



Eunice Kennedy Shriver National Institute  
of Child Health and Human Development



*1967-2017 • 50th ANNIVERSARY*

**2017 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.



Constantine A. Stratakis  
MD, D(med)Sci

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 2017 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. Finally, 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**, MD, D(med)Sci  
*Acting Director, DIPHR, NICHD*

## POPULATION HEALTH ACROSS THE LIFE COURSE: CELEBRATING 50 YEARS OF DISCOVERIES AND CONTRIBUTIONS BY NICHD

In 1967, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development added population health to the mission of its Intramural Research Program. The objective was to conduct high-risk, innovative research on maternal and child health and to develop novel methods for addressing pressing research questions in substantive areas within the mission of the Institute. Today, this program is called the Division of Intramural Population Health Research (DIPHR). In 2017, the DIPHR reached a significant milestone: 50 years in existence.

DIPHR celebrated the anniversary on May 15-16, 2017 by hosting a celebratory kick-off dinner followed by a full-day scientific program. The anniversary served as an impetus to document and publicize the Division's contributions to improving health for the many populations served by the Institute's mission. The program on "Population Health Across the Life Course" highlighted the Division's history and major discoveries over the past 50 years (displayed on the timeline below). The invited speakers also reflected on future directions in support of promoting the health of all populations. In addition, the events enhanced external relationships with a trans-disciplinary group of scientists. The 50th Anniversary Planning Committee, chaired by Dr. Una Grewal, led the conception, planning and implementation of these activities, working closely with the Scientific Program Committee, chaired by Dr. Stephen Gilman.



## Office of the Director

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 Health Behavior Branch. Dr. Buck Louis served as the Director until her retirement from federal service in September 2017. 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. During her tenure as Division Director, Dr. Buck Louis maintained an active research program focusing on environmental influences and human reproduction and development. She was the Principal Investigator for the LIFE Study, ENDO Study and the Exposome of Normal Pregnancy Study, and Co-Principal Investigator for the NICHD Fetal Growth Studies.

Dr. Jagteshwar (Una) Grewal is the Deputy Director for the Division. In this capacity, she assumes considerable responsibility for scientific administration and managerial leadership in the Division. She oversees the training/mentoring program for all fellows and supervises the continued professional development of all DIPHR scientists. As a population scientist, Dr. Grewal continues her research on fetal growth and development, perinatal epidemiology, and birth defects. She is a collaborator with the NICHD Fetal Growth Studies where she leads research on the nutritional component. In addition, Dr. Grewal serves as the Contracting Officer's Representative for the Division's Data Coordinating Center support contract.

Dr. Jennifer Weck is a Laboratory Health Specialist who provides guidance and support for the Division's extensive biospecimen

collection protocols and repository. Dr. Weck contributes her expertise in reproductive endocrinology, and her training as a physiologist is most relevant for the Division's research initiatives. Dr. Weck oversees the [Division's Biospecimen Repository Access and Data Sharing \(BRADS\)](#) program, which is an online resource for researchers looking to leverage existing data and biospecimens for a host of health and disease outcomes. Additionally, Dr. Weck serves as the Contracting Officer's Representative for the Division's two support laboratories and the NICHD's Biospecimen Repository.

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.



Constantine A. Stratakis, MD, D(med)Sci



Germaine M. Buck Louis, Ph.D., M.S.



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



Jennifer Weck, Ph.D.

### Staff

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

Germaine M. Buck Louis, Ph.D., M.S.,  
Senior Investigator and Director (retired  
September 2017)

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

Adrienne Lonaberger, Program Analyst

### Fellows

Melissa Smarr, Ph.D., Postdoctoral IRTA Fellow

Mohammad L. Rahman, MD, SD, MPH,  
Postdoctoral IRTA Fellow

# Environmental Influences on Human Reproduction and Development

Human reproduction and development is dependent upon the successful completion of a series of timed and highly interrelated biologic processes involving both partners of the couple. While important research advances have markedly increased our understanding of the biologic basis of reproduction and development, critical data gaps exist regarding the identification of the determinants that impact men and women's reproductive health. Examples of such data gaps include our inability to explain the marked variation in time couples require for becoming pregnant, our limited understanding of the natural history of pregnancy loss, our inability to identify factors that diminish or enhance male and female fecundity and fertility, and the limited power of semen analysis in predicting fertility, conception delays or pregnancy outcomes. These and other data gaps are in the context of novel and emerging research paradigms that suggest human fecundity and fertility may originate early, including before or during pregnancy with further modification during childhood

and adolescence depending upon lifestyle, behavior and other environmental exposures during these sensitive windows. Moreover, evolving data suggests that human fecundity, defined as the biologic capacity of men and women for reproduction irrespective of pregnancy intentions, may be predictive of health status during pregnancy and later onset adult diseases.

Our Division-wide research teams design and complete trans-disciplinary epidemiologic investigations with the overarching goal of identifying potential reproductive and/or developmental toxicants arising from contemporary living, as well as factors that enhance reproductive health. This work is often conducted in conjunction with our extramural collaborators at various academic institutions. The overarching goal of this avenue of research is to identify environmental (defined as non-genetic) factors that positively and negatively impact reproduction and development, and to design appropriate population level intervention.



Germaine M. Buck Louis,  
Ph.D., M.S.

## LONGITUDINAL INVESTIGATION OF FERTILITY AND THE ENVIRONMENT (LIFE STUDY)

The [LIFE Study](#) is a prospective cohort study that recruited 501 couples discontinuing contraception for purposes of becoming pregnant, and followed them while trying for pregnancy and through pregnancy.

The overarching goals of the study are to determine whether endocrine disrupting chemicals (EDCs) and lifestyle affect male and female fecundity and fertility, which are defined as the biologic capacity for reproduction and live births, respectively. Longitudinal data collection included baseline interviews with each partner, daily reporting of lifestyle and behaviors for up to 12 months of trying or until pregnant. Women achieving pregnancy completed daily then monthly journals until delivery. Metals and other persistent (i.e., organochlorine pesticides, polybrominated biphenyls, polybrominated diphenyl ethers, polychlorinated biphenyls, and perfluoroalkyls and polyfluoroalkyls) environmental chemicals were measured in blood, and non-persistent chemicals (i.e., benzophenones, bisphenol A, parabens, phthalates, and trace elements) were measured in urine along with paracetamol. Men also provided semen samples for the assessment of semen quality. Women were instructed in the use of the Clearblue® Easy Fertility Monitor to help time intercourse relative to ovulation along with the use of Clearblue® (digital) home pregnancy test kits for the detection of pregnancy.

Among some of the notable discoveries continuing in 2017 include a 37% reduction in fecundability for female partners in the highest versus lowest quartile of urinary methyl paraben concentrations, and similarly for ethyl paraben (Smarr et al.

2017a). In terms of lifestyle behaviors, couples whose body mass indices were categorized as obese class II ( $\geq 35$  kg/m<sup>2</sup>) had a 59% reduction in fecundability or longer time-to-pregnancy relative to leaner couples. Relative to semen quality, male partners' paracetamol (acetaminophen) concentrations were negatively associated with sperm motility and the metabolite p-aminophenol was negatively associated with sperm head size (Smarr et al. 2017b). These findings underscore the importance of environmental influences on human reproductive health.

**The environment impacts human fecundity and fertility, including specific endocrine disruptors and also lifestyle. Maintaining or adopting a healthy lifestyle is important for maximizing reproductive health.**

### Principal Investigator

Germaine M. Buck Louis, Ph.D., M.S.

### Division Collaborators

Zhen Chen, Ph.D.

Sunni Mumford, Ph.D., M.P.H.

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

Rajeshwari Sundaram, Ph.D.

Melissa Smarr, Ph.D., M.P.H.

### Key Publications

Buck Louis GM, Smarr MM, Sundaram R, Steuerwald AJ, Sapra KJ, Lu Z, Parsons PJ. Low-level environmental metals and metalloids and incident pregnancy loss. *Reproductive Toxicology*. 2017; 69:68-74. PMID: 28163209. PMCID: PMC5406243

Smarr MM, Kannan K, Chen Z, Kim S, Buck Louis GM. Male urinary paracetamol and semen quality. *Andrology*. 2017; 5(6):1082-1088. PMID: 28853221

Smarr MM, Sundaram R, Honda M, Kannan K, Louis GM. Urinary Concentrations of Parabens and Other Antimicrobial Chemicals and Their Association with Couples' Fecundity. *Environmental Health Perspectives*. 2017; 125(4):730-736. PMID: 27286252. PMCID: PMC5381974

Sundaram R, Mumford SL, Buck Louis GM. Couples' body composition and time-to-pregnancy. *Human Reproduction*. 2017; 32(3):662-668. PMID: 28158570. PMCID: PMC5400044

# ENDO

## ENDOMETRIOSIS: NATURAL HISTORY, DIAGNOSIS AND OUTCOMES (ENDO) STUDY



Germaine M. Buck Louis,  
Ph.D., M.S.

Endometriosis is a gynecologic disorder affecting menstruating women resulting in the implantation of endometrial glands and stroma outside the uterine cavity. The etiology of endometriosis is unknown, but increasing evidence suggests that endocrine disrupting chemicals (EDCs) may play an important role. The goals of the ENDO Study were to assess the association between EDCs and endometriosis, and to assess the consistency of the findings across diagnostic criteria, biologic media used for quantifying lipophilic chemicals and choice of comparison group. We matched an operative group of women with a population group for study purposes. Women in the operative group underwent laparoscopy/laparotomy examination, while women in the population underwent pelvic magnetic resonance imaging for the diagnosis of endometriosis. Blood and urine samples were collected for the quantification of benzophenones, bisphenol A, metal(loids)s, organochlorine pesticides, perfluoroalkyl and polyfluoroalkyl phthalates, polybrominated diphenyl ethers, and polychlorinated biphenyls. We used the clinical gold standard of surgically visualized disease to define endometriosis.

**With increasing evidence that endometriosis increases women's risk of later onset cancers and coronary vascular disease, it is important to delineate its pathophysiology to prevent disease occurrence. Body habitus may be informative about underlying mechanisms and requires further study.**

EDCs also are suggested to impact body composition as measured by body mass index (BMI), which prompted us to perform standardized anthropometric assessments on the women. Endometriosis

has been associated with a lean body habitus as typically measured by BMI in contrast to other gynecologic diseases,

such as polycystic ovarian syndrome that is associated with a heavier BMI. The ENDO Study is the first to more fully assess body composition beyond BMI in affected and unaffected women, viz., adipose tissue distribution and amount of visceral adipose tissue. We found that weight, skinfold thickness, waist and hip circumference, and upper arm muscle area were inversely associated with endometriosis. Heavier women had approximately a 20% to 30% reduction in the odds of an endometriosis diagnosis relative to lean women (Backonja et al. 2017). Our findings are strengthened by our methodologic investigation assessing the reliability of physician-diagnosed endometriosis, which was found to be quite good in this study (Schliep et al. 2017).

We continue our investigation of non-chemical environmental estrogens and endometriosis, particularly those from dietary sources. Despite assessing several phytoestrogens, we found no evidence with an association with endometriosis (Mumford et al. 2017).

### Principal Investigator

Germaine M. Buck Louis, Ph.D., M.S.

### Division Collaborators

Zhen Chen, Ph.D.

Sunni Mumford, Ph.D., M.P.H.

Jennifer Weck, Ph.D.

### Key Publications

Backonja U, Hediger ML, Chen Z, Lauver DR, Sun L, Peterson CM, Buck Louis GM. Beyond Body Mass Index: Using Anthropometric Measures and Body Composition Indicators to Assess Odds of an Endometriosis Diagnosis. *Journal of Women's Health (Larchmt)*. 2017; 26(9):941-950. PMID: 28537460. PMCID: PMC5646748

Mumford SL, Weck J, Kannan K, Buck Louis GM. Urinary Phytoestrogen Concentrations Are Not Associated with Incident Endometriosis in Premenopausal Women. *Journal of Nutrition*. 2017; 147(2):227-234. PMID: 28031375. PMCID: PMC5265693

Schliep KC, Chen Z, Stanford JB, Xie Y, Mumford SL, Hammoud AO, Boiman Johnstone E, Dorais JK, Varner MW, Buck Louis GM, Peterson CM. Endometriosis diagnosis and staging by operating surgeon and expert review using multiple diagnostic tools: an inter-rater agreement study. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2017; 124(2):220-229. PMID: 26435386. PMCID: PMC4821828

### EXPOSOME OF NORMAL PREGNANCY



Germaine M. Buck Louis,  
Ph.D., M.S.

The exposome paradigm is an evolving framework for assessing mixtures of exposures in relation to health outcomes. To evaluate its utility for pregnancy research, we randomly selected 50 healthy pregnant women with uncomplicated pregnancies from a pregnancy cohort which had serum/urine samples in each trimester for measuring 144 persistent and 48 non-persistent environmental chemicals. We have recently completed analysis and find evidence that woman-level variation in concentrations can be differentiated from the variance explained by time supporting the utility of the exposome paradigm for pregnancy research. We currently have a paper under review.

#### **Principal Investigator**

Germaine M. Buck Louis, Ph.D., M.S.

#### **Division Collaborators**

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

Rajeshwari Sundaram, Ph.D.

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

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

#### **Key Publications**

Buck Louis GM, Smarr MM, Patel CJ. The Exposome Research Paradigm: an Opportunity to Understand the Environmental Basis for Human Health and Disease. *Current Environmental Health Reports*. 2017; 4(1):89-98. PMID: 28194614. PMCID: PMC5363405

Stingone JA, Buck Louis GM, Nakayama SF, Vermeulen RC, Kwok RK, Cui Y, Balshaw DM, Teitelbaum SL. Toward Greater Implementation of the Exposome Research Paradigm within Environmental Epidemiology. *Annual Review of Public Health*. 2017; 38:315-327. PMID: 28125387. PMCID: PMC5664945

## Biostatistics and Bioinformatics Branch

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.



Aiyi Liu, Ph.D.

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 code) 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) the characterization of longitudinal menstrual cycle and circadian rhythm patterns; and 3) the development of new approaches for designing and analyzing correlated data subject to informative cluster size, where the number of measurements is related to the underlying process of interest.

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 2017 has been on developing new statistical methods for modeling of complex data, including menstrual cycle length and fecundity, longitudinal measurements and binary events, and on methods for biomarkers of various types. In particular, BBB investigators have proposed a Bayesian joint model of menstrual cycle length and fecundity, a semi-parametric transformation approach for modeling fecundity in the presence of a sterile

fraction, and a class of joint models for multivariate longitudinal measurements and a binary event.

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 including *Biometrics* and *Statistics and Medicine* and as officers in our leading statistical associations. BBB investigators also serve as editorial board members of leading substantive journals including *Clinical Trials* and *Fertility and Sterility*.

**Staff**

Aiyi Liu, Ph.D., Senior Investigator and Acting Chief  
Rajeshwari Sundaram, Ph.D., Senior Investigator  
Zhen Chen, Ph.D., Investigator  
Danping Liu, Ph.D., Investigator (departed 10/2017)

**Fellows**

Sedigheh Mirzaei, Ph.D., Postdoctoral Fellow  
Wei Zhang, Postdoctoral Fellow  
Yu-Bo Wang, Ph.D., Postdoctoral Fellow  
Chi-Yang Chiu, Ph.D., Postdoctoral Fellow  
(departed 06/2017)  
Wondwosen Yimer, Ph.D., Postdoctoral Fellow  
(departed 04/2017)

## Collaborative Research

BBB investigators are essential members of the research team on all major projects in the Epidemiology Branch (EB) and Health Behavior Branch (HBB), often with a primary and a secondary statistical investigator being on most projects. We also lead some substantive studies where the primary objectives focus on complex analytical questions, which require new innovative statistical methodology to solve. An example includes the NICHD Consecutive Pregnancy Study whose goal is to characterize complex associations among pregnancy outcomes and neonatal morbidity across subsequent pregnancies, and the Physicians Reliability Study to investigate the agreement on diagnosis of endometriosis among physicians.

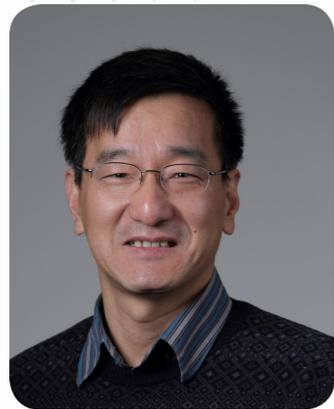
BBB investigators also collaborate with basic and clinical scientists in the NICHD's Division of Intramural, as well as with researchers in other NIH institutes and in the extramural academic community.

### ANALYSIS OF BIOMARKER DATA

Most of the studies within the Division collect biomarkers as either measures of exposure or outcome and often repeatedly. Often, these biomarkers are subject to large biological and technical errors as well as issues pertaining to detection limits. BBB investigators have developed efficient estimation for interaction effects using pooled biospecimens in a case-control study, methods for repeated significance tests of linear combinations of sensitivity and specificity of a diagnostic biomarker, and effective combination of biomarkers to improve diagnostic accuracy.



Zhen Chen, Ph.D.



Aiyi Liu, Ph.D.



Paul Albert, Ph.D.

### Principal Investigators

Zhen Chen, Ph.D.

Aiyi Liu, Ph.D.

Paul Albert, Ph.D.

### ANALYSIS OF TIME-TO-EVENT DATA



Rajeshwari Sundaram,  
Ph.D.

An important analytical issue for many Division studies is the characterization of time to an event. 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, gap times between accidents in teenage driving) and interest focusing on identifying 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 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.

Statistical modeling of human fecundity has been an important area of Branch research in this area. Other areas include developing new approaches for modeling consecutive pregnancy outcomes subject to competing risks (e.g., incidence of pre-term birth due to preeclampsia) and modeling the gap times between pregnancies.

**Using novel newly developed statistical methods, one can identify the distribution of the time needed for per-centimeter increase in cervical dilation in first stage of spontaneous labor. Thus allowing one to identify the percentiles at which a woman's labor is progressing.**

#### Principal Investigator

Rajeshwari Sundaram, Ph.D.

#### Key Publications

Lum KJ, Sundaram R, Barr DB, Louis TA, Buck Louis GM. Perfluoroalkyl Chemicals, Menstrual Cycle Length, and Fecundity: Findings from a Prospective Pregnancy Study. *Epidemiology*. 2017; 28(1):90-98. PMID: 27541842. PMCID: PMC5131715

Ma L, Sundaram R. Analysis of Gap Times Based on Panel Count Data With Informative Observation Times and Unknown Start Time. *Journal of the American Statistical Association*. 2017:1-12

Sundaram R, Ma L, Ghoshal S. Median Analysis of Repeated Measures Associated with Recurrent Events in Presence of Terminal Event. *International Journal of Biostatistics*. 2017; 13(1). PMID: 28453440

## LONGITUDINAL AND CORRELATED DATA ANALYSIS



Sung Duk Kim, Ph.D.



Danping Liu, Ph.D.



Paul Albert, Ph.D.

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. Longitudinal studies have inherent methodological challenges over time, including the problem of attrition, difficulties in making statistical inference when data are correlated, and difficulties in characterizing complex longitudinal patterns. Many of the Branch's independent research projects address one or more of these issues in the context of substantive problems related to one or more of the Division's studies. Particular methodological problems that have been addressed include: 1) the joint modeling of longitudinal data and time-to-event for understanding the association of longitudinal profiles and an outcome of interest. Branch Investigators have proposed approaches for inference and prediction with applications to the Longitudinal Investigation of Fertility and the Environment (LIFE) Study as well as to the NICHD Fetal Growth Studies; 2) characterizing longitudinal relapsing-remitting and circadian rhythm patterns in longitudinal data with applications to the studying of bacterial vaginosis in women and the NEXT Study; and 3) development of new modeling approaches for multivariate longitudinal measurements and a binary event.

### Principal Investigators

Danping Liu, Ph.D.

Sung Duk Kim, Ph.D.

Paul Albert, Ph.D.

## Epidemiology Branch



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

The [Epidemiology Branch](#)'s mission is threefold: 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, 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, and/or pediatric epidemiologic research.

The Branch is organized around key areas of epidemiologic research spanning across the life course from reproductive health, to pregnancy, infant and child health, in addition to methodologic research. Regardless of title, Branch members work collaboratively to advance the Division and Institute's mission. The Branch conducts team science and is committed to using trans-disciplinary, cutting-edge techniques to address critical data gaps throughout the life course. In particular, 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, allowing for substantial possible public health impact. 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 gestational

diabetes, 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 international collaborations, and the impacts of conception using advanced reproductive technologies on subsequent child growth, motor development, and cardiovascular health. Collectively, the Branch is committed to 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 will aid in the design of effective interventions and preventive strategies to improve the health of many population subgroups. The Branch is uniquely positioned with the freedom and opportunity to pursue trans-disciplinary, high-risk research in novel and emerging areas of reproductive, perinatal, and pediatric epidemiology and epidemiologic methods.

**Staff**

Enrique F. Schisterman, Ph.D., M.A.,  
Senior Investigator and Chief  
Katherine Laughon Grantz, M.D., M.S., Investigator  
Stefanie N. Hinkle, Ph.D., Staff Scientist  
Pauline Mendola, Ph.D., M.S., Investigator  
James L. Mills, M.D., M.S., Senior Investigator  
Sunni L. Mumford, Ph.D., M.S., Earl Stadtman Investigator

**Fellows**

Griffith Bell, Ph.D., Postdoctoral Fellow  
Alaina Bever, B.S., Postbaccalaureate Fellow  
Matt Connell, D.O., Clinical Fellow  
Andreas Giannakou, M.D., Postdoctoral Fellow  
Sandie Ha, Ph.D., Postdoctoral Fellow (departed in 2017)  
Tiffany Holland, B.A., Postbaccalaureate Fellow  
Keewan Kim, Ph.D., Postdoctoral Fellow  
Dan Kuhr, B.S., MSRP Fellow (departed in 2017)  
Yuan Lin, M.D., Visiting Fellow (departed in 2017)  
Carrie Nobles, Ph.D., M.P.H., Postdoctoral Fellow  
Ukpebo Rebecca Omosigho, B.S., MSRP Fellow  
(departed in 2017)  
Pranati Panuganti, B.S., Postbaccalaureate Fellow  
(departed in 2017)  
Hyojun Park, Ph.D., Postdoctoral Fellow  
Melissa Amyx, Ph.D., M.P.H., Postdoctoral Fellow

Neil J. Perkins, Ph.D., M.S., Staff Scientist  
Lindsey A. Sjaarda, Ph.D., M.S., Staff Scientist  
Fasil Tekola-Ayele, Ph.D., M.P.H.,  
Earl Stadtman Investigator  
Edwina H. Yeung, Ph.D., Sc.M., Investigator  
Cuilin Zhang, M.D., Ph.D., M.P.H., Senior Investigator

Elizabeth Devilbiss, Ph.D., M.P.H., M.S., Postdoctoral Fellow  
Elise Heisler, B.S., Postbaccalaureate Fellow  
Lindsay Levine, B.A. Postbaccalaureate Fellow  
Mengying Li, Ph.D., M.S.P.H., Postdoctoral Fellow  
Mohammad Rahman, M.D., Sc.D., M.P.H., Visiting Fellow  
Deepika Shrestha, Ph.D., M.Sc., Visiting Fellow  
Andrew Williams, Ph.D., M.P.H., Postdoctoral Fellow  
Tsegaselassie Workalemahu, M.S., Predoctoral Fellow  
Sarah Pugh, Ph.D., M.P.H., Postdoctoral Fellow  
(departed in 2017)  
Rose Radin, Ph.D., M.P.H., Postdoctoral Fellow  
(departed in 2017)  
Shristi Rawal Ph.D., Postdoctoral Fellow (departed in 2017)  
Indulaxmi Seeni, B.S., Postbaccalaureate Fellow

### 2017 Awards

Griffith Bell, Ph.D., Postdoctoral Fellow (Mentors: Edwina Yeung, Ph.D.; James Mills, M.D.), Fellows Award for Research Excellence, National Institutes of Health, Bethesda, MD.

Shristi Rawal, PhD, Postdoctoral Fellow (Mentor: Cuilin Zhang M.D., Ph.D.), Fellows Award for Research Excellence, National Institutes of Health, Bethesda, MD.

Cuilin Zhang, MD, Ph.D., Senior Investigator, NICHD Director Collaboration Award, NICHD Fetal Growth Studies, National Institutes of Health, Bethesda, MD.

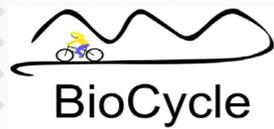
Katherine Grantz, M.D., M.S., Investigator, NICHD Director Collaboration Award, NICHD Fetal Growth Studies, National Institutes of Health, Bethesda, MD.

Keewan Kim, Ph.D., Research Fellow (Mentor: Sunni L. Mumford, Ph.D.), NIH-Korean Scientists Association (KSA) Excellent Research Award, Annual Bioscience and Engineering Symposium, Rockville, MD.

Dan Kuhr, B.S., MSRP Fellow (Mentor: Enrique Schisterman, Ph.D. M.A.), Poster Award, Society for Pediatric and Perinatal Epidemiologic Research, Seattle, WA.

## Reproductive Health

The field of reproductive epidemiology focuses on the many factors that affect human fecundity and fertility, which are defined as the biologic capacity of men and women for reproduction irrespective of pregnancy intentions and the ability to have a live birth, respectively. The discipline also investigates impairments and disorders such as conception delay, anovulation, infertility, and semen quality in relation to environmental, nutritional, and genetic factors. The Epidemiology Branch conducts important reproductive epidemiologic research studies, such as the BioCycle Study, Effects of Aspirin in Gestation and Reproduction (EAGeR) Trial, the Folic Acid and Zinc Supplementation Trial (FAZST), and the Impact of Diet, Exercise and Lifestyle (IDEAL) on Fertility Study. A brief description of each study and its key components follows.



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



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

## **BIOCYCLE STUDY: LONGITUDINAL STUDY OF HORMONE EFFECTS ON BIOMARKERS OF OXIDATIVE STRESS AND ANTIOXIDANT STATUS DURING THE MENSTRUAL CYCLE**

The BioCycle Study was a prospective longitudinal cohort study comprising 259 women aged 18 to 44 years (98% follow-up rate) followed for two menstrual cycles (2005-2007). The study was designed to better understand menstrual cycle function and the intricate relationships between reproductive hormone levels and oxidative stress. Since completion of the study, much progress has been made in the analysis of the BioCycle Study data. To date, over 80 papers have been published. The BioCycle Study has contributed substantially to the fields of nutritional, environmental, and social epidemiology, offering valuable insights into various factors associated with premenopausal women's reproductive and cardio-metabolic health. In particular, several dietary factors have been evaluated with regard to their associations with reproductive hormones and ovulation, including dairy food intake (Kim et al. *Journal of Nutrition* 2017). These findings have highlighted the important role of diet in reproductive function. Further research evaluating potential environmental factors, including blood lead, cadmium, and mercury, found that lead levels were associated with increased homocysteine, a marker of inflammation, which has potential implications for cardiovascular disease later in life (Pollack et al. *Environmental Health* 2017). In addition, it was also observed that plasma homocysteine was associated with altered hormone levels throughout the menstrual cycle, as well as with an increased risk of sporadic anovulation (Michels et al. *Human Reproduction* 2017). Further research into the mechanisms driving these associations is needed to understand the potential implications for women's health.

Overall, this body of work has been influential in describing not only the short-term impact of diet and lifestyle on

hormonal function and markers of menstrual cycle dysfunction (e.g., anovulation, luteal phase deficiency, and abnormal menses) but their potential long-term impact on chronic disease risk. The team intends to build upon its current findings from the BioCycle Study to fill critical research gaps in its quest to answer important public health questions for women of reproductive age.

**Results from the BioCycle Study have been integral in helping us understand the short term influences of lifestyle and dietary factors on hormonal function and menstrual cycle function in healthy women.**

### **Principal Investigators**

Enrique F. Schisterman, Ph.D., M.A.  
Sunni L. Mumford, Ph.D., M.S. (PI: Nutrition)

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### Key Publications from BioCycle

Kim K, Wactawski-Wende J, Michels KA, Plowden TC, Chaljub EN, Sjaarda LA, Mumford SL. Dairy Food Intake Is Associated with Reproductive Hormones and Sporadic Anovulation among Healthy Premenopausal Women. *Journal of Nutrition*. 2017; 147(2):218-226. PMID: 27881593. PMCID: PMC5265695

Michels KA, Wactawski-Wende J, Mills JL, Schliep KC, Gaskins AJ, Yeung EH, Kim K, Plowden TC, Sjaarda LA, Chaljub EN, Mumford SL. Folate, homocysteine and the ovarian cycle among healthy regularly menstruating women. *Human Reproduction*. 2017; 32(8):1743-1750. PMID: 28854586

Pollack AZ, Mumford SL, Sjaarda L, Perkins NJ, Malik F, Wactawski-Wende J, Schisterman EF. Blood lead, cadmium and mercury in relation to homocysteine and C-reactive protein in women of reproductive age: a panel study. *Environmental Health: A Global Access Science Source*. 2017; 16(1):84. PMID: 28789684. PMCID: PMC5549434



## EAGER: EFFECTS OF ASPIRIN IN GESTATION AND REPRODUCTION (EAGER) TRIAL



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

The EAGeR Study is a multi-site, prospective, double-blind, block-randomized trial designed to assess the effects of low-dose aspirin on implantation and pregnancy outcomes. In this trial, 1,228 regularly menstruating women aged 18-40 years with a history of one or two miscarriages and attempting pregnancy again were block-randomized to receive either daily low dose aspirin (81mg) or placebo. Treatment or placebo began before conception and continued for 6 months of trying or through week 36 of pregnancy among women who became pregnant. Participants were stratified into two groups: 1) original: women with one documented pregnancy loss at <20 weeks' gestation during the past 12 months; and 2) expanded: women with 1-2 prior pregnancy losses, regardless of gestational age of the loss or time since the loss. Women used fertility monitors to time intercourse and used home pregnancy tests to detect pregnancy.

Primary outcomes of the EAGeR trial were published in 2014 (Schisterman et al. Lancet 2014), with additional secondary outcomes published in 2015-2017. Overall, daily low-dose aspirin was not found to prevent subsequent pregnancy loss among women with a history of 1-2 prior losses (Schisterman et al. Lancet 2014; Mumford et al. Human Reproduction 2016).



Sunni L. Mumford,  
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Ukpebo Rebecca Omosigho, B.S.  
Neil J. Perkins, Ph.D., M.S.  
Torie Plowden, M.D.  
Sarah Pugh, Ph.D.  
Rose Radin, Ph.D., M.P.H.  
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**Findings from the EAGeR trial have emphasized the importance of understanding the inflammatory process and how it relates to reproductive health outcomes and the potential benefit of low dose aspirin for improving pregnancy outcomes among women with low-grade inflammation.**

Recently, we found that low-dose aspirin treatment increased live birth among women with low-grade inflammation. These results suggest that low-dose aspirin may restore otherwise diminished live birth rates in women with low-grade inflammation (Sjaarda et al. *Journal of Clinical Endocrinology and Metabolism* 2017). We also evaluated preconception maternal lipid levels, and found that elevated total and individual lipid subtypes were associated with a longer time-to-pregnancy (Pugh et al. *Human Reproduction* 2017). Since lipid levels are modifiable, these results may offer a target to improve female fecundability. We also evaluated the role of subclinical hypothyroidism and antithyroid antibodies and found no associations with preterm delivery, gestational diabetes, or preeclampsia, which are reassuring findings for women with subclinical hypothyroidism (Plowden et al. *American Journal of Obstetrics and Gynecology* 2017). The team intends to build upon current findings from EAGeR to fill research gaps in its quest to answer public health questions for reproductive-aged women.

### Key Publications

Plowden TC, Schisterman EF, Sjaarda LA, Perkins NJ, Silver R, Radin R, Kim K, Galai N, DeCherney AH, Mumford SL. Thyroid-stimulating hormone, anti-thyroid antibodies, and pregnancy outcomes. *American Journal of Obstetrics and Gynecology*. 2017; 217(6):697 e691-697 e697. PMID: 28917612. PMCID: PMC5712235

Pugh SJ, Schisterman EF, Browne RW, Lynch AM, Mumford SL, Perkins NJ, Silver R, Sjaarda L, Stanford JB, Wactawski-Wende J, Wilcox B, Grantz KL. Preconception maternal lipoprotein levels in relation to fecundability. *Human Reproduction*. 2017; 32(5):1055-1063. PMID: 28333301

Sjaarda LA, Radin RG, Silver RM, Mitchell E, Mumford SL, Wilcox B, Galai N, Perkins NJ, Wactawski-Wende J, Stanford JB, Schisterman EF. Preconception Low-Dose Aspirin Restores Diminished Pregnancy and Live Birth Rates in Women With Low-Grade Inflammation: A Secondary Analysis of a Randomized Trial. *Journal of Clinical Endocrinology and Metabolism*. 2017; 102(5):1495-1504. PMID: 28323989. PMCID: PMC5443323

# FAZST




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



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

## FOLIC ACID AND ZINC SUPPLEMENTATION TRIAL (FAZST)

Infertility affects approximately 16% of couples attempting to conceive. Male factor subfertility plays a role in about 50% of couples, though the etiology remains largely unknown. An intervention with even a small absolute effect on any component of male factor infertility has tremendous implications at the population level, given the large potential attributable benefit. Two micronutrients fundamental to the process of spermatogenesis, folate and zinc, are of particular interest as they offer a potential low-cost and widely available treatment. Though the evidence has been inconsistent, small randomized trials and observational studies show that folate and zinc have effects on spermatogenesis and improving semen parameters. These results support the potential benefits of folate on spermatogenesis, and suggest that supplementation with folic acid and zinc may improve semen quality, and perhaps, infertility treatment outcomes. In response to these emerging data, the FAZST Trial was designed.

FAZST was a multi-center, double-blind, block-randomized, placebo-controlled trial to assess the effects of folic acid and zinc dietary supplementation in male partners of couples seeking infertility treatment on semen quality, as well pregnancy rates and related outcomes (e.g., miscarriage). FAZST was designed to enroll 2,400 couples seeking assisted reproduction in 4 clinical sites (University of Utah, University of Iowa, Northwestern University, and the Center for Reproductive Medicine in Minnesota). Male partners were randomized to either the treatment (combined folic acid and zinc) or placebo arm and followed actively for six months with follow-up visits at 2, 4, and 6 months of treatment. Follow-up visits include the collection of biospecimens, including semen samples, and other study-related information. Couples are passively followed via chart abstraction through 9 months post-randomization, or throughout pregnancy

for couples that conceive during the trial. Primary outcomes of the trial include semen parameters (e.g. sperm count, motility, etc.) and live birth.

Recruitment was completed in December 2017, and follow-up is continuing in 2018. (See NCT Clinical Trials.gov Number: NCT01857310.)

**We eagerly await the results of the FAZST trial which has the potential to revolutionize the way we understand and study male reproductive health.**

### Principal Investigators

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

## IDEAL FERTILITY STUDY: IMPACT OF DIET, EXERCISE AND LIFESTYLE ON FERTILITY

Infertility affects approximately 16% of couples in the United States. Roughly one-third of infertility is attributed to male factors, one-third to female factors, and one-third to combined male and female factors. The couple-based definition of infertility, combined with possible individual-level reproductive disorders, highlights the importance of including both partners in any study assessing modifiable factors and reproductive success.

While urological and/or gynecological disorders are the primary underlying causes for infertility, diet and other modifiable lifestyle and psychosocial factors in both men and women can potentially mitigate or exacerbate fertility problems. Effects of lifestyle and psychosocial factors (here meant to describe dietary and supplement intake, physical activity, stress, depression, anxiety, weight, sleep patterns, smoking, alcohol, caffeine consumption, and sexual activity) on ovulation, conception, implantation, and embryonic and fetal development remain largely unexplored, but offer the potential for low-cost strategies to improve fertility. Well-conducted prospective studies are scarce in regard to how a couple's peri-conceptional and, for women, early pregnancy diet affect fertility. Thus, it is currently unclear how diet, exercise, stress, and other modifiable lifestyle factors impact reproductive outcomes both spontaneously and subsequent to the utilization of assisted reproductive technology. The objective of the IDEAL study is to evaluate the impact of dietary and other lifestyle factors in female partners on prospectively measured pregnancy outcomes among couples seeking fertility treatment (female partners of FAZST participants) in the context of a couple-based approach across a spectrum of fertility and treatment.

IDEAL participants will complete the same activities as male partners in FAZST (a baseline visit with a questionnaire and biospecimen collection; monthly questionnaires updating pregnancy and fertility treatment status; and follow-up for pregnancy outcomes).

**We look forward to the results of the IDEAL study to help us better understand the role of nutrition on fertility treatment success.**

The IDEAL study expands this follow-up to include additional at-home biospecimen collection and the addition of a fitness tracker to wear throughout follow-up. These women will have two scheduled follow-up questionnaires during their fertility treatment. If they become pregnant during the 9-month follow-up period, they will have three additional pregnancy follow-up clinic visits. Data regarding diet, exercise, and lifestyle will be collected throughout follow-up. Recruitment was completed in 2017 and follow-up will continue in 2018.

### **Principal Investigator**

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# Pregnancy

Epidemiologic research of pregnancy focuses on the health and well-being of pregnant women and pregnancy outcomes and their long-term health implications on women and offspring. Branch investigators use a life-course epidemiologic research paradigm. As such, pregnancy complications are understood in the context of pre- and peri-conceptual factors, as well as in relation to later onset diseases in women and effects on their offspring. Branch research includes efforts to understand common complications of pregnancy, such as gestational diabetes, which have short- and long-term implications for maternal and child health. Our work continues to advance the field of fetal growth assessment and to identify factors associated with the timing of delivery, areas where fundamental knowledge is lacking. In addition, our research explores the importance of maternal age and body mass index in relation to gravid diseases, given the increasing percentage of older and heavier first-time pregnant women. The Branch's perinatal research includes the following studies: 1) the Breathe-Wellbeing, Environment, Lifestyle and Lung Function Study; 2) Collaborative Perinatal Project Mortality Linkage; 3) Consortium on Safe Labor; 4) Diabetes & Women's Health Study; 5) NICHD Fetal Growth Studies; 6) Fetal 3D Study; 7) Genetic-epidemiology of early growth variations and links with cardiometabolic diseases; and 8) Gestational Diabetes Mellitus: Epidemiology, Etiology and Health Consequences. A brief description of each study follows.



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

## **BREATHE-WELLBEING, ENVIRONMENT, LIFESTYLE AND LUNG FUNCTION (B-WELL-MOM) STUDY**

The B-WELL-Mom Study 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. Asthma is a common chronic disease and some women experience exacerbation and worsening of their asthma during pregnancy while others improve. The maternal immune response to pregnancy suggests that humoral immune responses are preserved and allergy may be an important predictor in determining the clinical course of women with asthma during pregnancy. 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. Daily exposure to air pollutants provides another challenge to the maternal immune system, both for women with and without asthma. Among asthmatics, the change in severity/control may be differentially affected by external factors including air pollution and dietary antioxidants.

In collaboration with Northwestern University and the University of Alabama at Birmingham, we are recruiting women in early pregnancy (our goal is 400 women with asthma and 100 non-asthmatic women). Recruitment for women with asthma targets 200 with good asthma control and 200 women with poorly controlled asthma prior to pregnancy. Non-asthmatic women have no history of asthma. Three study visits during pregnancy and one post-partum visit are conducted as well as daily measures of lung function and symptoms. A total of 345 women were enrolled and more than 274 of them had delivered by the end of 2017. Enrollment is expected to end in 2018 and followup will continue for approximately one year after the last enrollment to capture the 4-month post-partum visit.

### **Principal Investigator**

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## COLLABORATIVE PERINATAL PROJECT (CPP) MATERNAL MORTALITY LINKAGE STUDY

The Collaborative Perinatal Project (CPP) was a prospective cohort study of 48,197 women with 55,908 pregnancies and 54,390 births enrolled at 12 U.S. clinical centers from 1959-1965. Detailed information was obtained for mothers and their pregnancies upon enrollment into the study and throughout pregnancy, when a physical exam and blood sample were obtained. Upon admission to labor and delivery, a research assistant obtained information on labor, delivery, postpartum course, and neonatal events. A senior obstetrician also completed a summary of the pregnancy and labor and delivery.

The overarching goal of the CPP mortality linkage study is to link this pregnancy cohort with the National Death Index (NDI) to investigate the long-term associations of overall and cause-specific mortality with a spectrum of pregnancy-related complications. The life-course approach in this linkage study will facilitate assessment of hypotheses regarding how early events during pregnancy influence future health at older age. The linkage to the NDI was successfully completed in 2017 and analyses are underway.

Examples of specific hypotheses to be examined are listed below:

1. Pregnancy-induced hypertension, preeclampsia, and gestational diabetes are associated with total mortality and cause-specific mortality.
2. Asthma in pregnancy is associated with total mortality and cause-specific mortality.
3. Preterm delivery is associated with total mortality and cause-specific mortality.
4. A longer-time-to-pregnancy is associated with total mortality and cause-specific mortality.
5. Placental characteristics (e.g. infarcts, thrombi) are associated with total mortality and CVD mortality in offspring.
6. Dysfunctional labor and cesarean delivery are associated with total mortality and cause specific mortality.

### Principal Investigator

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### Division Collaborators

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Lindsey A. Sjaarda, Ph.D., M.S.

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

**Consortium on Safe Labor**

Funded by the National Institutes of Health

Jagteshwar (Una) Grewal,  
Ph.D., M.P.H.Katherine Laughon  
Grantz, M.D., M.S.**CONSORTIUM ON SAFE LABOR**

The Consortium on Safe Labor (CSL) is a multicenter retrospective observational study comprising 228,438 deliveries at 12 U.S. clinical centers (2002-2008) to determine the course of labor associated with optimal maternal and neonatal outcomes. In 2017, researchers found that among women without chronic disease, maternal obesity was associated with preterm delivery and those risks differed by gestational age at delivery, preterm category, and parity, indicating that maternal weight likely influences indicated preterm delivery outside of the underlying chronic conditions that tend to co-occur with obesity. Furthermore, by examining gestational age at delivery in detail, they were able to provide a more comprehensive overview of variations in risk for both spontaneous and indicated preterm delivery. (Kim SS et al. *BJOG: An International Journal of Obstetrics and Gynaecology* 2016).

Gestational and pregestational diabetes complicate up to 9% and 1% of pregnancies in the United States, respectively. Researchers found that these complications were associated with increased risk of neonatal respiratory morbidity, regardless of the probability to deliver at term (Kawakita T et al. *Amer J Perinatol* 2017). Researchers also added to the understanding of the direct effects of placental abruption on neonatal morbidities in a study which determined that placental abruption is associated with increased risk of a number of neonatal morbidities, including stillbirth and neonatal mortality, and these associations persisted even after conditioning on gestational age at delivery and birthweight (Downes et al. *Am J Epidemiol* 2017). A systematic review on this same subject concluded that abruption is associated with a number of adverse outcomes for both mother and child (Downes et al. *Amer J Perinatol* 2017).

**Principal Investigators**

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Raji Sundaram, Ph.D.  
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**Key Publications**

Downes KL, Shenassa ED, Grantz KL. Neonatal Outcomes Associated With Placental Abruption. *American Journal of Epidemiology*. 2017; 186(12):1319-1328. PMID: 28595292

Ha S, Liu D, Zhu Y, Soo Kim S, Sherman S, Grantz KL, Mendola P. Ambient Temperature and Stillbirth: A Multi-Center Retrospective Cohort Study. *Environmental Health Perspectives*. 2017; 125(6):067011. PMID: 28650842. PMCID: PMC5743476

Kawakita T, Bowers K, Hazrati S, Zhang C, Grewal J, Chen Z, Sun L, Grantz KL. Increased Neonatal Respiratory Morbidity Associated with Gestational and Pregestational Diabetes: A Retrospective Study. *American Journal of Perinatology*. 2017; 34(11):1160-1168. PMID: 28738436

Another area of research explored in 2017 was the relationship between racial disparities and neonatal morbidities and mortality in preterm births. Researchers found that risk of neonatal mortality was similar across racial ethnic groups, however, black infants were at significantly higher risk of adverse neonatal morbidities and perinatal death relative to white infants. This finding challenged the notion that black neonates have a survival advantage in the context of preterm birth and emphasized the need to understand underlying mechanisms responsible for racial/ethnic differences in risk of neonatal morbidities (Wallace et al, *Am J Obstet Gynecol* 2017).

We have also linked modeled air pollution data on 30 pollutants to the CSL database to assess its impact on pregnancy outcomes. We quantified air pollution during the three months prior to conception and during pregnancy for each hospital referral region participating in the CSL. In 2017, we expanded our air pollution work to include changes in ambient temperature.

**“As infants of women with gestational and Pregestational diabetes are especially vulnerable to neonatal respiratory morbidity, the timing of delivery should be carefully considered.”**

We found that temperature was associated with early delivery (Ha, *Environmental Health Perspectives* 2017), term low birth weight (Ha, *Environmental Research* 2017), stillbirth (Ha, *Environmental Health Perspectives* 2017) and cardiovascular events at labor and delivery (Ha, *Epidemiology* 2017). We also observed relationships between several air pollutants and gestational hypertension (Zhu *American Journal of Epidemiology* 2017) and both a chronic and acute effect of ozone associated with stillbirth (Mendola *International Journal of Environmental Research and Public Health* 2017).

Collectively, this body of research continues to provide data useful for the ongoing development of clinical guidance regarding the management of contemporary pregnant women. The data is publicly available via the NICHD DASH website, <https://dash.nichd.nih.gov>.

**“We found chronic exposure to both cold and hot temperature was associated with stillbirth risk resulting in as many as 2,100 excess stillbirths each year in the United States.”**



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

## DIABETES & WOMEN'S HEALTH (DWH) STUDY

GDM is a common pregnancy complication. Women who develop impaired glucose tolerance in pregnancy and/or GDM are at substantially increased risk for type 2 diabetes (T2DM) and cardio-metabolic disorders in the years following pregnancy. The genetic and environmental factors underlying the transition from GDM to T2DM and co-morbidities are not well understood. The primary goal of the DWH study is to investigate genetic factors and their interactions with risk factors amenable to clinical or public health intervention in relation to the development of T2DM and co-morbidities among women at high risk, as well as to understand the underlying molecular mechanisms of these relationships.

Data collection for this study leveraged two large existing cohorts: The Nurses' Health Study II (NHS-II) and the Danish National Birth Cohort (DNBC). In the DWH Study, 4,477 women with a history of GDM were enrolled and followed for 2

years to collect information on clinical and environmental factors (e.g., diet, physical activity, sleep duration and quality, and anthropometry). Biospecimens (blood, urine, saliva, and toenails) were collected from women for measurement of genetic and biochemical markers (both pathway specific and non-targeted) relevant to glucose metabolism. The overall design paper was published in 2014 (Zhang et al. *Acta Obstetrica et Gynecologica*

*Scandinavica* 2014). Active data collection for the DWH study was completed in fall of 2016 and analyses are underway with multiple manuscripts in review.

In light of the study's unique design, data analysis was underway while the cohort was being followed. A key finding in the past year to date is our observations that women with prior gestational diabetes have a higher risk of cardiovascular disease, particularly heart attack and stroke; importantly, however, women may be able to reduce or even eliminate their risk for cardiovascular disease by following a healthy lifestyle in the years after giving birth (Tobias et al. *JAMA Internal Medicine* 2017).

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### Key Publications

Tobias DK, Stuart JJ, Li S, Chavarro J, Rimm EB, Rich-Edwards J, Hu FB, Manson JE, Zhang C. Association of History of Gestational Diabetes With Long-term Cardiovascular Disease Risk in a Large Prospective Cohort of US Women. *Journal of the American Medical Association Internal Medicine*. 2017; 177(12):1735-1742. PMID: 29049820.

**“While women with a history of gestational diabetes have a higher risk for cardiovascular disease later in life, it isn't inevitable if they adopt a healthy diet, maintain a healthy weight, exercise regularly and do not smoke”**

**- A hopeful message to women at high risk**



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## NICHD FETAL GROWTH STUDY

Determining optimal fetal growth remains a key research priority, as alterations in growth are associated with various pregnancy disorders and also infant/child morbidity and mortality. Moreover, the early origins of health and disease hypothesis posits that decrements in fetal size may be associated with various chronic diseases such as gynecologic/urologic disorders and non-communicable diseases later in life. Thus, delineating optimal fetal growth has implications for clinical care and population health. The NICHD Fetal Growth Studies is an ambitious observational epidemiologic study that recruited 2,334 low risk pregnant women from 12 U.S. clinical sites, 2009-2013. The cohort comprises 614 Caucasian women, 611 African American women, 649 Hispanic women, and 460 Asian women. Two other cohorts comprising obese women (n=468) and women with dichorionic twin pregnancies (n=171) were also enrolled. Study participants underwent longitudinal 2D- and 3D- ultrasounds at *a priori* defined gestational ages during pregnancy. Nutritional and anthropometric assessments were performed during clinical visits followed by the collection of blood specimens.

In 2017, researchers developed a new formula to calculate gestational age during pregnancy that is more accurate than an existing formula used in clinical practice since 1984, (Skupski et al. *Obstetrics and Gynecology*, 2017). Ultrasound biometric measurements of the fetus are entered into a calculator to estimate gestational age, a process that improves upon estimating gestational age from the reported date of last menstrual period. The study provides specific numbers of days difference between gestational age by ultrasonography and the reported last menstrual date. These data can guide recommendations for when pregnancies should be redated based on ultrasound measurements. Using the NICHD formula, 2–5%

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of women would have more accurate dating, thus preventing interventions for preterm or postterm pregnancy. Up to 25% of the US population undergoes labor induction, providing a significant potential to prevent morbidity from unnecessary interventions.

Researchers also found that greater burden of either stress or depressive symptoms as measured by the Cohen's Perceived Stress Scale and the Edinburgh Postpartum Depression Survey during pregnancy were not associated with alterations in overall fetal weight or individual biometric parameters. (Grobman et al. *Ultrasound Med.* 2017) The similarity in fetal growth existed whether women experienced the exposure of interest relatively

early in pregnancy or persistently throughout pregnancy and this lack of association of perceived stress and depression with fetal growth was extant to a similar degree for women of varying race and ethnicity. Additionally, researchers found that neonatal biometric measures did not vary by Cohen's Perceived Stress Survey class (Wing et al. AJOG. 2017). In this study, latent class trajectory models identified 3 groups/longitudinal trajectories of perceived stress over pregnancy: low, medium, and high scores. Neonatal measures did not vary by perceived stress, nor were the associations modified by maternal race/ethnicity.

Further, researchers found that weight loss or excessive weight gain in the first trimester were not associated with adverse birthweight outcomes, though in the 2nd and 3rd trimester

*NICHD fetal growth studies provide rich research resources for understanding and addressing questions related to fetal growth, pathogenesis of pregnancy complications and neonatal outcomes.*

gestational weight gain (GWG) above or below the reference trajectory was associated with small (SGA) or large for gestational age (LGA; Pugh et al. AJOG. 2017). In this study, latent class trajectory models were used to classify longitudinal

measures of maternal weight, resulting in 4 trajectories: low, reference (per Institute of Medicine recommendations), moderate-high, and high GWG. Compared to the referent group, low GWG increased risk of SGA, while moderate-high and high GWGs were associated with increased risk of LGA. However, these associations were not found when a low or high 1st trimester trajectory did not continue into the 2nd/3rd trimesters, highlighting the importance of GWG specifically in the 2nd/3rd trimesters.

## Obese Cohort

Obesity is common among women of reproductive age and is known to increase the risk for maternal and fetal pregnancy complications. The NICHD Fetal Growth Studies enrolled 468 obese women with singleton pregnancies with the goal of comparing fetal growth patterns between women with obesity and non-obese women. Furthermore, because pregnancy complications such as GDM and preeclampsia are more common in women with obesity, this additional cohort offers the opportunity to examine how fetal growth is impacted by such complications. The researchers found that as early as 32 weeks' gestation, fetuses of obese women had higher weights than fetuses of nonobese women (Zhang et al. JAMA Pediatrics 2018).

## Dichorionic Twin Cohort

Twin gestations represented 3.4% of U.S. births in 2013, yet there is limited contemporary data on the estimation of fetal growth trajectories in twins. The NICHD Fetal Growth Studies enrolled 171 dichorionic twin pregnancies. The primary objective was to empirically define the trajectory of fetal growth in dichorionic twins using longitudinal two-dimensional ultrasonography and to compare the fetal growth trajectories for dichorionic twins with those based on a growth standard developed by our group for singletons. Additional research is focusing on the influences of maternal and pregnancy characteristics on fetal growth.

Twin pregnancies put additional demands on maternal nutritional status due to the increased maternal and fetal tissue mass. However, the current gestational weight gain recommendations for twin pregnancies are provisional due to limited research specific to twins. In 2017, we studied the associations between maternal weight gain across pregnancy

and the growth of the twins as determined by ultrasonography (Hinkle et al. *American Journal of Clinical Nutrition* 2017). We found that maternal weight gain in the second trimester was associated with fetal growth of the twins. Specifically, the findings were driven by an association with the abdominal circumference earlier in second trimester and the long bones (femur and humerus length) later in the second trimester. The larger intrauterine size persisted to delivery, which was demonstrated by the significant association between maternal weight gain in the second trimester and birth weight. These findings should help to direct intervention studies to determine whether modification of a woman's weight gain trajectory can enhance fetal growth and pregnancy outcomes in women with dichorionic twin pregnancies.

### Biomedical Markers in Relation to Gestational Diabetes and Fetal Growth

The NICHD Fetal Growth Studies is the basis for studying the pathogenesis of gestational diabetes (GDM) and fetal growth and to identify factors that can improve early prediction of GDM. This work is grounded within an evolving body of research suggestive of important roles of maternal metabolism and nutrition in the development of GDM and in fetal growth. Pathway specific biomedical markers, and non-targeted metabolomics and lipidomics were measured longitudinally in 107 GDM cases and 214 non-GDM controls in the NICHD Fetal Growth Studies-Singleton Cohort (c.f. *Gestational Diabetes Mellitus: Epidemiology, Etiology, and Health Consequences*). Our recent findings suggest that elevated iron stores may be involved in the development of GDM from as early as the first trimester (Rawal et al. *Diabetologia* 2017). Following this finding, we recently completed an invited review which supports a potential link between greater iron intakes, body iron stores or status before or during pregnancy and an elevated GDM risk

(Zhang et al. *American Journal of Clinical Nutrition* 2017). Analyses on additional biomarkers on both GDM and fetal growth are ongoing.

### Genetics of Fetal Growth

In 2017 we have generated genome-wide data from biospecimens in the NICHD Fetal Growth studies to investigate genetic mechanisms in longitudinal fetal growth variations and to determine the contribution of genetic ancestry for observed disparities in fetal growth among diverse ancestral populations (c.f. *Genetic-epidemiology of early growth variations and links with cardiometabolic diseases*).

#### Key Publications

Grewal J, Grantz KL, Zhang C, Sciscione A, Wing DA, Grobman WA, Newman RB, Wapner R, D'Alton ME, Skupski D, Nageotte MP, Ranzini AC, Owen J, Chien EK, Craigo S, Albert PS, Kim S, Hediger ML, Buck Louis GM. Cohort Profile: NICHD Fetal Growth Studies-Singletons and Twins. *International Journal of Epidemiology*. 2017. PMID: 29025016

Skupski DW, Owen J, Kim S, Fuchs KM, Albert PS, Grantz KL; Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies. Estimating Gestational Age from Ultrasound Fetal Biometrics. *Obstetrics and Gynecology*. 2017 Aug;130(2):433-441. PMID: 28697101.

Zhang C, Hediger ML, Albert PS, Grewal J, Sciscione A, Grobman WA, Wing DA, Newman RB, Wapner R, D'Alton ME, Skupski D, Nageotte MP, Ranzini AC, Owen J, Chien EK, Craigo S, Kim S, Grantz KL, Louis GMB. Association of Maternal Obesity With Longitudinal Ultrasonographic Measures of Fetal Growth: Findings From the NICHD Fetal Growth Studies-Singletons. *Journal of the American Medical Association Pediatrics*. 2017; 172(1):24-31. PMID: 29131898



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

### **FETAL 3D STUDY**

Normal fetal growth is a critical component for a healthy pregnancy and for ensuring the health and well-being of infants throughout childhood and adolescence. Abnormal fetal growth is known to occur in pregnancies complicated by hypertensive disorders and gestational diabetes, among other gravid diseases. Identifying the patterns and timing of abnormal fetal growth in relation to specific pregnancy complications and their timing of onset can inform clinical management. One promising area of research suggests that changes in fetal soft tissue may be the earliest changes that occur in pathologic growth. Three-dimensional volume assessments may be used to detect these changes in soft tissue that result from pathologic growth earlier than conventional 2D measures.

The Fetal 3D Study involves ultrasound measurements from the NICHD Fetal Growth Studies, a prospective cohort of 2,334 low-risk, normal weight women divided among four self-identified race/ethnicity groups: 614 non-Hispanic White, 611 African American, 649 Hispanic, and 460 Asian women. An additional two cohorts included 468 obese women and 171 pregnant women with dichorionic twin gestations.

The overarching research aim of the Fetal 3D Study is to both establish standards for fetal body composition and organ volumes by race/ethnicity and to understand the relationship between gravid diseases and longitudinal changes in fetal body composition (subcutaneous fat, lean mass) and organ measurements (in singletons) over the course of pregnancy, thereby, complementing available data for the Cohort. A second aim is to investigate potentially modifiable factors including maternal BMI, weight gain, longitudinal changes in maternal body composition, nutrition and lifestyle factors with changes in fetal body composition and organ volumes with the goal

of helping to identify exposures or susceptibility that may be associated with adverse outcomes among women and the fetuses they carry. A third aim is to explore the association of biomarkers with longitudinal changes in fetal body composition and organ volumes. A collection of measurements of lean and fat body composition and volume data as proposed in the present study offers great potential of investigating associations of a wide spectrum of pregnancy complications and longitudinal changes in fetal body composition as well as visceral organ size. Data collection is in progress.

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## GENETIC-EPIDEMIOLOGY OF EARLY GROWTH VARIATIONS AND LINKS WITH CARDIOMETABOLIC DISEASES



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

Growth at early stages of human life is associated with cardiometabolic diseases in later life, and shows significant regional and population differences even under similar maternal socioeconomic and nutritional conditions. The underlying mechanisms in early growth-later life cardiometabolic disease links are not clearly known. Furthermore, what underlies population differences in fetal growth and consequent cardiometabolic outcomes has remained puzzling because environmental factors explain only a small proportion of these differences. Therefore, our genetic-epidemiology research program fuses genomic and environmental data with an aim to understand genetic influences in early growth, and genetic mechanisms underlying the link between early growth and cardiometabolic diseases/disparities in diverse ancestral populations. To answer these overarching research questions, genetic studies were designed using banked bio-specimens in two existing cohorts.

The first project aims to unravel the genetics of fetal growth and related maternal cardiometabolic traits in multi-ethnic US populations. Its specific aims are to determine (i) genetic mechanisms in longitudinal fetal growth variations and related maternal cardiometabolic traits, and (ii) the role of genetic ancestry in fetal growth disparities among diverse ancestral populations. For

this project, genome-wide single nucleotide polymorphism genotype data has been generated in 2017 from the NICHD Fetal Growth Studies, a US multi-ethnic study of fetal growth in low risk pregnancies (c.f. NICHD Fetal Growth Study). Data analysis is underway.

*What is the contribution of genetics to early growth variations and early growth-cardiometabolic disease links?*

The second project explores the potential to obtain DNA of high quality from sources other than whole blood. The long-term goal of this project is to leverage existing large-scale population biobanks in future genetic-epidemiology studies of early growth-cardiometabolic links. A pilot study has been designed to evaluate whether stored serum can yield sufficient DNA that is usable for future genomic research using banked serum samples from the Collaborative Perinatal Project, a national pregnancy cohort that enrolled more than 48,000 women and their offspring between 1959 and 1966. The pilot phase experiment is underway and is expected to accomplish extraction of DNA from serum samples, restoring damaged DNA, and evaluation of genotyping performance in genome-wide microarrays and real-time quantitative PCR assays.

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## GESTATIONAL DIABETES MELLITUS: EPIDEMIOLOGY, ETIOLOGY, AND HEALTH CONSEQUENCES



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**“Understanding the epidemiology and etiology of GDM is critical for a development of effective intervention strategies to prevent GDM and to interrupt the vicious cycle across generations involving maternal GDM, childhood obesity, and adulthood-onset diabetes.”**

Gestational diabetes mellitus (GDM), one of the most common pregnancy complications, is related to substantial short-term and long-term adverse health outcomes for both women and their offspring. Understanding the epidemiology and etiology of GDM is critical for the development of effective intervention to prevent GDM and to interrupt the vicious cycle across generations involving maternal GDM, childhood obesity, and adulthood-onset diabetes. Along this line of research, we are conducting studies based on a life course approach:

1. Identification of risk factors (e.g., diet, lifestyle, and genetic factors) for GDM. For instance, we recently observed that women taking supplemental vitamin D before pregnancy had a lower GDM risk (Bao et al. *Journal of Diabetes* 2017). Furthermore, during pregnancy achieving 8-9 hours of sleep a night was associated with a lower GDM risk (Rawal et al. *American Journal of Obstetrics and Gynecology* 2017). These findings suggest that lifestyle modifications before or early in pregnancy have the potential of preventing GDM.
2. Investigation of the pathogenesis of GDM using longitudinally collected biospecimens. Currently, this line of research focuses on a comprehensive panel of biomarkers that are putatively implicated in glucose homeostasis, fetal growth, or both. Targeted and non-targeted metabolomics and lipidomics were also analyzed for the discovery of new pathways. For instance, our recent findings suggest that elevated iron stores may be involved in the development of GDM from as early as the first trimester (Rawal et al. *Diabetologia* 2017). Following

this finding, we recently completed an invited review which supports a potential link between greater iron intakes, body iron stores or status before or during pregnancy and an elevated GDM risk (Zhang et al. *American Journal of Clinical Nutrition* 2017).

3. Investigation of the impact of adverse intrauterine environment such as hyperglycemia and malnutrition on offspring's health. Our recent findings suggest that exposure to GDM, and high levels of refined grains and artificially sweetened beverage in utero was associated with an increased risk of obesity among offspring. (Li et al. *International Journal of Epidemiology* 2017; Zhu et al. *International Journal of Epidemiology* 2017; Zhu et al. *American Journal of Clinical Nutrition* 2017).

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### Key Publications

Li S, Zhu Y, Yeung E, Chavarro JE, Yuan C, Field AE, Missmer SA, Mills JL, Hu FB, Zhang C. Offspring risk of obesity in childhood, adolescence and adulthood in relation to gestational diabetes mellitus: a sex-specific association. *International Journal of Epidemiology*. 2017; 46(5):1533-1541. PMID: 29024955

Zhang C, Rawal S. Dietary iron intake, iron status, and gestational diabetes. *American Journal of Clinical Nutrition*. 2017; 106(Suppl 6):1672S-1680S. PMID: 29070554. PMCID: PMC5701716

Zhu Y, Olsen SF, Mendola P, Halldorsson TI, Rawal S, Hinkle SN, Yeung EH, Chavarro JE, Grunnet LG, Granstrom C, Bjerregaard AA, Hu FB, Zhang C. Maternal consumption of artificially sweetened beverages during pregnancy, and offspring growth through 7 years of age: a prospective cohort study. *International Journal of Epidemiology*. 2017; 46(5):1499-1508. PMID: 28586472

## Infant and Child Health

Infant and child health epidemiology focuses on the factors that affect the growth, development, and health of children from infancy up to adulthood. In 1962, NICHD was established to understand human development throughout the life course, including developmental disabilities and important events during pregnancy. To continue this mission, the infant and childhood health research conducted by the Epidemiology Branch is exploring a multitude of factors associated with child health. These factors range from inherited genetic factors to in utero exposures to conception by infertility treatment, nutrition and pregnancy complications. As evidence accumulates, these early life exposures have also increased in importance as determinants of later health outcomes. As such, the research findings not only identify important determinants of human development early in childhood but may also shed light on long-term health outcomes. The Epidemiology Branch currently has three primary pediatric research areas, including the Birth Defects Research Group, Whole Exome Sequencing in Pediatric Endocrine Diseases, and the Upstate KIDS Studies.

**BIRTH DEFECTS RESEARCH**

James L. Mills,  
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The Birth Defects Research Group is an interdisciplinary team led by NICHD to investigate the causes of birth defects. A primary focus is the effect of dietary factors on birth defect risks including folate, B12 and their metabolites. The collaborating institutions are the NICHD and NHGRI, UC-Berkeley and Trinity College, Dublin.

This group has performed genome wide association genotyping and extensive biochemical testing of over 40 metabolites on 2500 students (Trinity Student Study-TSS) to explore the genetic and biochemical factors that relate to birth defects. The TSS quantitative traits genome wide association study (GWAS) has enabled us to collaborate with other institutions to search for genetic factors affecting metabolites of interest.

Circulating vitamin B12 concentration can be used to diagnose deficiency, but this test has substantial false positive and false negative rates. We conducted genome-wide association studies in which we resolved total serum vitamin B12 into the fractions bound to transcobalamin and haptocorrin: two carrier proteins with very different biological properties. We replicated reported associations between total circulating vitamin B12 concentrations and a common null variant in FUT2. Vitamin B12 bound to haptocorrin (holoHC) remained highly associated with FUT2 rs601338 (p.Trp154Ter). Transcobalamin bound vitamin B12 (holoTC) was not influenced by this variant. HoloTC is the bioactive the form of the vitamin and is taken up by all tissues. HoloHC is only taken up by the liver. Our findings explain some of the observed disparity between use of total B12 or holoTC tests of vitamin B12 status (Velkova et al. Hum Mol Genet).

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**Key Publications**

Boghossian NS, Sicko RJ, Giannakou A, Dimopoulos A, Caggana M, Tsai MY, Yeung EH, Pankratz N, Cole BR, Romitti PA, Browne ML, Fan R, Liu A, Kay DM, Mills JL. Rare copy number variants identified in prune belly syndrome. *European Journal of Medical Genetics*. 2017. PMID: 29174092

Dimopoulos A, Sicko RJ, Kay DM, Rigler SL, Druschel CM, Caggana M, Browne ML, Fan R, Romitti PA, Brody LC, Mills JL. Rare copy number variants in a population-based investigation of hypoplastic right heart syndrome. *Birth Defects Research*. 2017; 109(1):8-15. PMID: 28009100. PMCID: PMC5388571

Dimopoulos A, Sicko RJ, Kay DM, Rigler SL, Fan R, Romitti PA, Browne ML, Druschel CM, Caggana M, Brody LC, Mills JL. Copy number variants in a population-based investigation of Klippel-Trenaunay syndrome. *American Journal of Medical Genetics Part A*. 2017; 173(2):352-359. PMID: 27901321

Other research involves examining quantitative traits in The TSS GWAS. Samples have been stored for further analysis of genetic factors as well. Our team collaborates with groups that have a strong hypothesis that a metabolite of interest is influenced by genetic variants and wish to obtain samples to assay to test that hypothesis. By sharing our genome wide data, we can determine how genetic variants are related to high or low concentrations of the metabolite of interest.

Dr. Mills published a related editorial in JAMA on strategies for preventing neural tube defects by fortified foods and dietary supplements.

### **Genetic Factors in Birth Defects Study**

The Genetic Factors in Birth Defects Study is an interdisciplinary study led by NICHD to identify genetic risk factors for a wide range of major birth defects. The original collaborating institutions were NICHD, NHGRI and the NY Department of Health. Stanford University, the University of Iowa, CDC and the California Department of Health have joined the collaboration.

In 2017 we reported on copy number variants (CNV) in uncommon birth defects. We found that CNVs in Ebstein anomaly overlapped, or were close to, genes involved in early myocardial development and important transcription factors.

These findings add important support to the relationship between Ebstein anomaly and cardiomyocyte development.

Rare CNVs were found in almost half our cases of Prune Belly Syndrome. Several were involved in mesoderm development, muscle and urinary tract morphogenesis. These suggest that genetic factors are more important than previously appreciated in this syndrome.

Split hand/foot malformation genes are known, but most cases remain unexplained. We identified seven rare, presumed deleterious variants in our cases. Of note, one was in an important limb development gene.

In the first CNV study of the rare defect, hypoplastic right heart syndrome (HRHS), we found rare CNVs in 17 of 32 cases. Importantly, affected regions included LBH, a gene involved in right ventricular hypoplasia, SOS, a gene that is important in pulmonary valve and ventricular development, and a deletion upstream from a TGF-beta ligand (ITTB8) that causes lethal cardiac phenotypes. This work provides important leads for future research and strong evidence for a role in genetic factors in HRHS.

Klippel Trenaunay Syndrome (KTS) is a rare defect that was thought to be sporadic. However, we identified a total of 15 rare CNVs in seven of 17 cases. Two cases had deletions involving transcripts of HDAC9, a histone deacetylase essential for angiogenic sprouting of endothelial cells. Other CNVs including areas important in histone acetylation and chromatin modification were found. These findings suggest that chromatin modification may be important in regulation vascular development during embryogenesis.

In summary, our recent CNV investigations have demonstrated that genetic factors may be more important than previously appreciated.



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## UPSTATE KIDS STUDY

The Upstate KIDS Study was designed to determine if fecundity and various infertility treatments adversely affect the growth, motor, and social development of children from birth through three years of age. A matched-exposure cohort design was used to establish a primary cohort of infants conceived with and without infertility treatment who resided in the 57 counties comprising Upstate New York State (exclusive of New York City) using the “infertility check box” on the birth certificate for cohort selection. Parents and their infants were recruited at approximately 4-8 months of infant age. The cohort comprises 1,297 “exposed” infants with reported infertility treatment and 3,692 “unexposed” infants without reported treatment who were frequency matched on residence and plurality at 1:3 ratio. All co-twins of study participants and higher order multiples were enrolled in separate cohorts, and followed similarly.

Parental participation included completion of: 1) a baseline and longitudinal questionnaires on reproductive and medical history, environmental exposures and infant characteristics and 2) parental developmental rating instruments (i.e., Ages and Stages at 4, 8, 12, 18, 24, 30, 36 months of age and the Modified Checklist for Autism in Toddlers at 18 and 24 months). The cohort was linked with the Society for Assisted Reproductive Technologies’ database and additional linkages to New York State health registries for information such as immunizations, hospitalizations, lead screening, congenital malformations, and cancer diagnosis. With parental consent obtained at the 8-month screening, residual newborn dried blood spots were used for the analysis of immunoglobulins and inflammatory and environmental chemical biomarkers. Due to the low limit of detection of some of the environmental biomarkers, a novel pooled sampling approach with the consented blood spots was

designed and implemented. Diagnostic visits with 601 children were conducted at three specialized developmental centers across the state. The study ended data collection in June 2014. The two main publications of the study found that children conceived by infertility treatment did not grow or develop differently from birth through 3 years of age than children not conceived by treatment, presenting a reassuring message to couples considering such treatments and also health practitioners.

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### **Key Publications**

Broadney MM, Chahal N, Michels KA, McLain AC, Ghassabian A, Lawrence DA, Yeung EH. Impact of parental obesity on neonatal markers of inflammation and immune response. *International Journal of Obesity (Lond)*. 2017; 41(1):30-37. PMID: 27780976. PMCID: PMC5209273

Ghassabian A, Sundaram R, Chahal N, McLain AC, Bell E, Lawrence DA, Yeung EH. Determinants of neonatal brain-derived neurotrophic factor and association with child development. *Development and Psychopathology*. 2017; 29(4):1499-1511. PMID: 28462726

Yeung EH, Sundaram R, Ghassabian A, Xie Y, Buck Louis G. Parental Obesity and Early Childhood Development. *Pediatrics*. 2017; 139(2). PMID: 28044047. PMCID: PMC5260147



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### UPSTATE KIDS CVD FOLLOW-UP STUDY

The Upstate KIDS Cohort described above is being followed to age 8-9 years with particular focus on childhood cardio-metabolic outcomes (i.e., obesity, high blood pressure, metabolism). Recent studies have drawn attention to the concern that children conceived by infertility treatment may have higher cardio-metabolic risk than spontaneously conceived children. Low birth weight and preterm birth, both outcomes, which are increased among singletons and twins conceived by IVF and other treatments, are tied to cardiovascular risk and mortality later in adult life. These links suggest that children conceived by infertility treatment may have increased cardio-metabolic risk later in life. Increased risk among those having good birth outcomes, however, cannot be ruled out, with some studies showing differences in subclinical measures of vascular function. In addition, the mechanisms of such effects on health differences among those conceived by infertility treatment remain unclear. Although scientists have suggested epigenetic mechanisms for the underlying differences, the supporting evidence has been scarce. As such, a secondary objective of the Upstate KIDS CVD Follow-Up Study is to assess epigenetic differences as measured by DNA methylation using collected biospecimens among approximately 900 children.

In collaboration with the University at Albany-SUNY, the study is continuing to re-enroll 3,200 children from the original cohort and follow them for an additional three years by annual questionnaires. Clinic visits are being conducted for measures of anthropometry, body fat, blood pressure, arterial stiffness and lung inflammation as well as collection of blood, urine, and saliva. Families will also be invited to mail saliva samples when the children reach 8 years of age. Epigenetic analyses will be conducted using collected biospecimens. Re-enrollment began the fall of 2015 and will continue through spring of 2019.

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## WHOLE EXOME SEQUENCING IN PEDIATRIC ENDOCRINE DISEASE

Genetic factors are known to be important causes of a number of pediatric endocrine diseases. The potential genetic contribution to others has yet to be investigated. Dr. Mills has set up a research group in collaboration with Dr. Constantine Stratakis, Scientific Director, NICHD to investigate potential genetic causes of rare pediatric endocrine diseases. Whole exome sequencing has been performed on several diseases through DIPHR via a contract with the University of Minnesota. Laboratory follow up studies are being performed by the DIR, NICHD. The collaborating institutions are NICHD (DIPHR and DIR), NINDS, the University of Minnesota, and the New York State Department of Health.

The *CABLES1* cell cycle regulator participates in the adrenal-pituitary negative feedback, and its expression is reduced in corticotropinomas, pituitary tumors with a largely unexplained genetic basis. We investigated the presence of *CABLES1* mutations/copy number variations and their associated clinical, histopathological and molecular features in patients with Cushing's disease. Four potentially pathogenic missense variants in *CABLES1* were identified. The variants impaired the ability of *CABLES1* to block cell growth in a mouse corticotropinoma cell line (AtT20/D16v-F2). *CABLES1* might link two of the main molecular mechanisms altered in corticotropinomas: the cyclin-dependent kinase/cyclin group of cell cycle regulators and the epidermal growth factor receptor signaling pathway.

Somatic mutations in the ubiquitin-specific protease 8 (*USP8*) gene have been recently identified as the most common genetic alteration in patients with Cushing disease (CD). However, the frequency of these mutations in the pediatric population has not been extensively assessed. The *USP8* gene was fully sequenced in both germline and tumor DNA samples from 42 pediatric patients with CD. Five different *USP8* mutations

(three missense, one frameshift, and one in-frame deletion) were identified in 13 patients (31%), all of them located in exon 14 at the previously described mutational hotspot. Patients harboring somatic *USP8* mutations had a higher likelihood of recurrence.

In contrast with other pituitary tumor types, the genetic causes of corticotropinomas are largely unknown. This study reports a case of Cushing disease (CD) due to a loss-of-function mutation in *PRKARIA*, providing evidence for association of this gene with a corticotropinoma.

### Principal Investigator

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

### Division Collaborators

Wei Zhang, Ph.D.

### Key Publications

Faucz FR, Tirosh A, Tatsi C, Berthon A, Hernandez-Ramirez LC, Settas N, Angelousi A, Correa R, Papadakis GZ, Chittiboina P, Quezado M, Pankratz N, Lane J, Dimopoulos A, Mills JL, Lodish M, Stratakis CA. Somatic *USP8* Gene Mutations Are a Common Cause of Pediatric Cushing Disease. *Journal of Clinical Endocrinology and Metabolism*. 2017; 102(8):2836-2843. PMID: 28505279. PMCID: PMC5546857

Hernandez-Ramirez LC, Gam R, Valdes N, Lodish MB, Pankratz N, Balsalobre A, Gauthier Y, Faucz FR, Trivellin G, Chittiboina P, Lane J, Kay DM, Dimopoulos A, Gaillard S, Neou M, Bertherat J, Assie G, Villa C, Mills JL, Drouin J, Stratakis CA. Loss-of-function mutations in the *CABLES1* gene are a novel cause of Cushing's disease. *Endocrine-Related Cancer*. 2017; 24(8):379-392. PMID: 28533356. PMCID: PMC5510591

Hernandez-Ramirez LC, Tatsi C, Lodish MB, Faucz FR, Pankratz N, Chittiboina P, Lane J, Kay DM, Valdes N, Dimopoulos A, Mills JL, Stratakis CA. Corticotropinoma as a Component of Carney Complex. *Journal of the Endocrine Society*. 2017; 1(7):918-925. PMID: 29264542. PMCID: PMC5686778

## Methodologic Research in Epidemiology

The Epidemiology Branch conducts methodologic research motivated by the many unique aspects of human reproduction and development across the lifespan. The specific methodologic areas in which the Epidemiology Branch is conducting research include biomarker analytical development and causal inference in reproductive epidemiology.

## **BIOMARKER ANALYTICAL DEVELOPMENT**



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



Neil J. Perkins, Ph.D., M.S.

Biomarkers are, and will continue to be, an integral part of epidemiological research, making substantial contributions to our understanding of disease pathways and processes. New and emerging biomarkers are essential to this continued understanding. As such, novel study designs that reduce cost and leverage statistical efficiency are also a major focus of Division researchers (Lash and Schisterman, *Epidemiology* 2017; Schildcrout JS et al. *Epidemiology* 2017; Schildcrout JS et al. *Epidemiology* 2017). These methods focus on outcome dependent sampling where cost are reduced by measuring biomarkers in a principally designed subset of the samples in the full cohort. Efficiency is maximized by designing a subset guided by the outcome of interest which is often known prior to expensive biomarker exposure measurement. Division researchers continue to adapt these efficient designs and developed methods making outcome dependent sampling equally useful in the analysis of a broad spectrum of cross sectional as well as longitudinal epidemiologic data. These issues have served as the motivation for numerous papers, as well as a collaborative effort funded by the Long-Range Research Initiative of the American Chemistry Council, with the goal of providing the methodological tools necessary to assess and address issues related to study design, biomarker measurement, and biomarker analytic assessment.

### **Principal Investigators**

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

Neil J. Perkins, Ph.D., M.S.

### **Division Collaborators**

Lindsey A. Sjaarda, Ph.D., M.S.

Jennifer Weck, Ph.D.

### **2017 Biomarker Analytical Development Publications**

Lash TL, Schisterman EF. New Designs for New Epidemiology. *Epidemiology*. 2017; 29(1):76-77. PMID: 29068839

Schildcrout JS, Schisterman EF, Aldrich MC, Rathouz PJ. Outcome-related, Auxiliary Variable Sampling Designs for Longitudinal Binary Data. *Epidemiology*. 2017; 29(1):58-66. PMID: 29068841. PMCID: PMC5718926

Schildcrout JS, Schisterman EF, Mercaldo ND, Rathouz PJ, Heagerty PJ. Extending the Case-Control Design to Longitudinal Data: Stratified Sampling Based on Repeated Binary Outcomes. *Epidemiology*. 2017; 29(1):67-75. PMID: 29068838. PMCID: PMC5718932



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

## CAUSAL INFERENCE IN REPRODUCTIVE EPIDEMIOLOGY

Causal inference and the usefulness of directed acyclic graphs (DAGs) as a tool for evaluating causal relations and addressing questions of model specification are well established in epidemiology. Division researchers have the goal of extending the methodological framework for causal inference to reproductive and perinatal epidemiology. The objective of this research is to develop methods using causal inference tools, specifically as they improve researchers' understanding of various sources of bias including model misspecification, the role of gestational age (GA) in analysis of perinatal data and time-varying confounding. Division researchers demonstrate how highly correlated data ubiquitous in epidemiologic research, particularly in nutritional and environmental epidemiology, arise and provide analytic guidance, using a directed acyclic graph approach for three fundamental structural scenarios: intermediates, confounders, and colliders (Schisterman et al. *Epidemiology* 2017). The findings highlight, via bias and variance, the importance of considering the causal framework under study when specifying regression models. They also highlight that choosing to ignore the causal structure can lead to biased effect estimation that is more harmful than increased variance from high correlation.

Researchers here have diligently investigated data issues concerning sources of laboratory measurement errors and missing data. This understanding has provided insight to data issues commonly present, yet largely ignored, in epidemiological research. These issues motivated a collaborative effort funded by the Long-Range Research Initiative of the American Chemistry Council, to provide the methodological tools necessary to understand, assess and perform proper inference in the presence of missing data. Through a three paper series, the group demonstrates the impact of missing data under various missingness mechanisms and educates on the principle use and

impact of simple parametric and semi-parametric methods to account for missing data. These papers should be an impactful and vital resource to increase efficiency and reduce bias due to missing data, and improve analyses across the field of epidemiology.

### Principal Investigator

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

### Division Collaborators

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

Neil J. Perkins, Ph.D., M.S.

### 2017 Causal Inference in Reproductive Epidemiology Publications

Harel O, Mitchell EM, Perkins NJ, Cole SR, Tchetgen Tchetgen EJ, Sun B, Schisterman EF. Multiple Imputation for Incomplete Data in Epidemiologic Studies. *American Journal of Epidemiology*. 2017. PMID: 29165547

Perkins NJ, Cole SR, Harel O, Tchetgen Tchetgen EJ, Sun B, Mitchell EM, Schisterman EF. Principled Approaches to Missing Data in Epidemiologic Studies. *American Journal of Epidemiology*. 2017. PMID: 29165572

Schisterman EF, Perkins NJ, Mumford SL, Ahrens KA, Mitchell EM. Collinearity and Causal Diagrams: A Lesson on the Importance of Model Specification. *Epidemiology*. 2017; 28(1):47-53. PMID: 27676260. PMCID: PMC5131787

Sun B, Perkins NJ, Cole SR, Harel O, Mitchell E, Schisterman EF, Tchetgen Tchetgen EJ. Inverse Probability Weighted Estimation for Monotone and Nonmonotone Missing Data. *American Journal of Epidemiology*. 2017. PMID: 29165557

## Health Behavior Branch

The mission of the [Health Behavior Branch](#) is to: 1) conduct research on child and adolescent health and health-related behavior; 2) provide service to the Division, Institute, and scientific community through consultation, collaboration and assistance to advance the goals of science and population health; and 3) mentor and train young researchers.



Stephen E. Gilman, Sc.D.

The Health Behavior Branch's research identifies determinants of health, health-related behavior, and health disparities from the prenatal period to early childhood, adolescence, and young adulthood, and tests the effectiveness of social, behavioral and environmental strategies to improve and protect child, adolescent and maternal health. The research is conducted within a life course, developmental framework and emphasizes family and neighborhood contexts as key aspects of the social and physical environments that influence health, health-related behaviors, and healthy development. In addition, our branch is committed to understanding the dynamic interplay between social and biological characteristics of individuals and their environments in order to identify modifiable factors at multiple levels that could be targeted by social and behavioral interventions. Our studies are guided by theories and methods from the social and behavioral science disciplines, ranging in focus from basic science approaches to understand the etiology of health and health-related behaviors to the translation of social and behavioral science research into the design and evaluation of interventions.

The Branch's research is organized along axes of substantive areas of research and key developmental stages. Our program of research on young drivers centers on adolescence, and our program of research on behavioral interventions in health care focuses on pregnancy and early childhood. Our branch's studies on mental health and health disparities take a life course approach, spanning the prenatal period through childhood and adolescence, including developmental mechanisms that reach into middle and older adulthood. Finally, our branch has a dedicated program of research on adolescent health.

### Staff

Stephen E. Gilman, Sc.D., Investigator and  
Acting Branch Chief  
Risë B. Goldstein, Ph.D., M.P.H., Staff Scientist  
Denise Haynie, Ph.D., M.P.H., Staff Scientist  
Leah Lipsky, Ph.D., Staff Scientist  
Tonja Nansel, Ph.D., Senior Investigator  
Bruce G. Simons-Morton, Ed.D., M.P.H.,  
Senior Investigator

A defining feature of our branch's research is its integration of approaches from diverse disciplines including psychology (community, clinical, and developmental), nutrition, health education, and epidemiology (social, psychiatric, developmental). Collaborations with researchers in the Division and, more broadly, throughout the NIH's Intramural Research Program, further enhance the trans-disciplinary nature of our work. Our research portfolio addresses major contributors to the population burden of disease including obesity, cardiovascular disease, mental illness, and injury. Its developmental focus strives to identify and intervene on pathways to disease early in the life course so as to have maximal impact on population health.

### Fellows

Lauren Blau, B.A., Summer Intern  
Katie Dempster, B.A., Postbaccalaureate Fellow  
(departed in 2017)  
Johnathon Ehsani, Ph.D. (departed in 2017)  
Miriam Eisenberg, Ph.D., Postdoctoral Fellow  
(departed in 2017)  
Brian Fairman, Ph.D., Postdoctoral Fellow  
Pnina Gershon, Ph.D., Postdoctoral Fellow  
Matthew Grossman, B.A., Postbaccalaureate Fellow  
(departed in 2017)  
Christine Hill, B.S., Postbaccalaureate Fellow  
Kuba Jeffers, B.A., Postbaccalaureate Fellow  
Indra Kar, B.A., Postbaccalaureate Fellow  
(departed in 2017)  
Liat Korn, Ph.D., Special Volunteer (departed in 2017)  
Awapuhi Lee, B.A., Postbaccalaureate Fellow  
(departed in 2017)  
Jeremy Luk, Ph.D., Postdoctoral Fellow  
Namrata Sanjeevi, Ph.D., Postdoctoral Fellow

### 2017 Awards

NEXT Generation Health Study, NICHD Collaboration Award  
Tonja Nansel, NICHD Merit Award



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

## ADOLESCENT HEALTH BEHAVIOR

Adolescence is a critical period for the development of patterns of behavior associated with subsequent morbidity and mortality. These behaviors include diet, physical activity, sleep, substance use, and driving. Influences on these behaviors include personal and environmental factors, including social influences and physical contexts (e.g., place of residence, local programs, policies, and resources). Longitudinal patterns of and changes in adolescent behavior are of particular interest, given the general lack of cohort data. Currently, we are conducting the NEXT Generation Health Study, a longitudinal study of adolescent health behavior in a national cohort of 10th graders followed for seven years.

## NEXT GENERATION HEALTH STUDY

Adolescence is a critical period for the development of unhealthy patterns of behavior associated with subsequent morbidity and mortality. The influences of the social (peers and parents) and physical (e.g., place of residence, local programs, policies, and resources) environments may be important during transitions in development. The NEXT Generation Health Study (NEXT) follows a nationally representative sample during the transition from high school to early adulthood.

The NEXT cohort of adolescents, approximately 16 years of age, was recruited in 2010 and assessed annually for seven years. The primary goals are to examine trajectories of adolescent health status and behaviors. NEXT assesses cardiovascular risk factors and adolescent health behaviors. At the Wave 7 data collection, we retained 81% of the originally enrolled cohort. A subsample of 560 study participants (NEXT Plus) provided additional objective data on diet, physical activity, sleep, peer networks, and driving. Blood samples were obtained to assess cardiovascular risk, along with



### **Principal Investigator**

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

### **Division Collaborators**

Stephen E. Gilman, Sc.D.

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Danping Liu, Ph.D. (departed in 2017)

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

Leah Lipsky, Ph.D.

Risë B. Goldstein, Ph.D., M.P.H.

Liat Korn, Ph.D.

Jeremy Luk, Ph.D.

Brian Fairman, Ph.D.

Namrata Sanjeevi, Ph.D.

Miriam Eisenberg, PhD. (departed in 2017)

Joseph Bible, Ph.D. (departed in 2017)

Benjamin Gee, B.A.

Indra Kar, B.A.

Christine Hill, B.S.

Kellienne Sita, B.S.

Jacob Jeffers, B.A.

Kathleen Dempster, B.S. (departed in 2017)

Awapuhi Lee, B.A. (departed in 2017)

Matthew Grossman, B.A. (departed in 2017)

saliva for genetic analysis. Eighty-one percent of this subsample was retained at the Wave 7 assessments.

In 2017, we examined patterns of tobacco and cannabis use during the transition from high school to post high school, and found that participants not enrolled in post-secondary education were more likely to smoke tobacco compared to those attending

***The NEXT Generation Health Study is one of very few national studies to follow cohorts from adolescence to early adulthood, assessing a range of health behavior and health status outcomes.***

a four-year college; no associations were found for participant residence nor work status. No associations were found for cannabis use. A longitudinal analysis of sleep characteristics and alcohol use revealed a preference for later morning wake time and bedtimes was predicted by previous year alcohol use and, simultaneously, alcohol use predicted by previous year bedtimes. Peer influence on driving behavior was examined. Participants with peers who report frequent texting while driving were more likely to text while driving one year later.

Earlier work on trajectories of health behaviors will be extended to include patterns of these behaviors four years post-high school. Several studies are examining longitudinal objective measures of dietary intake (ASA24 dietary recalls), physical activity (accelerometer data), and sleep (actigraphy data).

Six waves of the survey data were released on the NICHD Data and Specimen Hub (DASH).

### Key Publications

Haynie DL, Lewin D, Luk JW, Lipsky LM, O'Brien F, Iannotti RJ, Liu D, Simons-Morton BG. Beyond sleep duration: Bidirectional associations between chronotype, social jetlag, and drinking behaviors in a longitudinal sample of US high school students. *Sleep*. 2017. PMID: 29237053

O'Brien F, Simons-Morton B, Chaurasia A, Luk J, Haynie D, Liu D. Post-High School Changes in Tobacco and Cannabis Use in the United States. *Substance Use and Misuse*. 2017; 53(1):26-35. PMID: 28742412

Simons-Morton B, Haynie D, O'Brien F, Lipsky L, Bible J, Liu D. Variability in measures of health and health behavior among emerging adults 1 year after high school according to college status. *Journal of American College Health*. 2017; 65(1):58-66. PMID: 27661849. PMCID: PMC5549460



Tonja Nansel, Ph.D.



## EATING BEHAVIORS IN CHILDREN AND FAMILIES

Poor diet (not including malnutrition) is now the largest contributor to early death globally. Relative to dietary guidelines, diet quality in the U.S. population is characterized by excessive intake of total energy, added sugar, fat and sodium, and inadequate intake of fruits, vegetables and whole grains. Our program of research uses experimental and observational methods to investigate influences on, and interventions to improve, eating behaviors leading to optimal growth and development in children and families.

## CULTIVATING HEALTHFUL ENVIRONMENTS IN FAMILIES OF YOUTH WITH TYPE 1 DIABETES (CHEF)

Medical nutrition therapy in type 1 diabetes focuses on integrating the insulin regimen and carbohydrate estimation into the family's lifestyle, conforming to preferred meal routines and food choices. Diets of children with type 1 diabetes are low in fruits, vegetables, and whole grains, and high in saturated fat. Poor diet quality is particularly concerning due to the increased risk of cardiovascular disease associated with type 1 diabetes. However, scant research has examined individual and family determinants of dietary intake, the effectiveness of intervention to improve dietary intake, or the impact of improved diet quality on glycemic control in youth with type 1 diabetes. Intervention studies in other clinical populations demonstrate substantial challenges in promoting healthful eating, and suggest the importance of family-based approaches that enhance motivation, facilitate skills, and assist families in overcoming barriers to healthful eating.

This program of research includes the Cultivating Healthy Environments in Families of Youth with Type 1 Diabetes Study (CHEF), a randomized controlled trial of a behavioral nutrition intervention, and the Pregnancy Eating Attributes Study (PEAS), an observational study investigating influences on dietary intake and weight change during pregnancy and postpartum.

### **Principal Investigator**

Tonja R. Nansel, Ph.D.

### **Division Collaborators**

Aiyi Liu, Ph.D.

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Jennifer Weck, Ph.D.

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The CHEF randomized controlled trial demonstrated the efficacy of a family-based behavioral intervention to improve overall diet quality and specifically intake of whole plant foods (Nansel et al. 2015). Our work on the CHEF study in 2017 built on the successful primary outcomes of the intervention by examining additional subsidiary research questions. Child pickiness is commonly believed to be a substantial barrier to improving diet quality, as these children typically demonstrate food refusal, limited dietary variety, and poor diet quality. However, among youth in the CHEF trial, diet quality improved to a greater extent in picky eaters compared to non-picky eaters, suggesting that diet quality of picky eaters can be improved without changing their underlying pickiness (Nansel et al. 2017). Additionally, we demonstrated the key role of parents in influencing child's dietary intake, showing parent's cognitions about, and motivations for, healthful eating were associated with the child's diet quality for both children and adolescents (Eisenberg et al. 2017). We also examined the longitudinal associations of BMI and body composition with cardiovascular risk factors, finding that BMI and adiposity were positively associated with several indicators of increased cardiometabolic risk including higher triglycerides and low-density lipoprotein cholesterol, c-reactive protein, and blood pressure (Lipsky et al. 2017).

### Key Publications

Eisenberg MH, Lipsky LM, Gee B, Liu AY, Nansel TR. Parent healthful eating attitudes and motivation are prospectively associated with dietary quality among youth with type 1 diabetes. *Vulnerable Children and Youth Studies*. 2017; 12(3):226-240. PMID: WOS:000418528200005

Lipsky LM, Gee B, Liu A, Nansel TR. Body mass index and adiposity indicators associated with cardiovascular biomarkers in youth with type 1 diabetes followed prospectively. *Pediatric Obesity*. 2017; 12(6):468-476. PMID: 27417272

Nansel T, Lipsky L, Haynie D, Eisenberg M, Dempster K, Liu A. Picky eaters improved diet quality in a randomized behavioral intervention trial in youth with type 1 diabetes. *Journal of the Academy of Nutrition and Dietetics*. In Press.



Tonja Nansel, Ph.D.

## **PREGNANCY EATING ATTRIBUTES STUDY (PEAS)**

The rising prevalence of maternal overweight/obesity and excessive gestational weight gain poses serious public health concerns due to the contribution of these factors to increased risk of adverse maternal and child health outcomes. Weight management and dietary change interventions in the general population and pregnant women alike have achieved only marginal success characterized by suboptimal initial and/or long-term maintenance of weight control and diet change, indicating the need to identify more effective modifiable targets and strategies. An emerging hypothesis, supported by recent findings from neuroscience research, posits that energy homeostatic processes are overridden by “hedonic eating,” in which food intake is motivated by the neural reward response to food in the absence of energetic requirements. The relative strength of this reward response (“food reward sensitivity”) varies between individuals and has been positively associated with body weight and weight change in small samples, supporting the need for further investigation in population-based samples.

PEAS is an observational cohort study examining the role of food reward sensitivity in weight change and dietary intake during pregnancy and postpartum. The study further examines the importance of food reward in the context of behavioral control, the home food environment, and other aspects of eating behavior, as well as weight-related biomedical, psychosocial and behavioral factors including physical activity, stress, sleep, depression, and genetics. Four hundred and fifty-eight women of varying baseline weight status were enrolled early in pregnancy (before 12 weeks postpartum) and are being followed until 1 year postpartum. Data collection methods include multiple non-consecutive 24-hour diet recalls, anthropometrics, biospecimens, medical record abstraction, questionnaires, functional magnetic

resonance imaging (fMRI), focus groups, and the laboratory-based eating in the absence of hunger (EAH) paradigm. Infant anthropometrics and feeding practices are also assessed. Primary exposures of interest include maternal food reward sensitivity, behavioral control and the home food environment. Primary outcomes include gestational weight gain, postpartum weight retention and maternal diet quality. Recruitment for the study was completed in 2016. Follow-up of participants is ongoing.

### **Principal Investigator**

Tonja R. Nansel, Ph.D.

### **Division Collaborators**

Aiyi Liu, Ph.D.

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

Leah Lipsky, Ph.D.

Miriam Eisenberg, Ph.D.

Namrata Sanjeevi, Ph.D.

Jennifer Weck, Ph.D.

Katie Dempster, B.A.

Christine Hill, B.A.

Lauren Blau, B.A.

## Research on Young Drivers

Crash risk is highest early in licensure, declining rapidly for a period of months, then slowly over a period of years, reaching adult levels when young adults are in their mid-twenties. Compared with older drivers, teenagers and young adults are more likely to speed, drive in a risky and illegal manner, and engage in distracting secondary tasks, characteristics that contribute to their increased crash rates. However, little is known about how teenage driving behavior varies over time. Research questions of compelling interest to our research team include the following: How and what do novices learn that contributes to safe driving behavior? What is the variability in teen driving risk over time from individual characteristics and environmental conditions? How can teen driving safety be improved?

The HBB program of research on young drivers encompasses studies covering multiple aspects of driving risk and prevention. Our research includes survey, observation, naturalistic driving, test track, and simulation methods. Notably, we have conducted several of the first naturalistic driving studies with teenage

drivers using highly sophisticated data acquisition systems installed in teenagers' vehicles. Recently, we conducted a unique series of experimental studies using driving simulation to evaluate the effects of teenage passengers on teenage driving performance, with functional magnetic resonance imaging (fMRI) and assessments of executive functioning integrated into this research. Thus, we employ sophisticated methodology to answer key research questions about teenage driving. HBB studies on teenage driving performance include the following: (1) the Teen Passenger Experimental Study, a series of experimental simulated driving studies; (2) the Supervised Practice driving study, a naturalistic driving study with instrumented vehicles that follows a cohort of 90 teens and their parents during the learner and independent driving period; (3) the Uniform Naturalistic Teenage Driving Study that combines data from three naturalistic driving studies to enable examination of changes in crash and kinematic (speeding and elevated gravitational force event) rates according to driver age and experience; and (4) NEXT Generation Health Study Driving Research.

## NATURALISTIC TEENAGE DRIVING STUDY: THE EFFECT OF DRIVING EXPERIENCE ON THE DRIVING PERFORMANCE OF NEWLY LICENSED TEENS (NTDS)



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

The NTDS was among the first studies to assess driving risk objectively among teenage drivers. The purpose was to assess the prevalence and determinants of crash/near crash and dangerous driving behavior. The sample included 42 newly licensed teenage drivers and their parents. The primary vehicle of each participating teen was instrumented with data acquisition systems that included an accelerometer, GPS, and cameras mounted near the rear-view mirror that looked forward and rearward and at the driver's face. A blurred still photo was taken of the vehicle occupants using a fisheye lens to enable identification of occupants by age and sex. Data were continually recorded and stored over the first 18 months of driving. Data collection was completed in 2014. Publications based on this study have examined methods, driving exposure, crash risk, and dangerous driving.

### Principal Investigator

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### Division Collaborators

Johnathan Ehsani, Ph.D.

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Federico Vaca, M.D.

### Key Publications

Ehsani JP, Haynie D, Ouimet MC, Zhu C, Guillaume C, Klauer SG, Dingus T, Simons-Morton BG. Teen drivers' awareness of vehicle instrumentation in naturalistic research. *Journal of Safety Research*. 2017; 63:127-134. PMID: 29203010. PMCID: PMC5728669

Ehsani JP, Klauer SG, Zhu C, Gershon P, Dingus TA, Simons-Morton BG. Naturalistic assessment of the learner license period. *Accident Analysis and Prevention*. 2017; 106:275-284. PMID: 28654843. PMCID: PMC5610634

Li Q, Guo F, Klauer SG, Simons-Morton BG. Evaluation of risk change-point for novice teenage drivers. *Accident Analysis and Prevention*. 2017; 108:139-146. PMID: 28881279. PMCID: PMC5644313

## SUPERVISED PRACTICE DRIVING STUDY: THE EFFECT OF SUPERVISED PRACTICE DRIVING ON INDEPENDENT DRIVING PERFORMANCE (SPD)



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

It is logical that more supervised practice driving prior to licensure would lead to improved independent driving outcomes. It may be that at least some adolescents who quickly learn to manage a vehicle receive little supervised practice driving prior to licensure while other adolescents for whom managing the vehicle is more difficult receive a great deal of supervised practice driving prior to licensure. Only one previous naturalistic study of supervised practice driving has been conducted. In that study, however, no exposure data were collected, nor did the authors analyze associations between supervised practice driving and independent driving outcomes. In collaboration with the Virginia Transportation Technology Institute (VTTI), we recruited a sample (n=90) of adolescents soon after they obtained their learner's permits, instrumented their vehicles with a data acquisition system, and began following them through the

learner period (a minimum of 9 months in Virginia) and 12 months after licensure. Data collection was completed in 2015. One

unique aspect of the study is the evaluation of audio recordings of teen-parent verbal communications during instructional drives. Analyses of the practice driving period are underway. Analyses have focused on the amount and quality of practice driving (Simons-Morton & Ehsani, 2016); and predictors of licensure (Ehsani et al., 2016).

***“While practice driving is essential for learning to manage a vehicle, it does not seem to train novice drivers to drive safely upon licensure.”***

### Principal Investigator

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

### Division Collaborators

Joe Bible, Ph.D.

Johnathan Ehsani, Ph.D.

Pnina Gershon, Ph.D.

Indra Kar, B.A.

Danping Liu, Ph.D.

Fearghal O'Brien, Ph.D.

### Key Publications

Ehsani JP, Haynie D, Ouimet MC, Zhu C, Guillaume C, Klauer SG, Dingus T, Simons-Morton BG. Teen drivers' awareness of vehicle instrumentation in naturalistic research. *Journal of Safety Research*. 2017; 63:127-134. PMID: 29203010. PMCID: PMC5728669

Ehsani JP, Klauer SG, Zhu C, Gershon P, Dingus TA, Simons-Morton BG. Naturalistic assessment of the learner license period. *Accident Analysis and Prevention*. 2017; 106:275-284. PMID: 28654843. PMCID: PMC5610634

Gershon P, Zhu C, Klauer SG, Dingus T, Simons-Morton B. Teens' distracted driving behavior: Prevalence and predictors. *Journal of Safety Research*. 2017; 63:157-161. PMID: 29203014.

## **EFFECT OF TEENAGE PASSENGERS ON TEENAGE SIMULATED DRIVING PERFORMANCE (TEEN PASSENGER STUDY)**



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

The presence of teenage passengers has been shown to increase crash risk. However, in previous research we found that teen passengers of both sexes provided a modest protective effect on crash/near crash (C/NC) and kinematic risky driving compared to the no passenger condition (e.g., teens drove in a more-risky manner and were at greater C/NC risk when driving alone). Perhaps some teenage passengers increase risk and some decrease risk under certain driving conditions? The Teen Passenger Study includes a series of driving simulation studies designed to learn more about the nature of teen passenger influences.

The Teen Passenger Study 2 (TPS2) tested the effect of male teenage peer pressure on male teenage risky driving performance. Drivers were rewarded by reaching a particular destination within a limited time without error. The confederate passenger served as the navigator and at key points in the drive verbally encouraged the

driver to hurry (in the role of a risk-accepting teen) or make no errors (in the role of a risk-averse teen). Assessment of fMRI and psycho-social tasks were also conducted. Analyses indicated that the study participants drove in a more risky manner in the presence of a peer exerting mild pressure to engage in risk compared with those who drove in the presence of a confederate passenger who exerted mild pressure not to take risk (Bingham et al., under review). Significant interactions of passenger presence (passenger present vs. alone) by risk condition (risk-accepting vs. risk-averse) were observed for the driving measures. In all cases, greater risky driving by participants was more likely

with a risk-accepting passenger versus a risk-averse passenger present and a risk-accepting passenger present versus driving alone (Bingham et al. 2016). Using fMRI data collected prior to the simulated driving tasks, we also found that neural regions involved in susceptibility to social influence also predicted social influence on driving risk one week later in a full-cab driving simulator.

### **Principal Investigator**

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

### **Division Collaborators**

Johnathan Ehsani, Ph.D.

Danping Liu, Ph.D.

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### **Key Publication**

Cascio CN, O'Donnell MB, Simons-Morton BG, Bingham CR, Falk EB. Cultural context moderates neural pathways to social influence. *Culture and Brain*. 2017; 5(1):50-70.

***“Teenage driver behavior is susceptible to social influences, which may be moderated by cultural context, social inclusion, and social norms.”***



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

## UNIFORM NATURALISTIC TEENAGE DRIVING STUDY (UNTDS)

One of the limitations of naturalistic research to date has been small sample sizes. Larger samples are needed for analyses of risk by driving conditions and among subgroups. To create a large unified database, the HBB has gained access to data from the Strategic Highway Research Program 2 (SHRP2) Naturalistic Driving Study, the largest ever naturalistic driving study, which used similar instrumentation as the Naturalistic Teenage Driving Study (NTDS) and Supervised Practice Driving (SPD) studies. SHRP2 obtained driving data from over 2,000 drivers of varying ages. The UNTDS analyzes data from samples of 200 from each of the following age groups: 16-17, 18-19, 20-24, and 35-45 years. This will allow us to assess many of the same outcomes and determinants as in the completed Naturalistic Teenage Driving Study, and in many cases to combine the NTDS, SPD, and SHRP2 data sets to provide large samples for analyses not previously possible. The large combined

database will allow subgroup analyses and will allow us to answer key questions such as the following: (1)

What are individual level

predictors of risky driving? (2) Does crash risk and risky driving vary according to driving conditions? (3) Does the presence of teenage passengers affect teenage driving differently under certain driving conditions, such as weekend nights? (4) What is the relationship between kinematic risky driving behavior and crash risk? (5) To what extent does a small proportion of high-risk drivers account for the overall high crash risk of young drivers? One early analysis of these data compared kinematic risky driving before and after a crash and found that teenage drivers did reduce their kinematic event rates after a crash for at least two months. Coders measured elevated g-force event rates and collision-involvement over a one-year period of 254

16-17 year-old drivers whose vehicles had been instrumented with accelerometers and video cameras. Among the 41 participants who experienced a severe collision, the rate of elevated g-force events dropped significantly in the first month after the collision, remained unchanged for the second month, and significantly increased in the third month. There were no changes in rates of g-force events at comparable times for drivers not involved in collisions. Being involved in a collision led to a decrease in risky driving, but this may have been a temporary effect (O'Brien et al. 2016).

### Principal Investigator

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### Key Publication

O'Brien F, Bible J, Liu D, Simons-Morton BG. Do Young Drivers Become Safer After Being Involved in a Collision? *Psychological Science*. 2017; 28(4):407-413. PMID: 28406372. PMCID: PMC5556688

*Analyses of relatively large naturalistic driving data sets, such as from SHRP2, will enable analyses of the contexts of risky driving behavior.*

**NEXT GENERATION HEALTH STUDY - DRIVING RESEARCH**

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

The NEXT Generation Study, which has followed a cohort from 10th grade for six years after high school, provides a great opportunity for research on teenage and young adult driving. In analyses of self-reported risky driving behavior we found that secondary task engagement, and self-reported driving we found that cell phone use while driving among high school students carried over into emerging adult driving (Trivedi et al., 2017). Also, we conducted analyses of the possible associations between environmental contexts and acquisition of a driving license. There was a statistically significant main effect for the respective environmental variable but not for licensure and a significant interaction between the respective environmental variable and licensure. Compared to on-campus residents, those living at home or on their own engaged in significantly less Transportation Physical Activity (TPA). However, licensure interaction contrasts showed a significant difference by licensure for those living at home. Compared to four-year university students, non-students and technical school/community college students showed significantly less TPA engagement. The interaction contrasts indicated a significant difference by licensure among non-students and technical school/community college students. Compared to non-workers, those who worked 1-30 hours/week or 30+ hours/week engaged in significantly less TPA. The interaction contrasts indicated a significant difference by licensure among people who worked 1-30 hours/week or 30+ hours/week (Kar et al., 2017).

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Neha Trivedi, M.P.H.

**Key Publications**

Trivedi N, Haynie D, Bible J, Liu D, Simons-Morton B. Cell phone use while driving: Prospective association with emerging adult use. *Accident; Analysis and Prevention*. 2017; 106:450-455. PMID: 28735180. PMCID: PMC5610622

Kar IN, Li K, Haynie DL, Simons-Morton BG. Emerging adults without a driver's license engage in more transportation-related physical activity to school/work in certain environmental contexts. *Preventive Medicine*. 2017; 96:42-48. PMID: 28011136. PMCID: PMC5328841



Stephen E. Gilman, Sc.D.

## MENTAL HEALTH AND HEALTH DISPARITIES

Mental disorders, and health disparities more broadly, have significant developmental origins. This work is ideally situated within our Branch and Division—whose overarching mission is to generate discoveries in the areas of reproduction, development, and developmental mechanisms.

Mood and substance use disorders have significant impacts on population health. Both have early life origins, with established risk factors beginning in the prenatal period and extending throughout development. Moreover, they disproportionately affect individuals during their peak reproductive years. The guiding principle of this research program, at the intersection of disparities and development, is that reducing disparities requires an understanding of how and when developmental processes unfold to lead to profound social inequalities in mental illness during childhood, into adulthood, and in successive generations.

Our team's research in this area has demonstrated both that the social circumstances of early childhood affect children's mental health and that they convey continuing risk for poor

mental health into adulthood. An important emphasis in the field of life course epidemiology is the identification of developmentally sensitive periods in which risk

processes emerge, and which may therefore be amenable to public health intervention. Accordingly, age of onset is a key variable in our studies. We have shown that not only is early childhood disadvantage associated with an elevated lifetime risk of depressive illness, but this lifetime risk is characterized by an

***Our work is revealing that disparities in mental disorders – which persist across the life course and into the next generation – might begin as early as the prenatal period.***

### Principal Investigator

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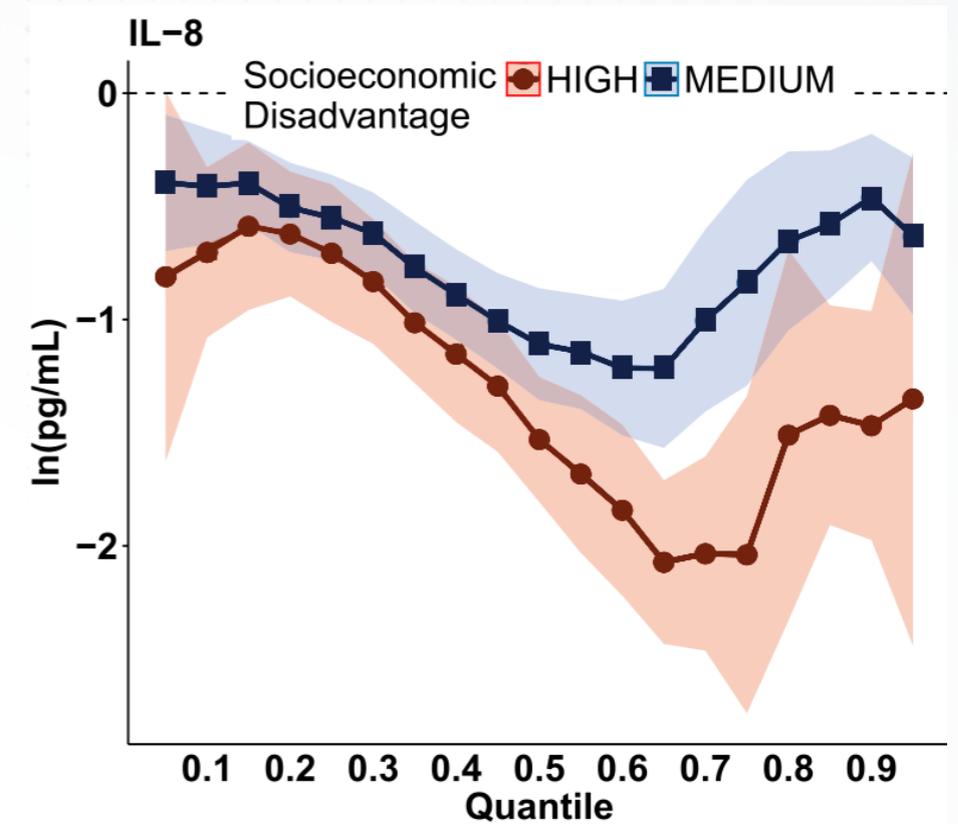
Jeremy Luk, Ph.D.

early-onset subtype of depression, an elevated risk for recurrent episodes in adulthood, and a decreased likelihood of subsequent recovery.

Highlights of our work in 2017 include our study on parental socioeconomic disadvantage, maternal immune activity during pregnancy, and offspring neurodevelopment (Gilman, Hornig, et al., 2017). Published in the *Proceedings of the National Academy of Sciences*, this study found lower concentrations of a biomarker of maternal immune activity – Interleukin-8 – in pregnancies characterized by high socioeconomic disadvantage (see Figure). In fact, the differences were most pronounced at higher quantiles of the distribution of Interleukin-8. The study also demonstrated that these differences are transmitted to the developing offspring through higher rates of neurologic abnormalities in the first year of life. We are following up on these findings through a new initiative on maternal immune activity during pregnancy and offspring neurodevelopment. Additional findings of interest

from our program's collaborators in 2017 focus on adolescent mental health, demonstrating sex differences in adolescent onset depression (Breslau et al., 2017) and higher rates of adolescent psychiatric disorders following exposure to interpersonal violence in childhood (Dunn et al., 2017). Finally, with collaborators at Harvard and University of Ottawa, we published one of the longest running studies of the impact of depression on mortality – showing elevated mortality risk associated with depression over a period of 6 decades (Gilman, Sucha, et al., 2017).

Ongoing collaborative work in the area of mental health and health disparities includes research with investigators on the NEXT Generation Health Study to investigate the neighborhood influences on adolescent health status, including mood and behaviors. For example, we are pursuing the role of neighborhood factors in adolescents' risk of depression and suicidal behaviors. The “NEXT” study offers a highly unique opportunity to advance the field of neighborhoods and health because of its geographically and socioeconomically diverse and nationally representative sample.



### Key Publications

Breslau J, Gilman SE, Stein BD, Ruder T, Gmelin T, Miller E. Sex differences in recent first-onset depression in an epidemiological sample of adolescents. *Translational Psychiatry*. 2017; 7(5):e1139. PMID: 28556831. PMCID: PMC5534940

Gilman SE, Hornig M, Ghassabian A, Hahn J, Cherkerzian S, Albert PS, Buka SL, Goldstein JM. Socioeconomic disadvantage, gestational immune activity, and neurodevelopment in early childhood. *Proceedings of the National Academy of Sciences of the United States of America*. 2017; 114(26):6728-6733. PMID: 28607066. PMCID: PMC5495226

Gilman SE, Sucha E, Kingsbury M, Horton NJ, Murphy JM, Colman I. Depression and mortality in a longitudinal study: 1952-2011. *CMAJ: Canadian Medical Association Journal*. 2017; 189(42):E1304-E1310. PMID: 29061855. PMCID: PMC5654987

## DEVELOPMENTAL ORIGINS OF SUICIDE MORTALITY



Stephen E. Gilman, Sc.D.

Our prior work on suicide set the stage for a major new effort that is currently ongoing to understand the developmental origins of suicide mortality. This project comprises what will be the largest cohort study to date in the United States to understand the early childhood precursors of suicide death. Using data from over fifty thousand children born in the Collaborative Perinatal Project, we will identify suicide deaths through a linkage with the National Death Index, and will be able for the first time in the United States to conduct a large, population-based investigation of perinatal, social, and developmental risk factors for suicide.



Risë B. Goldstein, Ph.D.

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Stephen E. Gilman, Sc.D.

## MATERNAL IMMUNE ACTIVITY DURING PREGNANCY AND OFFSPRING NEURODEVELOPMENT

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 throughout gestation in children's neurocognitive development. This is important because impairments in neurocognitive functioning 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. Prior studies have not resolved the question of the timing of immune involvement during the course of gestation, nor investigated its role in the context of a chronic social stressor such as socioeconomic disadvantage. In 2017 we launched a study to investigate the association between fetal exposure to biomarkers of maternal immune activity throughout gestation and children's neurocognitive development up to age 7 years.

Associations of maternal immune activity with offspring neurodevelopmental phenotypes reinforce the importance of immune molecules such as cytokines for normal neurodevelopment given their involvement in tightly regulated neural migration and synaptic plasticity processes. Therefore, both extremely high and extremely low levels of cytokines could be detrimental to the developing brain.

Participants in the current study will be approximately 1,000 mother-child pairs enrolled in the Collaborative Perinatal Project (CPP) between 1959 and 1966. The CPP was designed to examine the relationships between perinatal events and neurological deficits in the offspring of a total of 55,908 women across 12 hospitals. Offspring were followed through age 7, with approximately 70% retention for the duration of the study. Maternal serum was extracted from blood collected serially during pregnancy from the date of study registration through delivery and stored in the National Institutes of Health repositories at minus 20 degrees Celsius. We will obtain CPP prenatal serum samples from the NIH repository and conduct assays for concentrations of immune markers, which will then be linked with a broad range of offsprings' neurocognitive outcomes.

### Principal Investigator

Stephen E. Gilman, Sc.D.

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## Contraceptive Development Program

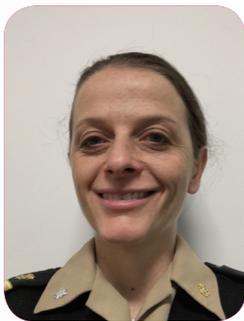
The mission of the Contraceptive Development Program is to conduct innovative research to develop new methods of contraception for men and women.



Diana Blithe, Ph.D.



Min S. Lee, Ph.D.



Jill Long, M.D., M.P.H.,  
M.H.S., F.A.C.O.G.

NICHD is the lead Federal agency for conducting research on contraception. In 1968, the Secretary of Health Education and Welfare established the NICHD Center for Population Research. The Contraceptive Development Branch was created with the goal of developing new contraceptive methods. Promising new leads have been identified. In 2017, the Contraceptive Development Program (CDP) was established in DIPHR, with the mission to advance clinical development of novel contraceptive methods for men and women. CDP uses R&D contracts to achieve this goal: a Chemical Synthesis Facility - synthesizes clinical grade active pharmaceutical ingredients that are not commercially available; a Biological Testing Facility - performs preclinical testing to qualify agents for FDA-approved studies; a Contraceptive Clinical Trials Network (CCTN) - comprised of experts in clinical contraceptive development. CDP scientists coordinate and integrate the program's components to produce groundbreaking contraceptive research. CDP utilizes technology transfer mechanisms to form partnerships, translating discoveries and clinical advances into products that address unmet contraceptive needs of men and women.

### Chemical Synthesis of New Drugs for Clinical Evaluation

Studies of new chemical entities (drugs) are conducted under an Investigational New Drug (IND) application, potentially leading to a New Drug Application (NDA). New entities that are not commercially available must be synthesized under current Good Manufacturing Practice (cGMP) that comply with all regulatory

standards of Chemistry, Manufacturing and Controls. CDP maintains a contracted Chemical Synthesis Facility to produce novel drugs required for the program.

### Preclinical Qualification of Drugs or Devices Prior to Clinical Evaluation

New chemical entities 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.

### Contraceptive Clinical Trials Network Evaluates Novel Contraceptive Methods for Women and Men

The goal of the CDP's CCTN is to evaluate safety and efficacy of new contraceptive drugs and devices for women and men. Results of 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. In 2017, three new clinical trials began recruitment. Protocol development was initiated on five new trials expected to begin enrollment in 2018, including the first trial to evaluate a novel transdermal hormonal male contraceptive method in couples seeking to prevent pregnancy.

### **Pipeline of New Contraceptive Methods for Men and Women**

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. Each product was developed to fill an unmet need or provide greater safety to vulnerable populations at risk of unintended pregnancy.

#### **Publication**

Blithe DL. Pipeline for contraceptive development. *Fertil Steril* 2016; 106(6):1295-1302. PMID: 27523300

### **Contraceptive Development Program Staff**

Diana Blithe, PhD, Chief, CDP, is director of the Contraceptive Clinical Trials Network. She integrates activities between clinical and preclinical components of the program and is principal investigator on a Cooperative Research and Development Agreement (CRADA) that has successfully developed products that are now commercially available for emergency contraception and treatment of uterine fibroids.

Min S. Lee, PhD, joined NICHD in 2010. He serves as expert medicinal chemist and project officer for preclinical research in small molecule synthesis and manufacture under current Good Manufacture Practice (cGMP) and IND-enabling preclinical studies conducted under Good Laboratory Practice (GLP).

Jill Long, MD, MPH, MHS, FACOG (board certified in Obstetrics & Gynecology), joined NICHD in 2017. She serves as CCTN Medical Officer and project officer. She served as MO in the STD Branch at NIAID (2012–2017) and performed premarket clinical review for OBGYN devices at FDA (2009-2012).

## DEVELOPMENT OF HORMONAL CONTRACEPTIVE METHODS FOR MEN

The only reversible male contraceptive method is the male condom. Although condoms also protect against sexually transmitted infections, the failure rate is relatively high and the method is not acceptable to many men. High testicular testosterone concentrations are needed to support sperm production; substantially lower testosterone levels in serum are sufficient to maintain other androgen-dependent functions. Reversible contraception can be achieved by giving exogenous hormones that suppress secretion of hypothalamic-pituitary hormones that stimulate testicular testosterone production. Taking a progestin can suppress testicular testosterone and stop sperm production. Exogenous testosterone is required to replace normal blood levels to maintain other androgen-dependent functions. The challenge that has prevented development of a male pill is that oral testosterone is cleared very rapidly, requiring multiple doses per day. Successful approaches have used progestins (oral, injectable or implants) to achieve sperm suppression consistent with contraceptive effectiveness (sperm <1 million/ml) and testosterone delivered by injections, implants or transdermal gels to maintain all other functions. New progestogenic androgens on the horizon may provide contraception with a single agent. Non-hormonal approaches that inhibit sperm production or sperm function are still in pre-clinical phase of research.

### **Nestorone®/Testosterone (Nes/Tes) Gel - Daily transdermal gel application**

We demonstrated that a potent progestin, Nestorone®, delivered in a gel formulation, caused gonadotropin suppression with resultant inhibition of testicular testosterone production. Daily application of Nestorone and testosterone gels suppressed sperm production but maintained other androgen-dependent

functions.<sup>1,2</sup> All men recovered normal sperm production after treatment ended. Inhibition of spermatogenesis, followed by recovery, indicates that the regimen may be effective and reversible for male contraception.

**Status:** Next step: test the combined Nes/Tes Gel for contraceptive effectiveness in couples who are willing to use this method for pregnancy prevention. Enrollment is anticipated to begin in 2018 at selected CCTN sites in the USA, UK, Sweden, Italy, Chile and Kenya.

### **Novel Progestogenic Androgens for Hormonal Male Contraception**

Novel agents, Dimethandrolone (DMA) and 11β-Methyl Nortestosterone, have been developed to have both androgenic and progestational activities, properties that may maximize gonadotropin suppression while maintaining libido and other androgen-dependent functions. We are evaluating two pro-drugs (modified agents) to determine if they suppress testicular testosterone production while maintaining androgen-dependent functions.

### **Dimethandrolone undecanoate (DMAU) - Daily oral dosing**

DMAU is an ester of the active compound, DMA. First-in-human single oral dosing indicated that the drug was well-tolerated and well-absorbed when taken with food.<sup>3,4</sup> Daily oral dosing for 28 days demonstrated effective gonadotropin suppression and inhibition of testicular testosterone production. Androgen-dependent functions (libido, ejaculation, etc.) were maintained and side effects were minimal.

**Status:** Next step: evaluate longer use of DMAU to demonstrate sperm suppression and recovery.

### **Dimethandrolone undecanoate (DMAU) – Long-acting injectable**

Studies of oral DMAU appear promising and most men say that they prefer a pill. However, a substantial proportion of men would prefer an injectable formulation because it does not require remembering to take a pill every day. First-in-human injectable DMAU dosing is underway. Single injections are evaluated in a dose-escalation design in which each group recovers before the next higher dose injections begin. This approach assures that safety and time-to-recovery is evaluated at a selected dose prior to increasing exposure to a higher level of drug.

**Status:** A dose-escalation study of the injectable DMAU formulation is ongoing.

### **11 $\beta$ -Methyl Nortestosterone dodecylcarbonate (11 $\beta$ -MNTDC) - Daily oral dosing**

11 $\beta$ -MNTDC is a dodecylcarbonate pro-drug of the active compound, 11 $\beta$ -Methyl Nortestosterone. First-in-human single dosing indicated that the drug was well-tolerated and well-absorbed if taken with food.

**Status:** Daily oral dosing for 28 days is ongoing to determine if 11 $\beta$ -MNTDC can suppress gonadotropins and inhibit testicular testosterone production while maintaining androgen-dependent functions.

#### **Publications**

Roth MY, Shih G, Ilani N, Wang C, Page ST, Bremner WJ, Swerdloff RS, Sitruk-Ware R, Bliethe DL, Amory JK. Acceptability of a transdermal gel-based male hormonal contraceptive in a randomized controlled trial. *Contraception* 2014; 90(4):407-412. PMID: 24981149

Ilani N, Roth MY, Amory JK, Swerdloff RS, Dart C, Page ST, Bremner WJ, Sitruk-Ware R, Kumar N, Bliethe DL, Wang C. A new combination of testosterone and nesterone transdermal gels for male hormonal contraception. *J Clin Endocrinol Metab* 2012; 97(10):3476-3486. PMID: 22791756

Ayoub R, Page ST, Swerdloff RS, Liu PY, Amory JK, Leung A, Hull L, Bliethe D, Christy A, Chao JH, Bremner WJ, Wang C. Comparison of the single dose pharmacokinetics, pharmacodynamics, and safety of two novel oral formulations of dimethandrolone undecanoate (DMAU): a potential oral, male contraceptive. *Andrology* 2017; 5(2):278-285. PMID: 27907978

Surampudi P, Page ST, Swerdloff RS, Nya-Ngatchou JJ, Liu PY, Amory JK, Leung A, Hull L, Bliethe DL, Woo J, Bremner WJ, Wang C. Single, escalating dose pharmacokinetics, safety and food effects of a new oral androgen dimethandrolone undecanoate in man: a prototype oral male hormonal contraceptive. *Andrology* 2014; 2(4):579-587. PMID: 24789057

## INCREASING CONTRACEPTIVE OPTIONS FOR WOMEN

In the USA, approximately 45% of pregnancies are unintended. Current contraceptive methods serve well for many women but not well for others, especially women with special health considerations such as obesity, hypertension or diabetes. Recent data indicate that one-third of reproductive age women are obese, putting them at increased risk of venous thromboembolism, hypertension and diabetes. As their risk factors increase, these women have contraindications to most hormonal contraceptive methods, yet they face even higher risks from pregnancy. Options are limited for those women wishing to avoid pregnancy. New or improved safe and effective contraception is needed. The CDP is developing methods designed to address unmet needs for safety, acceptability and effectiveness.

### Contraceptive Vaginal Rings

**Nestorone®/Ethinyl Estradiol Contraceptive Vaginal Ring – one ring for a full year of protection.**

In partnership with Population Council, the CCTN conducted a pivotal safety and efficacy study of a new contraceptive vaginal ring to be used for one year (13 cycles). The ring has unique advantages over existing products: does not require a new ring each month; no refrigeration for storage; better for the environment compared with disposal of 13 rings. Up to 13 cycles were evaluated in 1142 women. Three nested safety substudies evaluated clotting factors, vaginal microbiome and endometrial safety.

**Status:** The NDA for product approval is under FDA review. Additional manuscripts are in preparation.

**Nestorone® – Estradiol Contraceptive Vaginal Ring (Nes/E2 CVR) – one ring for 3 months protection.**

In partnership with Population Council, CDP has developed a novel ring that delivers the progestin, Nestorone®, to effectively block follicular development and deliver 17-β estradiol to support bone health but with low potential for increasing VTE risk, including in obese women. The ring used continuously (no removal interval) appeared safe and effectively inhibited ovulation. Most women liked the ring but some experienced unacceptable bleeding. A pilot study implementing a ring-out period (2 or 4 days) demonstrated that a ring-out period of 2 days could cause regular, predictable bleeding in most women. The ring appears to be safe and effective based on inhibition of ovulation, including in obese women. By either continuous or cyclical use of the ring, a woman may produce predictable and acceptable bleeding which, depending on her response, could be amenorrhea, occasional bleeding over a 90-day period, or a cyclical interval of bleeding resulting from removal of the ring for a 2-day period.

**Status:** Enrollment into a contraceptive efficacy trial of the Nes/E2 CVR will begin in 2018. Women will be randomized to continuous or cyclical use but can switch if not satisfied with her bleeding pattern.

### Multipurpose Prevention Technologies (MPT)

**Dapivirine/Levonorgestrel (LNG) Vaginal Ring – one ring for three months of protection.**

Most contraceptive methods do not protect against HIV infection. MPTs are designed to protect against pregnancy and

against infection from pathogens transmitted through sexual contact. One product is a Dapivirine/LNG releasing vaginal ring. Women with high HIV transmission risk had a lower incidence of HIV acquisition if they consistently used a vaginal ring delivering Dapivirine. A new ring that delivers both Dapivirine and LNG is designed to provide protection against pregnancy and HIV acquisition.

**Status:** Irregular bleeding caused by continuous progestin use is the major reason that women discontinue a progestin-only method. In 2018, a study to determine if use of the ring with a monthly ring-free interval will maintain sufficient levels of Dapivirine, effectively inhibit ovulation and cause regular bleeding.

#### **Woman's Condom (WC)**

MPTs provide protection against both pregnancy and pathogen infection. An iterative process was used by PATH to design a novel female condom (WC) that would be effective and acceptable to users. The CCTN undertook a pivotal contraceptive efficacy trial to determine effectiveness for up to 6 cycles of use. The efficacy of the WC was similar to that of male condoms.

**Status:** A Clinical Study Report to support regulatory approval is in progress.

### **Long-Acting Reversible Contraceptives (LARCs)**

#### **Mini-Copper Intrauterine Device for Nulliparous Women**

LARCs are the most effective and most highly acceptable methods of contraception for women. The copper IUD has almost no contraindications for use, making it a safe option for women with health risks who wish to avoid pregnancy. Increased bleeding and cramping associated with the Copper IUD has

deterred many clinicians from recommending this method to nulliparous women, especially adolescents. A Mini-Copper IUD may be less likely to cause increased bleeding in this population compared with the current copper IUD. In collaboration with Bill & Melinda Gates Foundation and FHI 360, a comparison study is underway to compare the Mini Copper IUD with ParaGard in nulliparous women. Outcomes are contraceptive effectiveness, continuation rate, expulsion rate, bleeding characteristics and pain.

**Status:** Enrollment began in 2017 and is ongoing in the CCTN.

### **Progestin-only Contraception**

#### **Levonorgestrel (LNG) Butanoate – a novel long-acting injectable method**

LNG is effective as a contraceptive and is not associated with increased venous thromboembolism (VTE) as seen with products containing ethinyl estradiol. Progestin-only methods are often prescribed for women who have conditions, including obesity, that increase risk of VTE. Injections of long-acting LNG esters, such as LNG Butanoate, may improve compliance over progestin-only pills which require daily pill intake within a narrow timeframe each day. LNG Butanoate injections successfully suppressed ovulation; however, duration of action was <3 months in some women, particularly obese women.<sup>4</sup> Modifications are underway to increase the particle size which may prolong the duration of action.

**Status:** Product production and protocol development is ongoing.

### Publications

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