



Eunice Kennedy Shriver National Institute
of Child Health and Human Development



1967-2017 • 50th ANNIVERSARY

2019 ANNUAL REPORT

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

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MESSAGE FROM THE DIRECTOR

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

I am privileged to be serving as the interim Division Director following the departure of Dr. Germaine Buck Louis in September 2017.

We accomplish our mission by conducting innovative etiologic and interventional research from preconception through adulthood, while working to translate our discoveries into clinical practice or public policy to maximize the health of all populations. While this is an ambitious undertaking, we readily embrace it by working in trans-disciplinary research teams across Branches and with external collaborators to find answers about how to become and stay healthy. In addition, Division scientists actively mentor a variety of fellows at varying professional stages (i.e., post-baccalaureate through post-doctoral) and generously provide their expertise as needed throughout the NICHD, National Institutes of Health and other governmental agencies, and to our professional societies.

The Division provides a unique opportunity for conducting a wide range of research initiatives focusing on health across the lifespan. Our 2019 Annual Report describes some of our recent discoveries including new evidence about how behaviors, lifestyles and environmental exposures affect men and women's reproductive health and pregnant women's ability to deliver a healthy newborn. Our research also focuses on keeping infants and children healthy, including for children with chronic diseases such as type 1 diabetes. We are also making advances regarding the onset and timing of risky adolescent behaviors that may or may not continue into early adulthood, and in the early origin of health disparities. Another exciting avenue of research is focusing on exposures during critical and sensitive

windows of human development and their implications for future generations. It is exciting and rewarding to conduct research that not only will keep people healthy across the lifespan, but the health of generations to come.

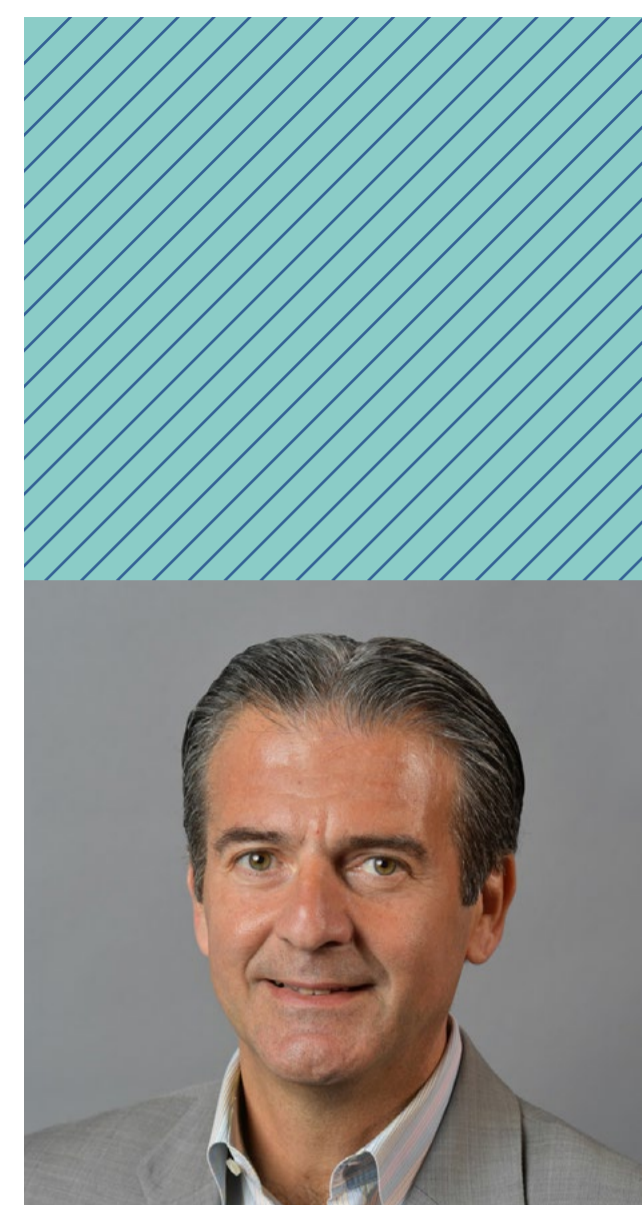
The development of new methods and statistical tools is another unique aspect of our research. We openly share our products. The Division practices reproducible research and was an early pioneer in building data sharing platforms. We encourage scientists and students to utilize and leverage our resources for advancing knowledge by reviewing materials at the Division's online data sharing platform and also the NICHD's platform.

Lastly, our work is not possible without the continued support of our Institute Director, Diana W. Bianchi. I am also looking forward to working with Dr. Bianchi on a national search to identify the next Division Director. Please visit our [website](#) for information about our research, training opportunities, collaborations, and career opportunities.

I welcome any questions or comments you may have about the Division.

Sincerely yours,

Constantine A. Stratakis, M.D., D(med)Sci.
Acting Director, DIPHR, NICHD



Constantine A. Stratakis,
M.D., D(Med)Sci.
Acting Director, DIPHR, NICHD

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



In 2017, the Division Director, Dr. Germaine Buck Louis, retired from federal service. The NICHD Director, Dr. Bianchi appointed **Dr. Constantine Stratakis** - the Scientific Director of NICHD - as Acting Director of DIPHR, in anticipation of conducting a national search for a permanent DIPHR Director.



Dr. Jagteshwar (Una) Grewal is the Deputy Director for the Division. In this capacity, she has considerable responsibility for managerial leadership and scientific administration in the Division. In particular, she oversees R & D contracting, NIH training requirements, personnel matters, mentoring, and facilities and operations. As a perinatal epidemiologist, Dr. Grewal has been at the forefront of multiple novel, large-scale research initiatives as a Co-Investigator for the [NICHD Fetal Growth Studies](#) (and Principal Investigator for the Dietary Patterns during Pregnancy component) and a Co-Principal Investigator for the [Consortium on Safe Labor](#) (CSL). The discoveries from the NICHD Fetal Growth Studies have national impact by answering lingering controversies as to whether all fetuses should be expected to grow similarly on average. Among the central findings was that fetal growth trajectories differ across four major racial/ethnic groups (Caucasian, African American, Hispanic, Asian). This finding underscores the need for race/ethnic-specific standards when monitoring fetal growth, especially to prevent misclassification of nonwhite fetuses as having aberrant growth based on inappropriate benchmarks.

Meanwhile, central findings from the CSL study indicate that contemporary labor patterns are longer than those 50 years ago and that current practices of labor process management, as well as routine interventions such as the use of oxytocin, warrant reconsideration. At present, Dr. Grewal serves as collaborator for two significant ongoing research initiatives: (1) The [NICHD Fetal Growth 3D Study](#) which relies on ultrasound images collected as a part of the NICHD Fetal Growth Studies to establish standards for fetal body composition and organ volumes, and (2) The [Genetic Epidemiology of Early Growth and Cardiometabolic Diseases](#) which uses the genome-wide data generated from biospecimens collected by the NICHD Fetal Growth Studies to investigate genetic mechanisms in longitudinal fetal growth variations and the contribution of genetic ancestry for fetal growth differences among populations.



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

STAFF

Constantine A. Stratakis, M.D., D(Med)Sci.
Acting Division Director

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

Adrienne Lonaberger,
Program Analyst

Jennifer Weck, Ph.D.,
Laboratory Health Specialist

FELLOWS

Samrawit Yisahak, Ph.D.,
Postdoctoral IRTA Fellow



OFFICE OF THE DIRECTOR

Finally, the Division would not be successful without the continued commitment and support of its program analyst - Adrienne Lonaberger - who oversees the many tasks essential for the Division's continued success. These efforts include assistance with strategic and fiscal planning, forecasting activities and the preparation and distribution of administrative and public reports.

The mission of the Biostatistics and Bioinformatics Branch (BBB) is to: 1) conduct both collaborative and methodological research that is important to the mission of the Division and Institute; 2) provide training in areas of statistical research that will advance the Division's and Institute's research programs; and 3) serve as a resource for the Division, Institute, NIH, and other professional and government organizations.

The research component of the BBB's mission is multifaceted. First, providing first-rate statistical collaboration requires understanding of the scientific issues and state-of-the-art statistical methodology relevant to the scientific problem. Therefore, investigators within the Branch play a key role in all aspects of the study. Second, the Branch develops new statistical methodology for designing and analyzing data. Analytical issues encountered in collaborative research directly motivate much of the Branch's independent research. An important component of our collective methodological research is the translation of our novel methodology back to the NICHD scientific constituents through the development of software using free-ware (e.g., R package) and in presenting our work at major scientific meetings.

A majority of the Division's studies are longitudinal and involve sampling frameworks such as schools, families (parent-child triads), couples, maternal/fetal pairs, and individuals. Particular methodological problems that have been addressed include: 1) the joint modeling of longitudinal data and time to event or understanding the association of longitudinal profiles and an outcome of interest; 2) multi-dimensional couple-based latent risk model with an application to infertility; and 3) the development of new approaches for designing and analyzing complex data.

An important analytical issue for many Division studies is the characterization of the time to an event. In many studies, correlated event times are measured (e.g., repeated time-to-pregnancy and gestation at birth in consecutive pregnancies) and interest is in identifying environmental, genetic, or behavioral factors that influence these durations. A major research focus during 2019 has been on developing new statistical methods for modeling of complex data, including couple-based modeling and fecundity, longitudinal measurements and binary events, and on methods for biomarkers of various types.

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



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Acting Chief*

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*Ruijin Lu, Ph.D.,
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*Abhisek Saha, Ph.D.,
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*Wei Zhang, Ph.D.,
Postdoctoral Fellow*

*Ndeah Terry, B.S.,
Post-Baccalaureate Fellow*

Aiyi Liu, Ph.D.

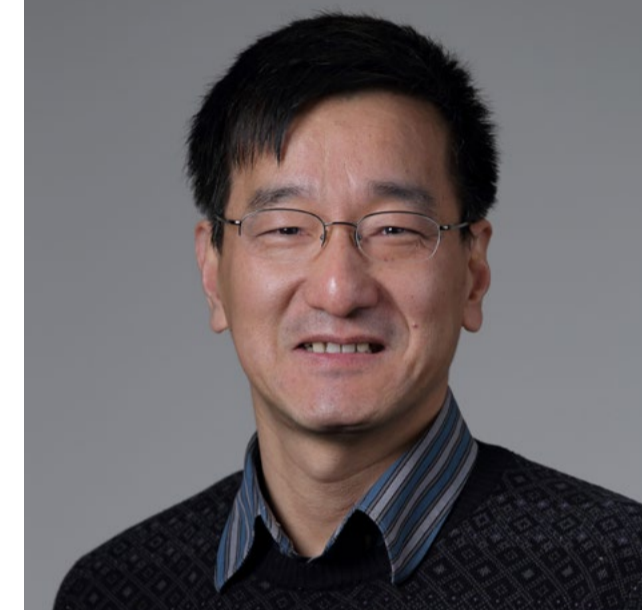
Dr. Liu's research in 2019 focused on developing innovative methods for disease screening and assessment of diagnostic biomarkers, and identification of dietary patterns for precision intervention. An example of each is listed below.

Screening for disease and estimation of prevalence

Group testing has been widely used as a cost-effective strategy to screen for and estimate the prevalence of a rare disease. While it is well-recognized that retesting is necessary for identifying infected subjects, it is not required for estimating the prevalence. For a test without misclassification, gains in statistical efficiency are expected from incorporating retesting results in the estimation of the prevalence. When the test is subject to misclassification, retesting subjects in either positive or negative groups can substantially improve the efficiency of the estimation and that retesting positive groups yields higher efficiency than retesting a same number or proportion of negative groups.

Dietary pattern analysis and intervention.

Dietary intake data of episodically consumed foods are often semicontinuous, characterized by a sizable number of zeros and observations from a continuous distribution. In analyzing such semicontinuous data, it is imperative that the excessive zeros be adequately accounted for to obtain unbiased and efficient inference. Although many methods have been proposed in the literature for the modeling and analysis of semicontinuous data, little attention has been given to clustering of semicontinuous data to identify important patterns that could be indicative of certain health outcomes or intervention effects. A Bernoulli-normal mixture model for clustering of multivariate semicontinuous data demonstrates its accuracy as compared to the well-known clustering method with the conventional normal mixture model. Compared with the conventional normal mixture model approach, the Bernoulli-normal mixture model successfully identified a dietary profile that significantly differentiates the intervention effects from others, providing a useful tool for personalized dietary intervention.



Aiyi Liu, Ph.D.
Senior Investigator and
Acting Branch Chief

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Wei Zhang, Ph.D.,
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HIGHLIGHTED REFERENCES

1. Zhang W, Liu A, Li Q, Albert PS. Incorporating retesting outcomes for estimation of disease prevalence. *Statistics in Medicine* 2020; 39:687-697. [DOI: 10.1002/sim.8439 PMID: 31758594]
2. Jiang T, Lu Y, Duan H, Zhang W, Liu A. A model-based approach for clustering of multivariate semicontinuous data with application to dietary pattern analysis and intervention. *Statistics in Medicine* 2020; 39:16-25. [DOI: 10.1002/sim.8391; PMID: 31702055]

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

Statistical methods for multivariate survival data

Many Division studies are interested in the characterization of time to an event, recurrent events and multistage models. In many studies, correlated event-times are measured (e.g., repeated time-to-pregnancy, gestation at birth in consecutive pregnancies, progression of labor in pregnant women, recurrent crashes or near crashes by teenage drivers). Furthermore, interest is also in focusing on identifying time-varying exposures, environmental or behavioral factors that influence these durations.

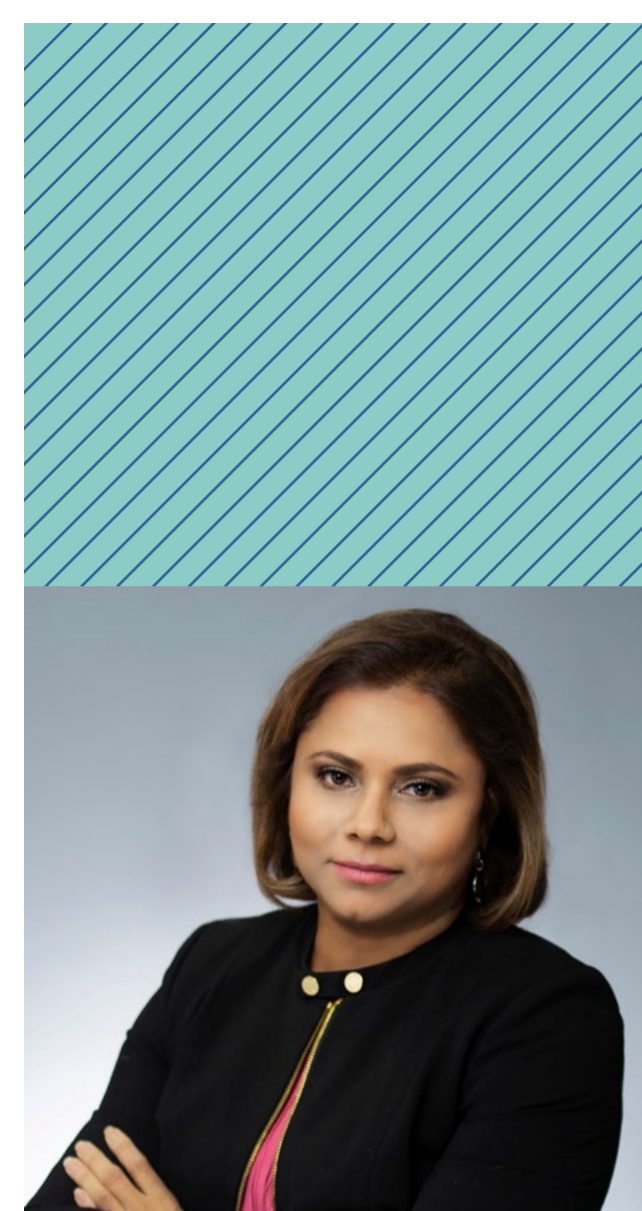
There are many new analytic challenges for appropriate analysis of such data. For example, progression of labor can be classified as a multistage data as women progress through various stages of labor and have only intermittent examinations

“Novel analytical approaches can differentiate woman-level or physiologic variation possibly associated with pregnancy from changes in chemical concentrations over pregnancy supporting the exposome’s feasibility and utility for etiologic research during sensitive windows of human development.”

and unobserved start time providing significant analytical challenges; 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. Naturalistic driving studies also provide such data on recurrent events where a driver is at-risk for crash/near crash only if they are driving.

My focus is in developing statistical methods to address these types of data in presence on non-standard missingness, as well as accounting for the underlying (biological/behavioral) structure of the event of interest. These methods have been developed with a view towards individualized risk predictions. I am also interested in studying joint modeling of the longitudinal processes with time-to-event with a view towards risk prediction. Lastly, another objective of the methods development also includes borrowing information across various studies to build better prediction models.

Another significant aspect of my research is in developing statistical methods to assess the associations of environmental pollutants and other biomarkers on reproductive outcomes. The focus in this part of research is in the context of assessing highly skewed exposures, issues of limits of detection as well as issues of highly correlated exposures to better assess mixtures of chemicals and in the context of assessing exposome.



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Postbaccalaureate Fellow

Abhisek Saha, Ph.D.
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KEY PUBLICATIONS

Mills JL, Ali M, Buck Louis GM, Kannan K, Weck J, Maisog J, Giannokou A, Wu Q, Sundaram R. Pregnancy loss and Iodine status: The LIFE Study Prospective Cohort Study. *Nutrients*, 11:534, 2019. PMID: 30823683

Louis GMB, Yeung EH, Kannan K, Maisog J, Zhang C, Grantz KL, Sundaram R. Patterns and Variability of Endocrine Disrupting Chemicals during Pregnancy: Implications for Understanding the Exposome of Normal Pregnancy. *Epidemiology*, 30, Suppl 2:S65-S75, 2019. PMID: 31569155

Zhen Chen, Ph.D.

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

Modeling placement values in the analysis of receiver operating characteristic curves

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

Bayesian regularized mediation analysis with multiple exposures

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



Zhen Chen, Ph.D.
Investigator

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Postdoctoral Fellow

Dr. Ruijin Lu, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS
Wang YB, Chen Z, Goldstein JM, Buck Louis GM, Gilman SE. A Bayesian regularized mediation analysis with multiple exposures. *Stat Med.* 2019; 38(5):828-843. [PMID: 30375022](https://pubmed.ncbi.nlm.nih.gov/30375022/)

▼ EPIDEMIOLOGY BRANCH

In 2019, the Epidemiology Branch of the Division of Intramural Population Health Research continued to pursue its threefold mission: 1) to plan and conduct investigator-initiated original epidemiologic research focusing on reproductive, pregnancy, and infant and child health endpoints to identify etiologic mechanisms, at-risk subgroups, and interventions aimed at maximizing health and preventing, diagnosing, and/or treating disease; 2) to provide service to the Division, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Department of Health and Human Services, and the profession via consultation, collaboration, and assistance to advance the scientific discipline of epidemiology and the goals of the Institute; and 3) to recruit highly qualified students at various stages of their professional careers for training in reproductive, perinatal, pediatric, and methodological epidemiologic research.

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

diabetes, alterations in fetal growth of both singletons and twins in relation to obesity and pregnancy complications, and the impact of air pollution on pregnant women and their offspring. To advance understanding of infant and child health, Branch investigators also focus on the genetic and lifestyle determinants of birth defects through strategic collaborations, and the impacts of conception using assisted reproductive technologies on subsequent child growth, development, and cardiovascular health. Collectively, the Branch is improving public health through providing evidence to help inform clinical guidance and public policy regarding care of individuals and couples intending to reproduce, pregnant women and their fetuses, and infants and children.

High quality scientific investigation in these various domains across the life course has yielded many awards recognizing the hard work of Epidemiology Branch team members. During 2019 alone, eleven Branch fellows received awards and honors from within NIH as well as international societies in their respective fields, highlighting the top notch training program and mentoring conducted in the Branch. In addition,



Enrique F. Schisterman,
Ph.D., M.A.,
Senior Investigator and Chief

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

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

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

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

Pauline Mendola, Ph.D., M.S.,
Senior Investigator

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

EPIDEMIOLOGY BRANCH (CONT.)

Branch investigators received several awards including the prestigious NIH Ruth L. Kirschstein Mentoring Award, numerous NICHD awards, and finalist for the Birth Defects Research and Prevention Society Research Innovator Award, among others. The excellence found within the Branch paired with the freedom and opportunity that comes with having large and unique data sets available makes the Branch uniquely positioned to pursue trans-disciplinary, high-risk research in novel and emerging areas of reproductive, perinatal, pediatric, and methodologic epidemiology.

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

Carrie J. Nobles, Ph.D., M.P.H.,
Research Fellow

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Diane L. Putnick, Ph.D., M.S.,
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Lindsey A. Sjaarda, Ph.D., M.S.,
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Earl Stadtman Investigator

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

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

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Aparna Ajjarapu, B.A.,
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(departed in 2019)

Zeina Alkhalaf, M.P.H.,
Postbaccalaureate Fellow
(departed in 2019)

Melissa Amyx, Ph.D., M.P.H.,
Postdoctoral Fellow
(departed in 2019)

Victoria Andriessen, B.S.,
Postbaccalaureate Fellow
(departed in 2019)

Suvo Chatterjee, Ph.D.,
Postdoctoral Fellow

Kerry Flannagan, Ph.D.,
Postdoctoral Fellow

Ellen Francis, M.S.,
Predoctoral Fellow
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Joshua Freeman, M.S.,
Predoctoral Fellow

Jessica Gleason, Ph.D.,
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Anisa Holloman, B.S.,
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Jenna Kanner, B.A.,
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Mengying Li, Ph.D., M.S.P.H.,
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Bryttany McClendon-Weary, B.S.,
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Marion Ouidir, Ph.D.,
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Georgia Pitsava, M.D.,
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Alexandra Purdue-Smith, Ph.D.,
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Jeannie Radoc, B.S.,
MRSP Fellow (departed in 2019)

Elijah Reische, B.S.,
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Sonia Robinson, Ph.D.,
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Deepika Shrestha, Ph.D., M.Sc.,
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Danielle Stevens, Ph.D.,
Postdoctoral Fellow

Mai-Han Trinh, B.S.,
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Yassamann Vafai, Ph.D., M.P.H.,
Postdoctoral Fellow

Andrew Williams, Ph.D., M.P.H.,
Postdoctoral Fellow
(departed in 2019)

Tsegasselassie Workalemahu, M.S.,
Postdoctoral Fellow
(departed in 2019)

Jessica Zolton, D.O.,
Clinical Fellow

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

The field of reproductive epidemiology focuses on factors that affect human reproduction, including conception delay, pregnancy loss, anovulation, and semen quality in relation to environmental, lifestyle, and genetic factors, among others.

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



The [EAGeR Trial](#): Analysis to identify relevant subgroups for whom

preconception-initiated low-dose aspirin therapy may be most beneficial demonstrated the highest efficacy in increasing pregnancy and birth rates in women with no or few components of the metabolic syndrome (PMCID: [PMC6548668](#)). These findings extended the ongoing story of discovery from EAGeR that low-dose aspirin restores a decrement in pregnancy rates attributable to low-grade inflammation (PMID: [30562044](#)). The team also identified that women reporting higher daily perceived stress experienced 30% poorer fecundability (less likelihood of becoming pregnant) compared to women with low stress (PMID: [31569156](#)).



[FASZT](#) enrolled 2,370 couples, representing the largest ever clinical trial focused on male fertility (PMID: [31712803](#)).

The team identified that folic acid and zinc supplementation in men did not improve semen quality parameters (e.g. sperm count, motility) and it modestly increased sperm DNA damage. Most importantly, the supplement did not improve couples' live birth rates. These results indicated for the first time that

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

despite the rapidly growing supplement industry marketing such supplements for improving male fertility based on

limited evidence, caution is warranted with use of specialized supplements for male fertility containing folic acid and zinc (PMCID: [PMC6990807](#)).

Methodologic work by Dr. Schisterman's team in 2019 featured several key developments. The team demonstrated a method for combining laboratory quality control data for [biomarker assays](#) to reduce measurement error (PMID: [31569147](#)), a practice valuable to studies of reproductive hormones, among others. Dr. Schisterman collaborated on valuable [analysis tools](#) for generalizing per-protocol treatment effect in clinical trials (PMCID: [PMC6693502](#)), which tie directly to his etiologic research. He continued his work on cost-effective and efficient study designs with pooling for skewed biomarkers with error (PMID: [31373355](#)) and generalized outcome dependent sampling in longitudinal case-control settings (PMID: [31165875](#)), innovations which improve study designs and solve common analytic challenges.



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Lindsey Sjaarda, Ph.D., M.S.,
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Postdoctoral Fellow shared with Dr. Mendola

Jessica Zolton, D.O.,
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Jeannie Radoc, B.S.,
MRSP Fellow (departed 2019)

Victoria Andriessen, B.S.,
Postbaccalaureate Fellow (departed 2019)

KEY PUBLICATIONS

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

Perkins NJ, Weck J, Mumford SL, Sjaarda LA, Mitchell EM, Pollack AZ, Schisterman EF. Combining biomarker calibration data to reduce measurement error. *Epidemiol* 2019;30 Suppl 2:S3-S9. [PMID: 31569147]

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

We are investigating the effect of iodine deficiency on multiple pregnancy outcomes. Iodine deficiency is common in pregnancy both in Europe and in the US where almost half of pregnant women are deficient. The LIFE study provided an excellent opportunity to examine the relationship between iodine status and pregnancy loss because women were monitored prospectively to ensure excellent ascertainment

“Half the pregnant women in the USA and many parts of Europe are iodine deficient by WHO standards, but little research has been done in the developed world on iodine deficiency and pregnancy outcomes.”

of conceptions. The LIFE study, a population-based prospective cohort study, monitored 501 women who had discontinued contraception within two months to become pregnant; 329 became pregnant, had urinary iodine concentrations measured on samples collected at enrollment, and were followed up to determine pregnancy outcomes. Of the 329, 196 had live births (59.5%), 92 (28.0%) had losses, and 41 (12.5%) withdrew or were lost to follow up. Urinary iodine concentrations were in the deficiency range in 59.6% of the participants. The risk of loss, however, was not elevated in the mildly deficient group (hazard ratio 0.69, 95% confidence interval 0.34, 1.38), the moderately deficient group (hazard ratio 0.81, 95% confidence interval 0.43, 1.51), or the severely deficient group (hazard ratio 0.69, 95% confidence interval 0.32, 1.50). This study provides some reassurance that iodine deficiency at levels seen in many developed countries does not increase the risk of pregnancy loss (PMCID: [PMC6471412](#)).

We conducted a population-based, nested case-control study within the Finnish medical system to determine whether iodine deficiency was associated with an increased risk for gestational diabetes mellitus (GDM). We randomly selected

224 GDM cases with singleton pregnancies and 224 controls without GDM from all singleton births. Very high thyroglobulin concentration, high concentrations of TSH, and low iodine levels were not associated with an increased odds ratio of GDM (PMID: [30580457](#)). Using the same nested case control design, we looked at the risk for preterm birth and being small for gestational age (SGA). Each log-unit increase in serum iodide was associated with higher odds of preterm birth (adjusted OR = 1.19, 95% CI = 1.02-1.40), but was not associated with SGA (adjusted OR = 1.01, 95% CI = 0.86-1.18). Tg was not associated with preterm birth (OR per 1 log-unit increase = 0.87, 95% CI = 0.73-1.05), but was inversely associated with SGA (OR per log-unit increase = 0.78, 95% CI = 0.65-0.94). Neither high nor low TSH (versus normal) were associated with either outcome (PMCID: [PMC6893669](#)). These findings suggest that among Finnish women, iodine status is not related to SGA. Higher serum iodide might be positively associated with preterm birth although a biological explanation is not apparent.

Genetic risk factors for birth defects and pediatric endocrine disease is our second major research area. In our ongoing investigation of potentially causal genetic variants in Cushing disease, we found that that germline CDKN1B loss-of-function variants are found in isolated pediatric Cushing disease (PMCID: [PMC7190031](#)). This has important implications for clinical screening and genetic counselling. We are active collaborators in large birth defects genomic studies. Our group identified BARX1 and EML4-MTA3 as new loci associated with infantile hypertrophic pyloric stenosis (PMCID: [PMC6322072](#)). Of note, BARX1 is an essential gene for stomach formation in embryogenesis. In another collaboration, we identified novel loci for isolated cleft palate at or near genome-wide significance on chromosomes 2 (near CTNNA2) and 19 (near SULT2A1) (PMCID: [PMC6400042](#)). SULT2A1 is active in mesenchymal cells in palate, palatal rugae and palatal epithelium in the fused palate.



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KEY PUBLICATIONS

Germline CDKN1B loss-of-function variants cause pediatric Cushing's disease with or without an MEN4 phenotype. Chasseloup F, Pankratz N, Lane J, Faucz FR, Keil MF, Chittiboia P, Kay DM, Hussein Tayeb T, Stratakis CA, Mills JL, Hernández-Ramírez LC. *J Clin Endocrinol Metab.* 2020 Jun; 150(6), dgaa160. PMID: 32232325
PMCID: [PMC7190031](#)

The Joint Role of Thyroid Function and Iodine Status on Risk of Preterm Birth and Small for Gestational Age: A Population-Based Nested Case-Control Study of Finnish Women. Purdue-Smithe AC, Männistö T, Bell GA, Mumford SL, Liu A, Kannan K, Kim UJ, Suvanto E, Surcel HM, Gissler M, Mills JL. *Nutrients.* 2019 Oct 25; 11(11), 2573. PMID: 31731400
PMCID: [PMC6893669](#)

Pauline Mendola, Ph.D.

Dr. Mendola leads the [Air Quality and Reproductive Health](#) study which added air pollution and ambient temperature data to the Consortium on Safe Labor, the LIFE Study, and the NICHD Consecutive Pregnancy Study. In 2019, key discoveries

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

included a replication of our earlier findings that different components of air pollution are associated with gestational hypertension and preeclampsia, both important hypertensive complications of pregnancy (PMCID: [PMC6620155](#)). This suggests that the etiology of gestational

hypertension may be differentiated from preeclampsia, a more severe complication which is often thought to be an exacerbation of gestational hypertension. We also described the risk of preterm birth in consecutive pregnancies associated with changes in air pollution over time in a low-risk population (PMCID: [PMC6765877](#)) and the increased risk of newborn NICU admission associated with acute maternal exposure to air pollution (PMCID: [PMC6755057](#)).

Residential zip code data for the [NICHD Fetal Growth Studies](#) Singleton and Twin cohorts were collected in order to better estimate ambient environmental exposures. Air pollution and temperature will be assessed in relation to acute changes in placental vascular resistance and maternal blood pressure as well as chronic exposure in relation to fetal growth and organ volumes.



The [B-WELL-Mom Study](#) (Mendola, PI), which aims to increase understanding of factors

that predict poor asthma control during pregnancy as well as add to our knowledge of the basic immunology of pregnancy, completed all follow-up visits in August 2019. In collaboration with Northwestern University and the University of Alabama at Birmingham, we recruited 311 women with asthma (164 with poor asthma control and 147 well-controlled asthmatics) and 107 women without asthma. We will examine in-depth immune function and lung inflammation to assess the impact of immune regulatory processes throughout pregnancy and the postpartum period that may be associated with changes in asthma control. Among asthmatics, we will identify whether changes in severity/control are differentially affected by external factors including air pollution and dietary antioxidants. Data analyses are ongoing based on three study visits during pregnancy and one post-partum visit and diary measures of lung function and symptoms. Study visits include flow cytometry for T-regulatory cells and other CD4 cell populations, spirometry and lung inflammation measures.

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



STAFF

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Marion Ouidir, Ph.D.,
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Danielle Stevens, Ph.D.,
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Andrew Williams, Ph.D.,
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Program Fellow*

KEY PUBLICATIONS

Nobles CJ, Williams A, Ouidir M, Sherman S, Mendola P. Differential effect of ambient air pollution exposure on risk of gestational hypertension and preeclampsia. *Hypertension*. 2019; 74(2):384-390. PMID 31230552 PMCID: PMC6620155

Mendola P, Nobles C, Williams A, Sherman S, Kanner J, Seeni I, Grantz K. Air pollution and preterm birth: Do air pollution changes over time influence risk in consecutive pregnancies among low-risk women? *International Journal of Environmental Research and Public Health* 2019; 16:3365. <http://dx.doi.org/10.3390/ijerph16183365>. PMID: 31547235 PMCID: PMC6765877

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

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

The [Diabetes & Women's Health Study](#) was a retrospective cohort study of more than 4,000 women from the U.S. and Denmark who had diabetes in pregnancy. The overarching

"Pre-pregnancy folic acid supplementation may offer a feasible, novel, and low-cost avenue to reduce the risk of gestational diabetes, further supporting the role of pre-pregnancy diet and lifestyle in the prevention of gestational diabetes"

goal was to set up a research framework for investigating long-term health consequences of gestational diabetes and their determinants. In 2019, the study team published the baseline paper summarizing key study findings to date which, for instance, demonstrate that women who had gestational diabetes experience a greater risk of type 2 diabetes, cardiovascular diseases, and kidney disorders later in life and that healthful diet and lifestyle factors and weight control may lower the risk (PMCID: [PMC6502016](#)). Furthermore, the team identified

additional long-term comorbidities of gestational diabetes including fatty liver disease (PMCID: [PMC6791726](#)), as well as identify lifestyle factors that may alleviate the burden. Although high-risk individuals are recommended to consume artificially sweetened beverages as a means of reducing sugar intake and risk for cardiometabolic diseases, artificially sweetened beverages did not improve, or worsen, cardiometabolic health in these high-risk women (PMCID: [PMC6599744](#)). Dr. Zhang also led her team in their continued efforts to identify potentially modifiable avenues for the prevention of gestational diabetes, such as supplemental folate before pregnancy (PMCID: [PMC6609948](#)).

Using data from the [NICHD Fetal Growth Studies](#) and a comprehensive panel of biomarkers based on system biology approach, Dr. Zhang's team identified targeted and non-targeted metabolomics implicated in [glucose homeostasis](#) and fetal growth. Notably, it was discovered that circulating levels of omega-6 fatty acids that are produced in the body in early to mid-pregnancy may be implicated in the development of gestational diabetes (PMCID: [PMC6743768](#)). Also, a shorter telomere length, an indicator of cellular aging, was associated with a woman's greater risk for gestational diabetes (PMID: [31569148](#)). Furthermore, her research provides insight into how maternal body fat may influence different aspects of fetal growth (PMCID: [PMC6529296](#)).

Lastly, analyses in 2019 (PMCID: [PMC7042706](#)) demonstrated the success of the linkage for the [Collaborative Perinatal Project Mortality Linkage Study](#), which aims to investigate long-term associations of overall and cause-specific mortality with a spectrum of pregnancy-related complications.



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KEY PUBLICATIONS

Zhang C, Olsen SF, Hinkle SN, Gore-Langton RE, Vaag A, Grunnet LG, Yeung EH, Bao W, Bowers K, Liu AY, Mills JL, Sherman S, Gaskins AJ, Ley SH, Madsen CM, Chavarro JE, Hu FB, Diabetes & Women's Health Study Team. Diabetes & Women's Health (DWH) Study: an observational study of long-term health consequences of gestational diabetes, their determinants and underlying mechanisms in the USA and Denmark. *BMJ Open*. 9(4), 2019. PMCID: PMC6502016

Li M, Li SS, Chavarro JE, Gaskins AJ, Ley SH, Hinkle SN, Wang XB, Ding M, Bell G, Bjerregaard AA, Olsen SF, Mills JL, Hu FB, Zhang C. Prepregnancy Habitual Intakes of Total, Supplemental, and Food Folate and Risk of Gestational Diabetes Mellitus: A Prospective Cohort Study. *Diabetes Care*. 42(6):1034-41, 2019. PMCID: PMC6609948

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

In her focus to understand the developmental origins of health and disease (DOHaD) (PMCID: [PMC7047653](#)), 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 2019, Dr. Yeung's team investigated whether infertility risk factors were related to children's health. In one manuscript using information collected at 7 years of age, children of women diagnosed with polycystic ovarian syndrome (PCOS) were found to have higher risk of anxiety, while hirsutism in mothers (i.e., high androgen levels) was associated with children's risk of attention deficit/hyperactivity disorder (ADHD) and other behavioral disorders (PMCID: [PMC7185046](#)). Key investigations in 2019 also

"Findings suggest that screen time habits develop as early as infancy."

include how adipokines and environmental chemicals, measured using newborn dried blood spots, and air pollution affect neonatal and early child health (PMCID: [PMC7047652](#), [PMC6541527](#)). In response to Congressional and national concerns about the effects of screen time in childhood, Dr. Yeung's team also investigated the trajectory of screen time and its determinants in early childhood using data from Upstate KIDS (PMCID: [PMC6902189](#)). They found that 87% of children below 3 years of age had higher screen time than recommended by the American Academy of Pediatrics. Moreover, children's screen time increased from 1 to 2 years of age while decreasing in school

age. Children who had higher screen time in early childhood (≤ 3 years), were more likely to have higher screen time at 7 years of age. Findings suggest that screen time habits develop as early as infancy. Future investigations include their impact on development and other health factors long-term.



In collaboration with the University at Albany, clinical visits at multiple sites across New York State for the Upstate KIDS CVD Follow-Up Study were completed in 2019. The clinical visits are aimed to capture childhood cardio-metabolic outcomes (i.e., obesity, high blood pressure, metabolism) and biospecimens in the children and the mothers. Details of the visit measures can be found online (www.upstatekidsstudy.org). A secondary objective of the Upstate KIDS CVD Follow-Up Study is to assess epigenetic differences as measured by DNA methylation using collected biospecimens. To this end, genetic consents were collected anew beginning in 2016 for using the dried blood spots previously stored, and in 2019 laboratory measures of DNA methylation were completed among over 1000 newborns whose parent provided genetic consent.



Dr. Yeung also initiated the [SPAN](#) cohort to investigate the paternal contribution to the developmental origins of health and disease. While much research has been devoted to maternal exposures, the information on paternal factors are greatly lacking despite evidence of potential epigenetic pathways.



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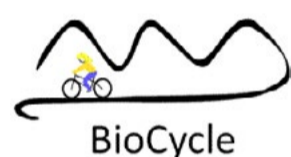
KEY PUBLICATIONS

Robinson SL, Ghassabian A, Sundaram R, Trinh MH, Lin TC, Bell EM, Mendola P, Yeung EH. The associations of maternal polycystic ovary syndrome and hirsutism with behavioral problems in offspring. *Fertility & Sterility* 2020 Feb;113(2): 435-443. PMID: 32106995 PMCID: PMC7185046

Trinh M, Sundaram R, Robinson S, Lin TC, Bell EM, Ghassabian A, Yeung E. Trajectory and covariates of children's screen media time. *JAMA Pediatrics* 2020;174(1):71-78. PMID: 31764966 PMCID: PMC6902189

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

Modifiable risk factors, such as nutrition, play a pivotal role in changing the landscape of fertility, pregnancy health, and developmental origins of disease. As such, Dr. Mumford's current and future research is focused on understanding the dietary and lifestyle factors that affect fertility and reproduction among women, men, and couples, irrespective of pregnancy intentions. To this end, her team's work has involved new initiatives in multiple Epidemiology Branch studies; Dr. Mumford was the PI of the diet-focused arms of the BioCycle study, EAGeR, and FAZST trials, and is the PI of the recently completed IDEAL study which uses a couple-based approach among couples seeking infertility treatment to evaluate dietary and lifestyle factors associated with infertility. Importantly, this work has resulted in novel discoveries linking dietary factors to multiple aspects of reproductive health.



BioCycle provides rich data to look at dietary and lifestyle factors in relation with reproductive hormones in healthy women.

Dr. Mumford's team found that B-vitamins (PMCID: [PMC7186155](#)), vitamin D (PMID: [32068843](#)), and sleep (PMCID: [PMC7054152](#)) were associated with hormone levels, highlighting their potential role in influencing ovulatory function in reproductive-aged women.



EAGeR has resulted in findings that have emphasized the importance of preconception and maternal nutrition and how it relates to time to pregnancy and reproductive health. Specifically, Dr. Mumford's team has demonstrated the role of maternal preconception fatty acid composition for healthy pregnancy outcomes (PMID: [31569151](#)), and newborn DNA methylation (PMCID: [PMC7049533](#)). In addition, Dr. Mumford's team found that homocysteine concentrations, rather than serum folate,

were associated with risk of pregnancy loss among folate-replete women (PMCID: [PMC6592753](#)). Dr. Mumford also led the team on identifying modifiable dietary factors, such as phytoestrogens (PMCID: [PMC7003981](#)), that potentially affect gynecologic health. Collectively, these findings underscore the importance of examining nutritional exposures preconceptionally, and Dr. Mumford's work has truly bridged the gap of our understanding of dietary intake and the complex role it has on fecundability.



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



IDEAL is Dr. Mumford's most recent large prospective cohort study, evaluating the impact of diet, exercise, and lifestyle on fertility and reproductive health. The IDEAL study is a detailed follow-up of the female partners of FAZST participants. Data regarding multiple aspects of diet, exercise, sleep, stress, and lifestyle were collected and the study completed follow-up and publications on this study are forthcoming.



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KEY PUBLICATIONS


Kim K, Browne RW, Nobles CJ, Radin RG, Holland TL, Omosigbo UR, Connell MT, Plowden TC, Wilcox BD, Silver RM, Perkins NJ, Schisterman EF, Nichols CM, Kuhr DL, Sjaarda LA, Mumford SL. Associations Between Preconception Plasma Fatty Acids and Pregnancy Outcomes. *Epidemiology*. 2019;30 Suppl 2:S37-S46. PMID 31569151.

Levine LD, Kim K, Purdue-Smith A, Sundaram R, Schisterman EF, Connell M, DeVilbiss EA, Alkhalaf Z, Radoc JG, Buck Louis GM, Mumford SL. Urinary Phytoestrogens and Relationship to Menstrual Cycle Length and Variability Among Healthy, Eumenorrheic Women. *J Endocr Soc*. 2019;4(2):bvz0003. PMID 32047868. PMCID: PMC7003981.


Katherine Laughon Grantz, M.D.


Empirical evidence is lacking on many key aspects of pregnancy management. Dr. Grantz's research focuses on developing evidence-based pregnancy management to maximize maternal, fetal and child health.

 Work from the [Consortium on Safe Labor Study](#) has provided evidence to inform clinical guidance regarding the management of pregnant women. Recent work includes exploring the optimal route of delivery for periviable birth, 23 0/7 - 25 6/7 weeks' gestation. Much of the literature had focused on neonatal risks. Dr. Grantz's team found that most women who attempted a vaginal delivery achieved one. Attempting vaginal delivery between 23 0/7 and 25 6/7 weeks' gestation compared to a planned cesarean delivery was associated with decreased risks of maternal infectious morbidity. Deciding the delivery route is challenging in women undergoing periviable delivery and these findings provide important information on short term maternal morbidity when considering the risks and benefits during these discussions. (PMCID: [PMC6930981](#))

 In the area of fetal growth, the primary [NICHD Fetal Growth Studies](#) singleton study demonstrated that racial/ethnic-specific differences in fetal growth can be detected as early as 10-16 weeks, suggesting that racial/ethnic specific fetal growth charts are needed to reduce misclassification of minority fetuses as too small or too big. (PMCID: [PMC4584427](#); PMID: [25258202](#)) Additional work determined that pregnancies developing severe preeclampsia experienced significant and persistent reductions in fetal growth diverging from normotensive pregnancies as early as 22 weeks. (PMCID: [PMC6888945](#)) The primary NICHD Fetal Growth - Twin study discovered that, compared with singleton fetuses, the mean abdominal

circumference and estimated fetal weight trajectories of dichorionic twin fetuses diverged significantly beginning at 32 weeks. (PMCID: [PMC4967402](#)) In follow-up work, Dr. Grantz's team demonstrated that the percent difference in estimated fetal weight (i.e. discordance) increased across gestation in dichorionic twins. However, inter-twin weight differences were stable among women with obesity or IVF conception for reasons that are unknown. Persistence of increasing percent difference in EFW within low-risk groups suggests that some of this progressive increase may be physiologic. (PMID: [31478227](#))

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

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

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



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

STAFF

Jessica Gleason, Ph.D.,
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Yassaman Vafai, Ph.D.,
Postdoctoral Fellow

KEY PUBLICATIONS

Mateus J, Newman R, Zhang C, Pugh SJ, Grewal J, Kim S, Grobman WA, Owen J, Sciscione AC, Wapner RJ, Skupski D, Chien E, Wing DA, Ranzini AC, Nageotte MP, Gerlanc N, Albert PS, Grantz KL. Fetal Growth Patterns in Pregnancy-Associated Hypertensive Disorders: NICHD Fetal Growth Studies. *American Journal of Obstetrics and Gynecology* 221(6): 635.e1-635.e16, 2019. PMID: 31226296 PMCID: PMC6888945

Amyx M, Albert PS, Bever A, Hinkle SN, Owen J, Grobman WA, Newman RB, Chien EK, Gore-Langton RE, Buck Louis GM, Grantz KL. Associations between percent estimated foetal weight discordance and clinical characteristics within dichorionic twins: the NICHD Fetal Growth Studies. *Paediatric and Perinatal Epidemiology* 33(5):332-342, 2019. PMID: 31478227

Fasil Tekola-Ayele, Ph.D.

Early life growth, an important determinant of health across the lifespan, varies across populations and correlates with cardiometabolic outcomes in late life. The mechanisms that underlie these variations are not well understood. The overarching goal of Dr. Tekola-Ayele's research is to determine genetic mechanisms of early growth variations and the link between early growth and cardiometabolic diseases/disparities in diverse ancestral populations. To achieve this goal, his group currently focuses on two overarching complementary research domains at the maternal-placental-fetal interface - genetics of fetal growth and placental epigenome.

The goal of the first research domain is to determine genetic influences on longitudinal fetal growth trajectories, the contribution of genetic ancestry to fetal growth differences, and the shared genetic architectures of fetal growth and cardiometabolic outcomes. Genome-wide single nucleotide polymorphism data have been generated from the NICHD Fetal Growth Studies, complemented by datasets obtained from consortia-based genetic databases and the NIH Database of Genotypes and Phenotypes. This project yielded the following key insights: 1) identified novel maternal genetic loci that influence fetal weight at specific in-utero time periods (PMCID: [PMC5940684](#)), 2) demonstrated that maternal genetic ancestry, independent of reported race/ethnicity and other socio-demographic factors, influences fetal growth (PMCID: [PMC5967042](#), [PMC5940684](#)), and 3) lay foundation for genetic link between birthweight and cardiometabolic disease risk (PMCID: [PMC6411883](#), [PMC6753636](#), [PMC6592626](#), [PMC6885118](#)). Further, to leverage existing large-scale population biobanks for future genetic-epidemiology studies of early growth-cardiometabolic links, Dr. Tekola-Ayele has designed a multi-step pilot project nested within the Collaborative Perinatal Project (CPP), a national pregnancy

cohort that enrolled more than 48,000 women and their offspring between 1959 and 1966. The pilot study examined the potential to obtain DNA of high quality in banked serum samples from the CPP. As serum has been stored for over 50 years, a series of approaches was developed and tested to extract high-quality DNA with yields usable for future genomics research. By providing proof-of-principle, the pilot paves the way for linking genetic data with the detailed phenotypic records of the CPP to address high impact long-standing biological questions in early growth, childhood adiposity and subsequent cardiometabolic health.

The goal of the second research domain is to investigate the role of placental genetic/ epigenetic/ transcriptomic mechanisms and the aging "clock" of the placenta in fetal growth and related maternal cardiometabolic factors. The findings of this project demonstrated that there are sexually dimorphic relationships between epigenetic aging of the placenta and fetal growth (PMCID: [PMC6710059](#)).



In 2019, Dr. Tekola-Ayele has initiated a new genetic study within [SPAN](#): 1) to identify fetal genetic factors that regulate fetal growth and the aging clock of the placenta and through discovery in African Americans followed by trans-ethnic meta-analysis, and 2) to investigate genetic, epigenetic and transcriptomic mechanisms in placental regulation of fetal growth.



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KEY PUBLICATIONS

Tekola-Ayele F, Workalemahu T, Amare AT. High Burden of Birthweight-lowering Genetic Variants in Africans and Asians. *BMC Medicine*. 2018; 16(1):1-8. PMID: 29792231.

Workalemahu T, Grantz KL, Grewal J, Zhang C, Louis GMB, Tekola-Ayele F. Genetic and Environmental Influences on Fetal Growth Vary During Sensitive Periods in Pregnancy. *Scientific Reports*. 2018; 8(1): 1-8. PMID: 29740100.

The mission of the Social and Behavioral Sciences Branch is to conduct research to understand the social and behavioral determinants of health and health-related behaviors; to develop and test educational, behavioral, and environmental strategies for improving health and health-related behaviors; and to conduct research on the problem of disparities in health, the developmental mechanisms underlying health disparities over the life course, and modifiable intervention targets to reduce disparities.

SBSB also recruits, trains, and mentors highly qualified students and trainees for professional careers in the social and behavioral sciences.

Our research integrates approaches from diverse disciplines including psychology (community, clinical, and developmental), nutrition, health education, and epidemiology (social, psychiatric, and developmental). Collaborations with other Division researchers and throughout the NIH's Intramural Research Program further enhance the trans-disciplinary nature of our work. Our research addresses key contributors to the population burden of disease including obesity, cardiovascular disease, mental illness, and injury. Its developmental focus strives to identify and intervene early in life on pathways to disease for maximal impact on population health.

The Branch's research programs are organized along axes of substantive research domains and key developmental stages.

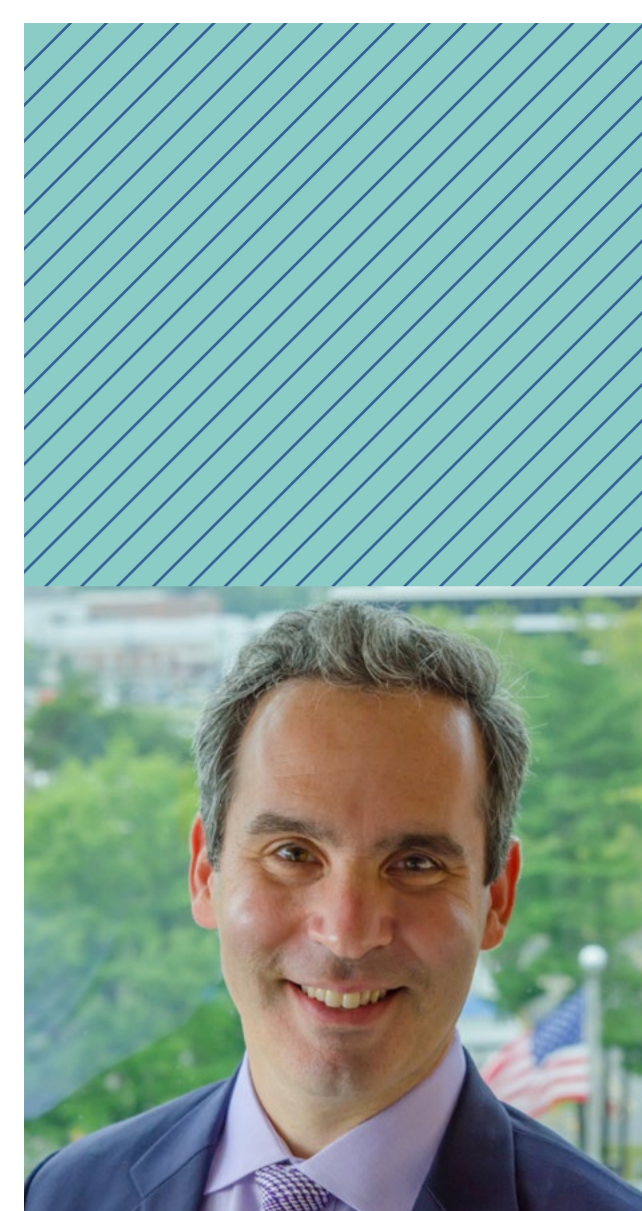
Our risk behavior and young driver research centers on adolescence. Adolescence is a critical period for the development of behavior patterns associated with subsequent morbidity and mortality, including diet, physical activity, sleep, substance use, and driving. Influences on these behaviors encompass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

young drivers employs state-of-the-art survey, observation, naturalistic driving, test track, simulation, and neuroimaging methodology to examine driving risk and prevention.

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.

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.

In 2019, SBSB congratulated our long-time colleague Dr. Bruce Simons-Morton on his retirement from federal service and his appointment as Scientist Emeritus in the NIH Intramural Research Program.



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Postdoctoral Fellow

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Postbaccalaureate Fellow

Kuba Jeffers, B.A.,
Postbaccalaureate Fellow
(departed in 2019)

Katherine Maultsby, B.S.,
Postbaccalaureate Fellow

Reeya Patel, M.S.,
Postbaccalaureate Fellow

Ndeah Terry, B.S.,
Postbaccalaureate Fellow

Jan Mooney, M.A.,
Summer Intern

Stephen E. Gilman, Sc.D.

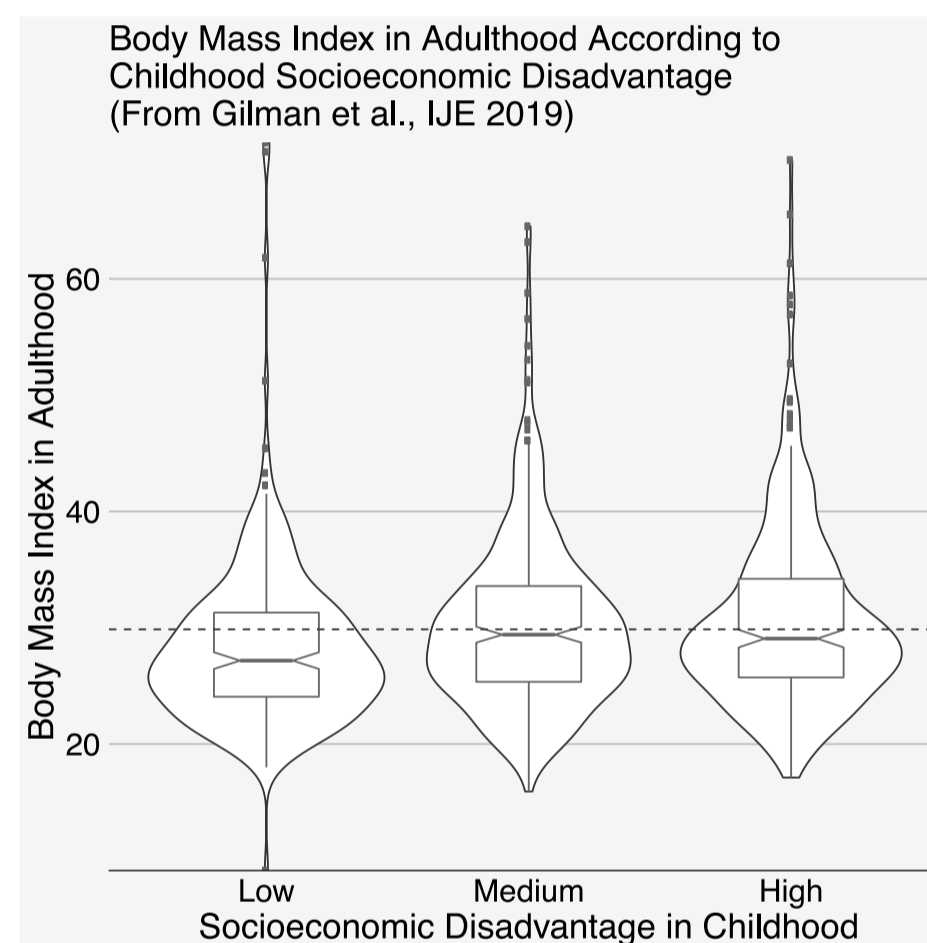
Socially mediated insults during early development have long-term consequences for mental and physical health. Our research seeks to better understand positive and negative environmental influences on development from the prenatal period onward to generate new insights into early origins of health disparities, 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 (individual, family, and neighborhood), 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 (PMID: [30699022](#)) to investigate how disparities in health originate in early life (e.g., as illustrated in the Figure from our study on adult adiposity, PMID: [30928911](#)).

The prenatal period and early childhood

Maternal immune activity during pregnancy has been repeatedly linked to neuropsychiatric disorders in offspring. To the extent that maternal inflammation during pregnancy causes deviations from typical neurodevelopment 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 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. In 2019 we initiated the ENRICHED, new cohort study to investigate the prenatal and childhood mechanisms of health disparities.



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 suicide mortality based on the historic United States Collaborative Perinatal Project.



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

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Risë B. Goldstein, Ph.D.,
Staff Scientist

Denise Haynie, Ph.D., M.P.H.,
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Brian Fairman, Ph.D.,
Postdoctoral Fellow
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Pablo Vidal-Ribas Belil, Ph.D.
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Kuba Jeffers, B.A.
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▼ SOCIAL AND BEHAVIORAL SCIENCES BRANCH (CONT.)

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.

Katherine Maultsby, B.A.
Post baccalaureate fellow

Reeya Patel, M.S.
Post baccalaureate fellow

KEY PUBLICATIONS

Gilman SE, Huang YT, Jimenez MP, Agha G, Chu SH, Eaton CB, Goldstein RB, Kelsey KT, Buka SL, Loucks EB. Early life disadvantage and adult adiposity: tests of sensitive periods during childhood and behavioural mediation in adulthood. *International Journal of Epidemiology*. 2019;48(1):98-107. PMID: 30277525; PMCID: PMC6380308.

Goldstein RB, Lee AK, Haynie DL, Luk JW, Fairman BJ, Liu D, Jeffers JS, Simons-Morton BG, Gilman SE. Neighbourhood disadvantage and depressive symptoms among adolescents followed into emerging adulthood. *Journal of Epidemiology and Community Health*. 2019;73(7):590-7. PMID: 30928911; PMCID: PMC6559828.

Bruce Simons-Morton, Ed.D., M.P.H.

Program of Research. I study adolescent health behavior using instrumented vehicle, survey, and other methods.



Driving Research. We study driving behavior among novice drivers using both experimental and observational research methods. Recent analyses have focused on the amount and quality of practice driving (PMID: [31442090](#)). We have also examined the effect of teen passengers on teen drivers using experimental design and concluded that risky driving behavior among teenage drivers is influenced by perceptions of acceptability of risk to passengers and experience of social isolation (PMID: [31133918](#)).



Adolescent Health Behavior. My research on adolescent health behavior is based on the NEXT Generation Longitudinal Study of Adolescent Health, which follows a nationally representative cohort from 10th grade for 7 years. According, we examine over-time patterns and influences on adolescent and young adult behaviors, including substance use, diet, physical activity, sleep, and driving, including aggressive and distracted driving, and driving or riding while impaired. In recent analyses we reported prospective associations between close friends' drinking and personal income and extreme drinking (PMID: [31790357](#)), sexual orientation and maladaptive dieting behaviors (PMID: [31030007](#)) and sleep behaviors (PMID: [31030007](#)). Additionally, we have published a study that found self-reported and measured BMI were strongly concordant in US emerging adults and provided nearly identical associations with cardiometabolic biomarkers (PMID: [31003807](#)).



Bruce Simons-Morton, Ed.D., M.P.H., *Senior Investigator*

STAFF

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Chelsie Temmen, Ph.D., *Postdoctoral Fellow*

Katherine Maultsby, B.A., *Post baccalaureate Fellow*

KEY PUBLICATIONS

Simons-Morton, B.G., Gensler, G., Ehsani JP, Gershon, P., Zhu C, Klauer S., Gore-Langton, R., Dingus T. (2019). Kinematic risky driving behavior among younger and older drivers: The effect of age and inexperience. *Traffic Injury Prevention*, 20(7):708-712. PMID: 31442090.

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Tonja Nansel, Ph.D.

Poor diet quality, characterized by excessive intake of discretionary foods (i.e., nutrient-poor foods high in energy, added sugar, fat, and sodium) and inadequate intake of fruits, vegetables, and whole grains, is the leading cause of global premature mortality. Insufficient evidence exists to inform approaches to achieve sustainable improvements in diet quality. The goal of this research program is to address this critical knowledge gap by investigating neurobehavioral influences on eating behaviors in children and families and developing novel intervention targets to facilitate dietary change. Current and recent projects include Cultivating Healthy Environments in Families of Youth with Type 1 Diabetes Study (CHEF), Pregnancy Eating Attributes Study (PEAS), and Sprouts: Development of Eating Behaviors in Early Childhood.



CHEF was a randomized controlled trial of a behavioral nutrition intervention in families of youth with type 1 diabetes. The trial demonstrated the efficacy of a family-based behavioral intervention grounded in health behavior theories to improve diet quality (PMID: [25952160](#)). Secondary analyses in the past year include a methodological paper addressing the potential for differential reporting bias by treatment assignment resulting from increased attention to food intake in dietary interventions. Our analyses indicated that the association of self-reported fruit and vegetable intake with a serum biomarker (carotenoids) did not change over time in either the intervention or control groups, and there was no difference by treatment assignment in constant systematic error in self-reported intake, suggesting that there was no differential reporting bias by treatment assignment (PMID: [30709403](#)). We further demonstrated that the association of carotenoid intake with serum carotenoids is not modified by hyperglycemia, validating the utility of serum carotenoids as a biomarker of intake (PMID: [31101482](#)). Finally, we found that children's diet quality resembled that of their parents' to a similar degree as observed in families of youth without type 1 diabetes

and that concordance of parent and child intake of intervention target food groups increased over follow-up in the intervention group (PMID: [30389377](#)).



PEAS was an observational prospective cohort study investigating relationships of reward-related eating, self-regulation, and the home food environment with dietary intake and weight change during pregnancy and postpartum. Participants were enrolled before 12 weeks gestation and followed, with their infants, until 1 year postpartum. The study includes data on dietary intake, anthropometrics, biospecimens, medical records, self-reported eating and other health-related behaviors, infant feeding, functional magnetic resonance imaging, focus groups, and an experimental measure of overeating. Manuscripts addressing the primary study aims are under review. Findings from a focus group substudy indicated that pregnant women experience cravings as intense and emotional, and that their decisions to resist or satisfy cravings have salient psychological aspects (PMID: [31813756](#)). Data from a postpartum neuroimaging substudy showed that blood oxygen level dependent responses to prediction error (receipt of a subpalatable taste after viewing a palatable cue) is processed in both gustatory and salience brain regions and was not associated with BMI or food reinforcement value (PMID: [30986423](#)).



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 3-5 years). Dietary intake, anthropometrics, biospecimens, laboratory-assessed behavioral data, and parent-reported feeding/eating behaviors will be collected from PEAS mothers, children and co-parents. Data collection began in 2019 and is ongoing.



Tonja Nansel, Ph.D.
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Ndeah Terry, B.S.,
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(50% time)

HIGHLIGHTED REFERENCES

Simons-Morton, B.G., Gensler, G., Ehsani JP, Sanjeevi N, Lipsky LM, Liu A., Nansel TR. Differential reporting of fruit and vegetable intake among youth in a randomized controlled trial of a behavioral nutrition intervention. *International Journal of Behavioral Nutrition and Physical Activity* 2019; 16(1):15. PMID: 30709403 PMCID: PMC6359852

Lipsky LM, Haynie DL, Liu A, Nansel TR. Resemblance of diet quality in families of youth with type 1 diabetes participating in a randomized controlled behavioral nutrition intervention trial in Boston, MA (2010-2013): a secondary data analysis. *Journal of the Academy of Nutrition and Dietetics*. 2019; 119(1):98-105. PMID: [30389377](#)

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.

NICHHD 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 utilizes technology transfer mechanisms to form collaborative partnerships, translating discoveries and clinical advances into products that address unmet contraceptive needs of women and men.

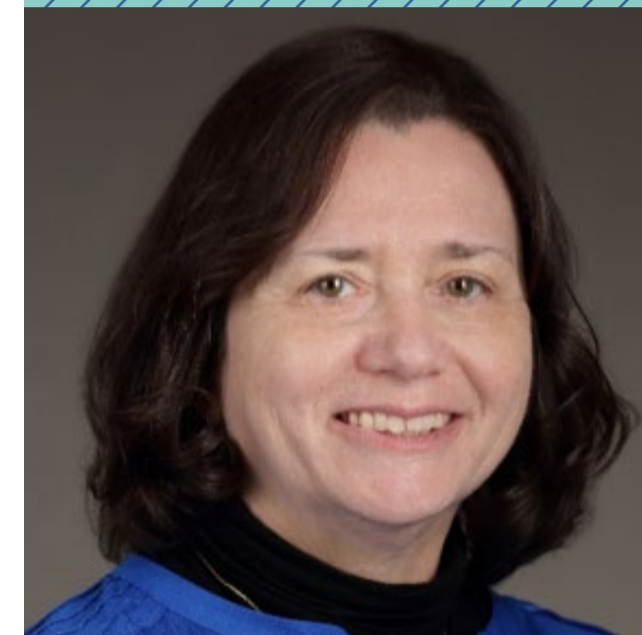
CDP uses R&D contracts to achieve the goal of new contraceptive method development. The Program evaluates new drugs that are not commercially available and must be synthesized under current Good Manufacturing Practice (cGMP) as recommended by FDA guidance. CDP maintains a contracted Chemical Synthesis 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 batch preparation required for first-in-human studies and longer toxicology studies for later Phase clinical trials.

The Contraceptive Clinical Trials Network (CCTN)

CDP's CCTN evaluates safety and efficacy of new contraceptive drugs and devices for women and men. Results from clinical trials on new entities form the basis for advancing candidate drugs and devices through development 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 2019, eight 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 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 three US sites and six international sites. Each product in development fills an unmet need or provides greater safety to vulnerable populations at risk of unintended pregnancy.



Diana Blithe, Ph.D.
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KEY PUBLICATIONS

Male Contraceptive Development:
Update on Novel Hormonal and Nonhormonal Methods. Long JE, Lee MS, Blithe DL. Clin Chem. 65:153-160, 2019. Review. PMID:30602479

Pipeline for contraceptive development. Blithe DL. Fertil Steril. 106:1295-1302, 2016. Epub 2016 Aug 11. Review. PMID: 27523300

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 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®/Ethinyl Estradiol CVR provides a year of protection. Advantages over existing rings: no refrigeration for storage; better for environment (use 1 ring vs 13 rings).

Nestorone®/17β Estradiol CVR is under clinical evaluation for effectiveness over one year of use. Nestorone® blocks follicular development; 17-β estradiol supports bone health without increasing VTE risk.

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. Evaluation of ovulation inhibition is underway.

Woman's Condom pivotal trial demonstrated acceptability and effectiveness of a novel female condom to prevent pregnancy and transmission of infection.

Long-Acting Reversible Contraceptives (LARCs)

LARCs are effective, highly acceptable methods. Copper IUD is a safe option for women with health risks to avoid pregnancy. Increased bleeding and cramping associated with Copper IUDs may deter use in nulliparous women, especially adolescents.

In collaboration with Gates Foundation and FHI-360, CDP is evaluating a Mini-Copper IUD to determine effectiveness, bleeding characteristics and pain.

Progestin-only Injectable Contraception

LNG-Butanoate (LB) is a novel injectable method with no increase in VTE risk. Injections of long-acting LB improves compliance over progestin-only pills (need intake at same time each day). Study is underway to optimize duration of ovulation inhibition.

DEVELOPMENT OF CONTRACEPTIVE METHODS FOR MEN

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

Nestorone®/Testosterone (Nes/Tes) Gel

Dr. Blithe's CCTN team demonstrated that Nestorone® (a potent progestin) and T gel caused gonadotropin suppression, inhibiting sperm production, which recovered after treatment ended; thus, the regimen may be reversibly effective for male contraception. A Nes/Tes Gel trial is underway to evaluate effectiveness in couples for pregnancy prevention. After a suppression phase, couples use the product for one year of contraception, then recovery to normal sperm production is followed. Enrollment is ongoing in CCTN sites in the USA, UK, Sweden, Italy, Chile and Kenya.



Diana Blithe, Ph.D.
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KEY PUBLICATIONS

Archer DF, Merkatz RB, Bahamondes L, Westhoff CL, Darney P, Apter D, Jensen JT, Brache V, Nelson AL, Banks E, Bártfai G, Portman DJ, Plagianos M, Dart C, Kumar N, Creasy GW, Sitruk-Ware R, Blithe DL. Efficacy of the 1-year (13-cycle) segesterone acetate and ethinylestradiol contraceptive vaginal system: results of two multicentre, open-label, single-arm, phase 3 trials. *Lancet Glob Health* 2019; 7(8):e1054-e1064. PMID: 31231065 PMID: PMC6624423

Anawalt BD, Roth MY, Ceponis J, Surampudi V, Amory JK, Swerdloff RS, Liu PY, Dart,C, Bremner WJ, Sitruk-Ware R, Kumar N, Blithe DL, Page ST, Wang C. Combined nesterone-testosterone gel suppresses serum gonadotropins to concentrations associated with effective hormonal contraception in men. *Andrology* 2019; 7(6):878-887. PMID: 30969032 PMID: PMC6768743 [Available on 2020-11-01]



CONTRACEPTIVE DEVELOPMENT PROGRAM

Novel Progestogenic Androgens for Male Contraception

Dimethandrolone (DMA) and 11 β Methyl 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).

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