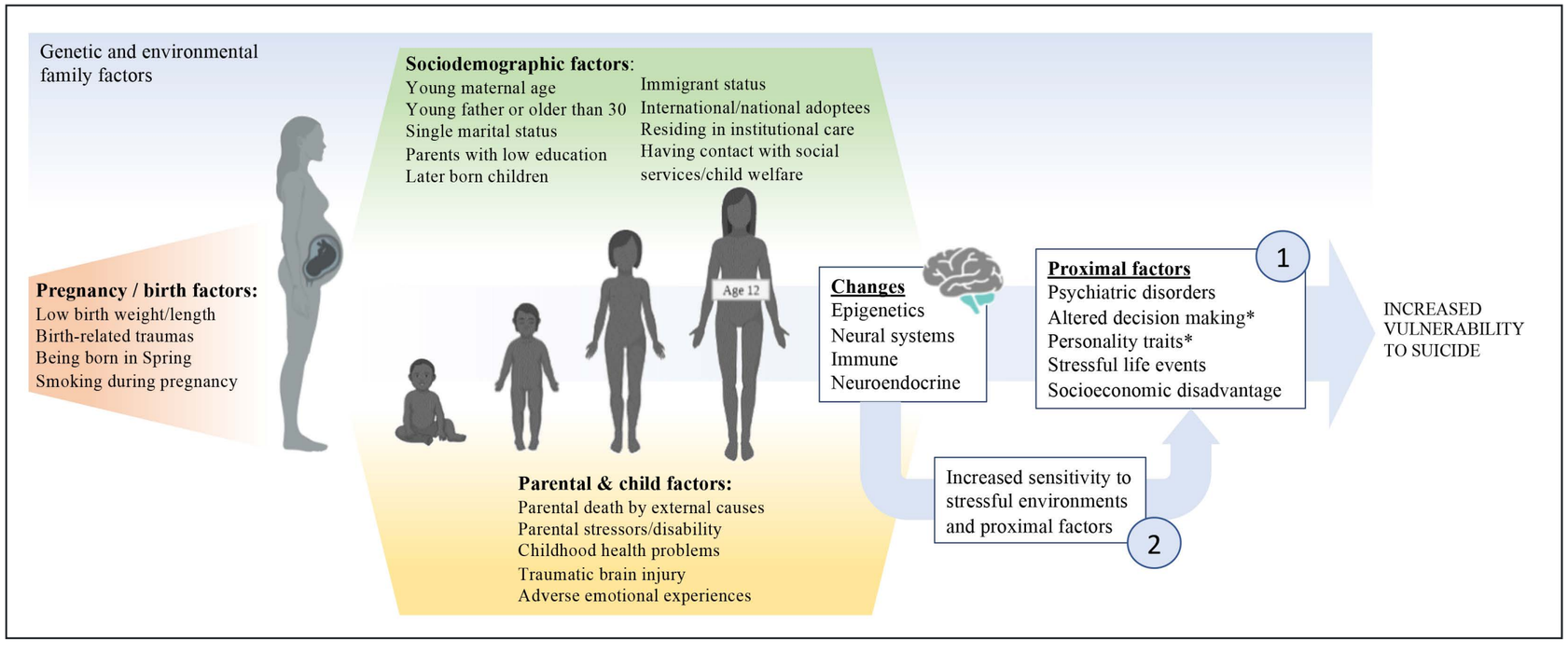
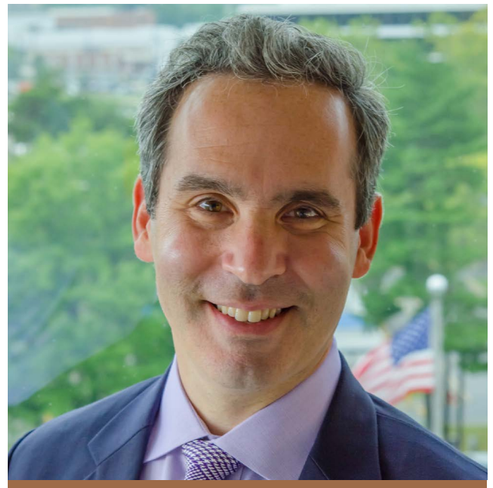


Fig. 1 Schematic representation of the effect of early life factors on increased vulnerability to suicide mortality. Pregnancy-related fac-tors, sociodemographic factors, and parental and child factors during first years of childhood are thought to influence epigenetic, neural, immune, neuroendocrine, social, and psychological changes with two potential long-term effects: (1) increased likelihood to exposure to more proximal and precipitant factors, which in turn increase vulnerability to suicide, and (2) increased sensitivity to stressful environments and effects of proximal factors if these occur. Genetic and environmental family factors might affect some of these effects. * Altered decision-making and personality traits are listed here under proximal factors given that this review focuses on early life factors; however, they are sometimes conceptualized as distal factors in the literature



Stephen E. Gilman, Sc.D., *Branch Chief*

STAFF

Diana Augustin, B.A., *Postbaccalaureate Fellow,* NICHD Developing Talent Scholar

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

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

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

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

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 (e.g., see Figure 1, from a systematic review of developmental origins of suicide led by Dr. Pablo Vidal-Ribas). 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 2, from a study on adverse childhood experiences and premature mortality risk led by Dr. Jing Yu). Related work in collaboration with our colleagues on the Next Generation Health Study concerns the social determinants of mental health problems during adolescence. Finally, we continue our work toward understanding the long-term and potentially intergenerational influences of the early environment on health.

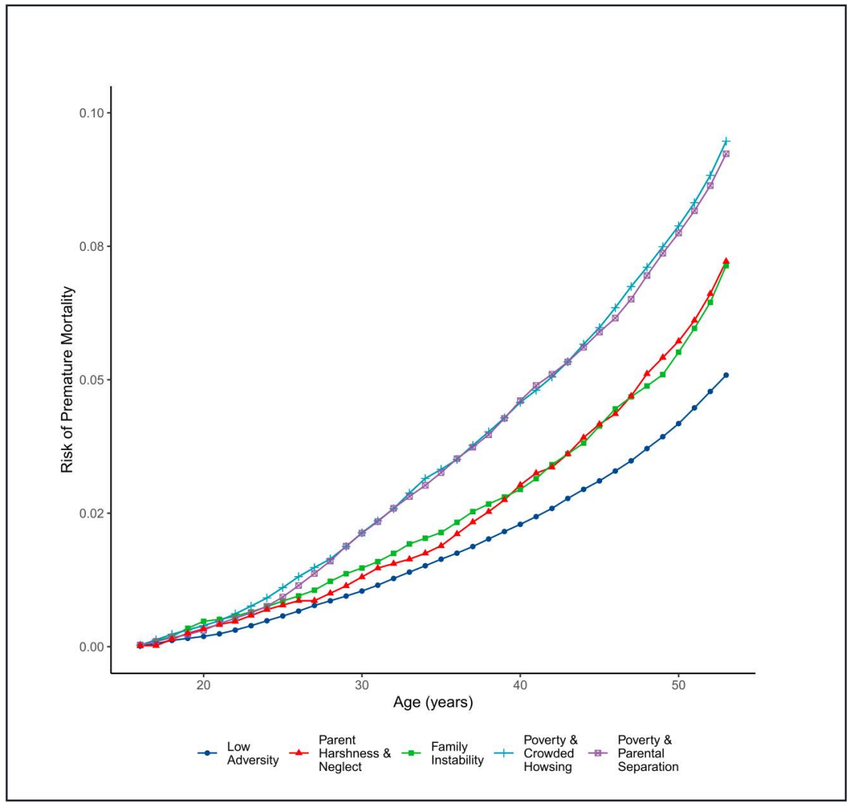


Fig. 2 Risk of premature mortality for individuals in each latent class of ACEs.

Note: All the other ACE classes had higher mortality risk than the low adversity class. The mortality rate (i.e., number of deaths per 100 000 individuals per year) was 183 for the Poverty & Crowded Housing class, 177 for the Poverty & Parental Separation class, 135 for the Family Instability class, 139 for the Parental Harshness & Neglect class, and 114 for the Low Adversity class.

KEY PUBLICATIONS

Babineau V, Fonge YN, Miller ES, Grobman WA, Ferguson PL, Hunt KJ, Vena JE, Newman RB, Guille C, Tita ATN, Chandler-Laney PC, Lee S, Feng T, Scorza P, Takacs L, Wapner RJ, Palomares KT, Skupski DW, Nageotte MP, Sciscione AC, Gilman S, Monk C. Associations of Maternal Prenatal Stress and Depressive Symptoms with Childhood Neurobehavioral Outcomes in the ECHO Cohort of the NICHD Fetal Growth Studies: Fetal Growth Velocity as a Potential Mediator. *J Am Acad Child Adolesc Psychiatry*. 2022; 61(9):1155-67. PMID: 35367322. PMCID: PMC9427685.

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Yu J, Patel RA, Haynie DL, Vidal-Ribas P, Govender T, Sundaram R, Gilman SE. Adverse childhood experiences and premature mortality through mid-adulthood: A five-decade prospective study. *Lancet Reg Health Am*. 2022; 15. PMID: 36467261. PMCID: PMC9718480.

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.

"Reducing ultra-processed food intake in pregnancy may represent a singular intervention target with broad impact on maternal diet quality and health."

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. Study data include 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 provide insights into potential dietary targets for improving maternal and child health. The timing and frequency of eating was associated with maternal diet quality and energy intake, with several differences between pregnancy and postpartum suggesting that efforts to support optimal dietary intake may require specific strategies for each developmental period (Schweldhelm et al. 2022 PMID 35334823). Findings also suggest the potential utility of targeting maternal ultra-processed food intake. Ultra-processed food comprised on average 53% of energy intake in pregnancy and was associated with worse diet quality, including lower intake of fruit, vegetables, plant protein, and total protein, and greater intake of refined grains and added sugar (Nansel et al. 2022 PMID 36235585). Greater intake of ultra-processed food in pregnancy was associated with greater risk of excess gestational weight gain, greater inflammation, and greater postpartum weight retention, but not with infant weight (Cummings et al. 2022 PMID 35619114). Further, greater maternal dietary intake of ultra-processed food and shorter duration of exclusive breastfeeding was associated with more obesogenic infant appetitive traits (Cummings et al. 2022 PMID 35922793). Our examination of infant appetitive traits also showed that lower infant enjoyment of food and greater speed of eating may be associated with suboptimal complementary feeding practices (Sanjeevi et al. 2022 PMID 34481014).

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. 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. Data collection is ongoing with planned completion in 2024.

Tonja R. Nansel, Ph.D.
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Jan Mooney, M.A.,
Predoctoral Fellow (departed 2022)

Evelyn Liu, B.S.,
Postbaccalaureate Fellow (departed 2022)

Mia Kwan, B.S.,
Postbaccalaureate Fellow

KEY PUBLICATIONS

Nansel TR, Cummings JR, Burger K, Siega-Riz AM, Lipsky LM. Greater ultra-processed food intake during pregnancy and postpartum is associated with multiple aspects of lower diet quality. *Nutrients* 2022: 14(19):3933. PMID: 36235585. PMCID: PMC9572643.

Cummings JR, Lipsky LM, Schwedhelm C, Liu A, Nansel TR. Associations of ultra-processed food intake with maternal weight change and cardiometabolic health and infant growth. *International Journal of Behavioral Nutrition and Physical Activity* 2022; 19(1):61. PMID: 35619114. PMCID: PMC9137185.

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 of children and families. 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 lab applies both experimental and population-health approaches to investigate how these types of socioeconomic vulnerabilities influence food-related preferences, behaviors, and health of children and parents.

"...efforts to address social disparities in diet-related health outcomes of children should not only focus on objective socioeconomic vulnerabilities, but also experiences of socioeconomic disadvantage that may be internalized and shape one's relationship with food in obesogenic ways."

In 2022, Dr. Cheon's lab has pursued multiple studies examining the role of disadvantaged social and economic status in children's eating behavior and growth. In collaboration with NICHD's Children's Growth and Behavior Study (CGBS), Dr. Cheon's team has identified that the interplay of family socioeconomic status (SES) and children's perceptions of their family's socioeconomic standing compared to other families may be associated with children's eating behaviors and adiposity. Specifically, among children from lower SES households, perception of relatively disadvantaged socioeconomic standing of their families was associated with more severe hyperphagic behaviors and higher levels of adiposity. We also observed in CGBS that eating in the absence of hunger due to negative emotions and adiposity of children who reported lower social status compared to peers was exacerbated when they also experienced other social stressors, such as teasing related distress.

These findings were further expanded in Dr. Cheon's research in the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort study, in which he prospectively tested whether children who exhibited greater stress reactivity to a laboratory-based experience of social ostracism by peers are more likely to develop higher body mass in future years. The findings revealed a moderated mediation, such that physiological stress to ostracism (measured by heart rate variability) predicted increased energy intake from a subsequent snack, which predicted higher child body mass index 1.5 years later, but only among children who reported greater concerns about being rejected or negatively evaluated by others.

Together, these findings suggest that while objective socioeconomic stressors like household income and social exclusion by peers may contribute to children's obesogenic eating behaviors and adiposity, the internalization of socioeconomic disadvantage may exacerbate these relationships. This work also demonstrates that efforts to address social disparities in diet-related health outcomes of children should not only focus on objective socioeconomic vulnerabilities, but also experiences of socioeconomic disadvantage that may be internalized and shape one's relationship with food in obesogenic ways.

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

STAFF
Julia Bittner, Ph.D.,
Postdoctoral Fellow

Meegan Smith, B.A.,
Postbaccalaureate Fellow

KEY PUBLICATIONS

Cheon, B. K., & Lee, L. L. (2022). Subjective socioeconomic disadvantage is indirectly associated with food portion selection through perceived disruption of personal resources during a nationwide COVID-19 stay-at-home order. *Appetite*; 178, 106158. PMID: 35780937. PMCID: PMC9245368.

Pink, A. E., Lim, P. X. H., Sim, A. Y., & Cheon, B. K. (2022). The effects of acute social media exposure on body dissatisfaction and eating behavior of male and female students. *Journal of Social and Clinical Psychology*; 41(4), 365-397. https://doi.org/10.1521/jscp.2022.41.4.365

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 2022, 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 seven international sites. Each product in development fills an unmet need or provides greater safety to vulnerable populations at risk of unintended pregnancy.

Diana Blithe, Ph.D.
Senior Scientist and Chief

STAFF

Jeffrey Kroopnick, M.D.,
Medical Officer

Min S. Lee, Ph.D.,
Chemist

Tamar Jacobsohn, B.S.,
Postbaccalaureate Fellow

Ahnyah Phillips, B.S.,
Postbaccalaureate Fellow

Danielle Gross, B.A.,
Postbaccalaureate Fellow

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 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. 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 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 demonstrate that the product can inhibit testicular production

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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 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.

KEY PUBLICATIONS

Page ST, Blithe D, Wang C. Hormonal Male Contraception: Getting to Market. Front Endocrinol 13:891589, 2022; PMID: 35721718. PMCID: PMC9203677.

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