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

2016 ANNUAL REPORT

Division of Intramural Population Health Research, NICHD

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

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

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 2016 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 also are making advances regarding the onset and timing of risky adolescent behaviors that may or may 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 Scientific Director, Dr. Constantine A. Stratakis, Institute Director, Diana W. Bianchi, and former Acting Director, Dr. Catherine Y. Spong. 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,

/Germaine M. Buck Louis/

Germaine M. Buck Louis, Ph.D., M.S.
Director & Senior Investigator, DIPHR, NICHD

Office of the Director

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

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

Jennifer Weck, Ph.D.

The Division of Intramural Population Health Research 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 serves as the Director, while maintaining an active research program focusing on environmental influences and human reproduction and development. She is 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 role, she is responsible for our training/ mentoring program and also for the continued professional development of all scientists. As a population scientist, Dr. Grewal continues her research on fetal growth and development, perinatal epidemiology, and birth defects. She is the Co-Principal Investigator for the Consortium on Safe Labor Study and a collaborator with the NICHD Fetal Growth Studies where she leads research on the nutritional component.

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. In addition, 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 two program analysts - Kaye Beall and Adrienne Lonaberger - who oversee 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. In July 2016, Ms. Beall retired from the NIH.

Staff

- **Germaine M. Buck Louis**, Ph.D., M.S., Senior Investigator and Director
- **Kaye Beall**, Program Analyst
- **Jagteshwar (Una) Grewal**, Ph.D., M.P.H., Deputy Director
- **Adrienne Lonaberger**, Program Analyst
- **Jennifer Weck**, Ph.D., Laboratory Health Specialist

Fellows

- **Katherine Sapra**, Ph.D., M.Phil., M.P.H., Postdoctoral IRTA Fellow
- **Melissa Smarr**, Ph.D., Postdoctoral IRTA Fellow

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 interventions.

LONGITUDINAL INVESTIGATION OF FERTILITY AND THE ENVIRONMENT (LIFE STUDY)

The goal of the LIFE Study is to determine whether endocrine disrupting chemicals (EDCs) in the context of lifestyle affect male and female fecundity and fertility, which are defined as the biologic capacity for reproduction and live births, respectively. The LIFE Study recruited a cohort comprising 501 couples who were discontinuing contraception for the purpose of becoming pregnant. Both partners of the couple completed daily journals while trying for pregnancy until they became pregnant or up to 12 months of trying. Women achieving pregnancy completed daily then monthly journals through

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) in urine. Men also provided semen samples for the assessment of EDCs and lifestyle relative to 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. These tools allowed us to measure ovulation and post-implantation pregnancy in a prospective manner.

Among some of the notable discoveries in 2016 included recognition that specific EDCs are associated with diminished couple fecundability, as measured by a longer time-to-pregnancy (TTP) and a reversal of the secondary sex ratio resulting in a female excess of live births (Bae et al. 2016a). Despite the importance of EDCs for human fecundity, we found that health status was also important. Male partners with diabetes and female partners with 2+ chronic diseases had a significant reduction (65%) in fecundability, resulting in a longer TTP. However, neither metals nor perfluoroalkyl and polyfluoroalkyl substances were associated with pregnancy loss (Buck Louis et al. 2016b, 2016c). In terms of lifestyle behaviors, couples consuming more than 2 daily caffeinated beverages while trying to become pregnant and during the first 7 weeks following conception were at increased risk for miscarriage (Buck Louis et al. 2016a). However, female partners who took daily multivitamins during these time periods had a significant reduction (55%) in miscarriage risk compared to women not taking vitamins. Use of tobacco products in either partner of the couple was associated with a longer TTP (Sapra et al. 2016c), as was the over-the-counter medication paracetamol (acetaminophen) in female but not male partners (Smarr et al. 2016b). In terms of the male partner, choice of underwear (boxer or brief) was not associated with semen quality or TTP (Sapra et al. 2016a) refuting claims in the print media. Collectively these and other findings underscore the importance of the physical environment and lifestyle for human fecundity and fertility.

Collaborators

- **Zhen Chen**, Ph.D.
- **Sung Duk Kim**, Ph.D.
- **Sunni Mumford**, Ph.D., M.P.H.
- **Rajeshwari Sundaram**, Ph.D.
- **Jisuk (Iris) Bae**, Ph.D.
- **Melissa Smarr**, Ph.D., M.P.H.
- **Katherine Sapra**, Ph.D., M.Phil., M.P.H.

Contact

For more information, email or visit the NICHD website.

LIFE Study Publications (*NICHD fellow authored)

*Bae J, Kim S, Kannan K, Buck Louis GM. Couples' urinary concentrations of benzophenone-type ultraviolet filters and the secondary sex ratio. *Science of the Total Environment*. 2016a;543(Pt A):28-36. doi: 10.1016/j.scitotenv.2015.11.019. PMID: 26575635

*Bae J, Kim S, Chen Z, Eisenberg ML, Buck Louis GM. Human Semen Quality and the Secondary Sex Ratio. *Asian Journal of Andrology* 2016b Mar 11. Doi: 10.4//103/1008-682X.173445. PMID: 26975484

Buck Louis GM, Sapra KJ, Schisterman EF, Lynch CD, Maisog JM, Grantz KL, Sundaram R. Lifestyle and pregnancy loss in a contemporary cohort of women recruited prior to conception: The LIFE Study. *Fertility and Sterility* 2016a;106(1):180-188. PMID: 27016456

Buck Louis GM, Sapra KJ, Barr DB, Lu Z, Sundaram R. Preconception perfluoroalkyl and polyfluoroalkyl substances and incident pregnancy loss, LIFE Study. *Reproductive Toxicology* 2016b;65:11-17. PMID: 27319395

Buck Louis GM, Barr DB, Kannan K, Chen Z, Kim S, Sundaram R. Paternal exposures to environmental chemicals and time-to-pregnancy: Overview of results from the LIFE Study. *Andrology* 2016c;4(4):639-47. PMID: 27061873

Eisenberg ML, Sundaram R, Maisog J, Buck Louis GM. Diabetes, medical comorbidities and couple fecundity. *Human Reproduction* 2016;31(10):2369-2376. PMID: 27591240

Jaacks LM, Barr DB, Sundaram R, Maisog JM, Zhang C, Buck Louis GM. Pre-pregnancy maternal exposure to polybrominated and polychlorinated biphenyls and gestational diabetes: A prospective cohort study. *Environmental Health*. 2016;15:11. doi: 10.1186/s12940-016-0092-5. PMID: 26792546

Jaacks LM, Boyd Barr D, Sundaram R, Grewal J, Zhang C, Buck Louis GM. Pre-pregnancy maternal exposure to persistent organic pollutants and gestational weight gain: A prospective cohort study. *International Journal of Environmental Research and Public Health* 2016;13(9). PMID: 27626435

Lum KJ, Sundaram R, Buck Louis GM, Louis \ TA. A Bayesian joint modeling of menstrual cycle length and fecundity. *Biometrics* 2016;72(1):193-203. PMID: 26295923

Lum KJ, Sundaram R, Barr DB, Louis TA, Louis GM. Perfluoroalkyl Chemicals, Menstrual Cycle Length, and Fecundity: Findings from a Prospective Pregnancy Study. *Epidemiology* 2016;28(1):90-98. PMID: 27541842

Patel CJ, Sundaram R, Buck Louis GM. A data-driven search for semen-related phenotypes of impaired human fecundity. *Andrology* 2017;5(1):95-102. PMID: 27792860

*Sapra KJ, Eisenberg ML, Kim S, Chen Z, Buck Louis GM. Choice of underwear and male fecundity in a preconception cohort of couples. *Andrology* 2016a;4(3):500-508. PMID: 26939021

*Sapra KJ, Buck Louis GM, Sundaram R, Joseph KS, Bates LM, Galea S, Ananth CV. Signs and symptoms associated with early pregnancy loss: Findings form a population-based preconception cohort. *Human Reproduction* 2016b;31(4):887-896. PMID: 26936888

*Sapra KJ, Barr DB, Maisog JM, Sundaram R, Buck Louis GM. Time-to-pregnancy associated with couples' use of tobacco products. *Nicotine and Tobacco Research* 2016c;18(11):2154-2161. PMID: 27190399

*Smarr MM, Grantz KL, Zhang C, Sundaram R, Maisog JM, Barr DB, Buck Louis GM. Persistent organic pollutants and pregnancy complications. *Science of the Total Environment* 2016a:551-552:285-91. PMID: 26878640

*Smarr MM, Grantz KL, Sundaram R, Maisog JM, Honda M, Kannan K, Buck Louis GM. Urinary paracetamol and time-to-pregnancy. *Human Reproduction* 2016b;31(9):2119-27. PMID: 27412248

*Smarr MM, Kannan K, Buck Louis GM. Endocrine disrupting chemicals and endometriosis. *Fertility and Sterility* 2016c;106(4):959-66. PMID: 27424048

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

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. Moreover, recent findings suggest that women with endometriosis may be at greater risk of reproductive site cancers and autoimmune disorders than unaffected women, underscoring the interrelatedness between gynecologic disorders and later onset disease, as conceptualized in the Ovarian Dysgenesis Syndrome (Buck Louis et al. 2011).

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. Our collective findings during the past 5 years were recently summarized relative to the available literature (Smarr et al. 2016).

Key discoveries during 2016 included findings that a lean body habitus over adolescence and adulthood is associated with endometriosis (Backjona et al. 2016), as is difficulty becoming pregnant or experiencing infertility prior to diagnosis (Buck Louis et al. 2016). This latter finding suggests that impaired fecundity and endometriosis may have a shared etiology and underscores the need to establish the temporal ordering between exposures, fecundity and gynecologic diseases. Pain was extensively studied in the ENDO Study and found to be prevalent, as was physical and sexual abuse. Specifically, both forms of abuse had a high reported prevalence – 43% for sexual and 49% for physical – but neither was associated with endometriosis. However, a history of physical abuse was significantly associated with a two-fold higher odds of having adhesions visualized intra-operatively in comparison to women without such a history (Schliep et al. 2016). Collectively, these findings highlight the complexity of endometriosis and other gynecologic disorders in terms of biologic and socio-behavioral factors.

Collaborators

- **Uba Backonja**, Ph.D.
- **Zhen Chen**, Ph.D.
- **Sunni Mumford**, Ph.D., M.S.
- **Karen Schliep**, Ph.D., M.P.H.
- **Jennifer Weck**, Ph.D.

Contact

For more information, email or visit the Endometriosis page.

2016 ENDO Study Publications (* NICHD fellow authored)

*Backonja U, Buck Louis GM, Lauver DR. Overall adiposity, adipose tissue distribution, and endometriosis: A systematic review. *Nursing Research* 2016;65(2):151-66. PMID: 26938364

Buck Louis GM, Backonja U, Schliep KC, Sun L, Peterson CM, Chen Z. Women's Reproductive History Before the Diagnosis of Incident Endometriosis. *Journal of Women's Health* 2016;25(10)1021-1029. PMID: 27379997

*Schliep KC, Mumford SL, Johnstone EB, Peterson CM, Sharp HT, Stanford JB, Chen Z, Backonja U, Wallace ME, Buck Louis GM. Sexual and Physical Abuse and Gynecologic Disorders. *Human Reproduction* 2016;31(8):1904-1912. PMID: 27334336

*Smarr MM, Kannan K, Buck Louis GM. Endocrine disrupting chemicals and endometriosis. *Fertility and Sterility* 2016;106(4):959-66. PMID: 27424048

EXPOSOME OF NORMAL PREGNANCY

The exposome research paradigm seeks to measure mixtures of exposures in keeping with its founder's original goal in measuring the totality of exposures from conception onward (Wild 2005). It offers promise for understanding environmental influences on human reproduction and development, given the highly integrated and timed sensitive windows from folliculogenesis and spermatogenesis to conception, implantation and pregnancy. We sought to assess the feasibility and utility of the exposome paradigm in this proof- of-concept initiative. Specifically, we designed research to determine if we could characterize and quantify the "normal" pregnancy exposome using the Calcium for Preeclampsia Prevention cohort study. This currently in progress research is important given the marked physiologic and behavioral changes that characterize pregnancy, which means it is important to determine if physiologic variation can be differentiated from changes in chemical concentrations. We have completed quantifying several classes of persistent and non-persistent EDCs during each trimester of pregnancy for 50 women (150 measurements). Analysis is near completion and the findings support being able to differentiate physiologic variation from woman-level changes in chemical concentrations over the course of pregnancy. These findings suggest that the exposome paradigm is feasible and has utility for exploring the mixture of environmental influences on pregnancy outcomes.

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.

Publications

Stingone JA, Buck Louis GM, Nakayama S, Vermeulen RC, Kwok RK, Cui Y, Balshaw DM, Teitelbaum SL. Toward greater implementation of the exposome research paradigm within environmental epidemiology. *Annual Reviews in Public Health*. 2016; doi10.1146/annurev-publhealth-082516-012750. PMID: 28125387

BIOSTATISTICS AND BIOINFORMATICS BRANCH

Aiyi Liu, Ph.D.

The mission of the Biostatistics and Bioinformatics Branch (BBB) is to: 1) conduct both collaborative and methodological research that is important to the mission of the Division and Institute; 2) provide training in areas of statistical research that will advance the Division's and Institute's research programs; and 3) serve as a resource for the Division, Institute, NIH, and other professional and government organizations. The research component of the BBB's mission is multifaceted. First, providing first-rate statistical collaboration requires understanding of the scientific issues and state-of-the-art statistical methodology relevant to the scientific problem. Therefore, investigators within the Branch play a key role in all aspects of the study. Second, the Branch develops new statistical methodology for designing and analyzing data. Analytical issues encountered in collaborative research directly motivate much of the Branch's independent research. An important component of our collective methodological research is the translation of our novel methodology back to the NICHD scientific constituents through the development of software using free-ware (e.g., R 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 2016 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, and innovative methods for gene-based association studies using functional data analysis. 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 have developed new statistical methods for analyzing biomarker data. For example, in 2016, BBB investigators (jointly with other colleagues) proposed efficient estimation of interaction effects using pooled biospecimens in a case-control study, an efficient screening procedure for selecting candidate diagnostic biomarkers based on combination of sensitivity and specificity, and a cross-validation approach for predicting a binary event with linear combination of biomarkers.

During 2016, BBB investigators have continued to develop functional regression models for gene-based association analysis of quantitative, qualitative, and survival traits using functional data techniques to reduce the dimensionality of genetic data and to model the relation among genetic variants and phenotypes of

complex disorders. Based on the functional regression models, test statistics are built to analyze high dimensional single nucleotide polymorphism (SNP) and next generation sequence (NGS) data adjusting for covariates. BBB investigators also developed methods for meta-analysis of complex diseases at gene level with generalized functional linear models.

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

- **Paul S. Albert**, Ph.D., Senior Investigator and Chief (departed 08/2016)
- **Aiyi Liu**, Ph.D., Senior Investigator and Acting Chief (effective 08/2016)
- **Rajeshwari Sundaram**, Ph.D., Senior Investigator
- **Zhen Chen**, Ph.D., Investigator
- **Ruzong Fan**, Ph.D., Investigator (departed 09/2016)
- **Danping Liu**, Ph.D., Investigator
- **Sung Duk Kim**, Ph.D., Staff Scientist (departed 08/2016)

Fellows

- **Joe Bible**, Ph.D., Postdoctoral Fellow
- **Olive Buhule**, Ph.D., Postdoctoral Fellow (departed 09/2016)
- **Chi-Yang Chiu**, Ph.D., Postdoctoral Fellow
- **Ling Ma**, Ph.D., Postdoctoral Fellow (departed 08/2016)
- **Sedigheh Mirzaei**, Ph.D., Postdoctoral Fellow
- **Ana Maria Ortega-Villa**, Ph.D., Postdoctoral Fellow
- **Yu-Bo Wang**, Ph.D., Postdoctoral Fellow
- **Wondwosen Yimer**, Ph.D., Postdoctoral Fellow

Aiyi Liu, Ph.D.

Paul Albert, Ph.D.

Zhen Chen, Ph.D.

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.

2016 Analysis of Biomarkers Publications

Danaher MR, Albert PS, Roy A, Schisterman EF. Estimation of interaction effects using pooled biospecimens in a case-control study. *Statistics in Medicine* 2016; 35(9):1502-13. PMID: 26553532

Kang L, Liu A, Tian L. Linear combination methods to improve diagnostic/prognostic accuracy on future observations. *Statistical Methods in Medical Research* 2016; 25: 1359–1380. PMID: 23592714

Malinovsky Y, Albert PS, Roy A. Reader reaction: A note on the evaluation of group testing algorithms in the presence of misclassification. *Biometrics* 2016;72(1):299-302. PMID: 26393800

Sun X, Liu A. Li Z. Maximizing an ROC-type measure via linear combinations of biomarkers. *Health Services and Outcomes Research Methodology* 2016; 16:103-116.

Wu MX, Shu Y, Li Z, Liu A. Repeated significance tests of linear combinations of sensitivity and specificity of a diagnostic biomarker. *Statistics in Medicine* 2016; 35: 3397-3412. PMID: 26947768

Wu MX, Zhang D, Liu A. Estimation of a diagnostic accuracy index of a biomarker when the reference gold standard is continuous and measured with error. *Journal of Biopharmaceutical Statistics* 2016; 26:1111-1117. PMID: 27548574

Ruzong Fan, Ph.D.

ANALYSIS OF GENETIC DATA

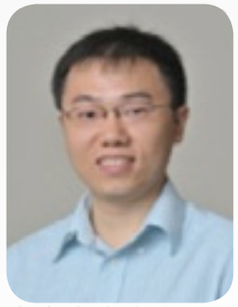
The analysis of genetics data is an active area of biostatistics research and presents unique opportunities and statistical challenges. BBB investigators address these issues by developing new methodologies for analyzing quantitative, qualitative, and survival traits, and in developing statistical methods for detecting gene-gene and gene-environmental interactions of complex diseases. In 2016, BBB investigators investigated gene-based association analysis for censored traits via functional regression analysis, meta-analysis of complex diseases at gene level with generalized functional linear models, and various methods with fixed and mixed effect models for gene level association studies of complex traits. To facilitate translation of our methods, R-codes are publicly available at our website. These R-codes were downloaded from the website over 3300 times.

2016 Analysis of Genetic Data Publications

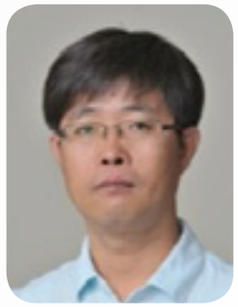
Fan RZ, Chiu CY, Jung JS, Weeks DE, Wilson AF, Bailey-Wilson JE, Amos CI, Chen Z, Mills JL, and Xiong MM (2016) A comparison study of fixed and mixed effect models for gene level association studies of complex traits. *Genetic Epidemiology* 40 (8):702-721. PMID: 27374056

Fan RZ, Wang YF, Chiu CY, Chen W, Ren HB, Li Y, Boehnke M, Amos CI, Moore J, and Xiong MM (2016) Meta-analysis of complex diseases at gene level with generalized functional linear models. *Genetics* 202 (2):457-470. PMID: 26715663

Fan RZ, Wang YF, Q Yan, Ding Y, Weeks DE, Lu ZH, Ren HB, Cook RJ, Xiong MM, and Chen W (2016) Gene-based association analysis for censored traits via functional regressions. *Genetic Epidemiology* 40 (2):133-143. PMID: 26782979



Danping Liu, Ph.D.



Sung Duk Kim, Ph.D

Paul Albert, Ph.D.

LONGITUDINAL AND CORRELATED DATA ANALYSIS

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.

Rajeshwari Sundaram, Ph.D.

ANALYSIS OF TIME-TO-EVENT DATA

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, 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, time to pregnancy and other outcomes related to maternal and child health poses 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.

2016 Longitudinal and Correlated Data Publications

Kim S, Albert PS. A class of joint models for multivariate longitudinal measurements and a binary event. *Biometrics* 2016;72(3):917-25. PMID: 26753988

Mulatya CM, McLain AC, Cai B, Hardin JW, Albert PS. Estimating time to event characteristics via longitudinal threshold regression models - an application to cervical dilation progression. *Statistics in Medicine* 2016;35(24):4368-4379. PMID: 27405611

2016 Time-to-Event Publications

Lum KJ, Sundaram R, Buck Louis GM, Louis TA. A Bayesian joint model of menstrual cycle length and fecundity. *Biometrics* 2016;72(1):193-203. PMID: 26295923 Free PMC Article

McLain AC, Sundaram R, Buck Louis GM. Modeling fecundity in the presence of a sterile fraction using a semi-parametric transformation model for grouped survival data. *Statistical Methods in Medical Research* 2016;25(1):22-36. PMID: 22374340

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.

2016 Collaborative Publications

Boghossian NS, Sicko RJ, Kay DM, Rigler SL, Caggana M, Tsai MY, Yeung EH, Pankratz N, Cole BR, Druschel CM, Romitti PA, Browne ML, Fan RZ, Liu A, Brody LC, Mills JL. Rare copy number variants implicated in posterior urethral valves. *American Journal of Medical Genetics Part A 2016;* 170(3):622-633. PMID: 26663319

Buck Louis GM, Backonja U, Schliep KC, Sun, L, Peterson M, Chen Z. Women's Reproductive History Prior to the Diagnosis of Incident Endometriosis. *Women's Health* 25(10):1021-9, 2016. PMID: 27379997

Buck Louis, GM, Barr, DB, Kannan, K, Chen, Z, Kim, S, Sundaram, R. Paternal Exposures to Environmental Chemicals and Time-to-Pregnancy: Overview of Results from the LIFE Study. *Andrology* 4(4):639-47, 2016. PMID: 27061873

Buck Louis GM, Sapra KJ, Schisterman EF, Lynch CD, Maisog JM, Grantz KL, Sundaram R. Lifestyle and pregnancy loss in a contemporary cohort of women recruited before conception: The LIFE Study. *Fertility and Sterility* 2016;106(1):180-8. PMID: 27016456

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Dimopoulos A, Sicko RJ, Kay DM, Rigler SL, Fan RZ, Romitti PA, Browne ML, Druschel CM, Caganna M, Brody LC, Mills JL (2016) Copy number variants in population based investigation of Klippel Trenaunay Weber syndrome. *American Journal of Medical Genetics Part A* 173A:352-359. PMID: 27901321

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The Epidemiology Branch's mission is threefold:

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

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 etiology, determinants, 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, pediatric, and methodologic epidemiology.

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
- **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

Fellows

- **Mehnaz Ali**, B.S., Postbaccalaureate Fellow (departed in 2016)
- **Griffith Bell**, Ph.D., Postdoctoral Fellow
- **Alaina Bever**, B.S., Postbaccalaureate Fellow
- **Nikhita Chahal**, B.S., Postbaccalaureate Fellow (departed in 2016)
- **Ellen Chaljub**, B.S., Postbaccalaureate Fellow (departed in 2016)
- **Matt Connell**, M.D., Clinical Fellow
- **Sharon Dar**, M.P.H., Special Volunteer (departed in 2016)
- **Angela Dimopoulos**, M.D., Postdoctoral Fellow (departed in 2016)
- **Akhgar Ghassabian**, Ph.D., Postdoctoral Fellow (departed in 2016)
- **Adreas Giannakou**, M.D., Postdoctoral Fellow
- Sandie Ha, Ph.D., Postdoctoral Fellow
- **Tiffany Holland**, B.S., Postbaccalaureate Fellow
- **Keewan Kim**, Ph.D., Postdoctoral Fellow
- **Sung Soo Kim**, Ph.D., Visiting Fellow (departed in 2016)
- **Dan Kuhr**, B.S., MSRP Fellow
- **Yuan Lin**, M.D., Visiting Fellow
- **Kara Michels**, Ph.D., Postdoctoral Fellow (departed in 2016)
- **Carrie Nobles**, Ph.D., Postdoctoral Fellow
- **Ukpebo Rebecca Omosigho**, B.S., MSRP Fellow
- **Torie Plowden**, M.D., Clinical Fellow (departed in 2016)
- **Pranati Panuganti**, B.S., Postbaccalaureate Fellow
- **Hyojun Park**, Ph.D., Postdoctoral Fellow
- **Sarah Pugh**, Ph.D., M.P.H., Postdoctoral Fellow
- **Rose Radin**, Ph.D., M.P.H., Postdoctoral Fellow
- **Shristi Rawal**, Ph.D., Postdoctoral Fellow
- **Indulaxmi Seeni**, B.S., Postbaccalaureate Fellow
- **Melissa Smarr**, Ph.D., Postdoctoral Fellow (departed in 2016)
- **Chandra Swanson**, B.S., Postbaccalaureate Fellow (departed in 2016)
- **Yeyi Zhu**, Ph.D., Postdoctoral Fellow (departed in 2016)

2016 Awards

Nikhita Chahal, *Postbaccalaureate Fellow* (Mentor: Edwina Yeung), NIH Postbac Poster Day Outstanding Poster Award, National Institutes of Health, Bethesda, MD.

Sarah Pugh, Ph.D., *Postdoctoral Fellow* (Mentor: Katherine Grantz, M.D., M.S.), Fellows Award for Research Excellence, National Institutes of Health, Bethesda, MD.

Rose Radin, Ph.D., *Postdoctoral Fellow* (Mentor: Enrique Schisterman, Ph.D.), Lilienfeld Postdoctoral Paper Prize Award, Society for Epidemiologic Research, Miami, FL.

Shristi Rawal, Ph.D., *Postdoctoral Fellow* (Mentor: Cuilin Zhang, M.D., Ph.D., MPH), Fellows Award for Research Excellence (FARE), NIH, Bethesda, MD.

Shristi Rawal, Ph.D., *Postdoctoral Fellow* (Mentor: Cuilin Zhang, M.D., Ph.D., MPH), Early Career Grant Challenge Award Finalist and Travel Grant Recipient, The Obesity Society, New Orleans, LA.

Enrique F. Schisterman, Ph.D., *Chief and Senior Investigator*, Mentoring Award, Society for Pediatric and Perinatal Epidemiologic Research, Miami, FL.

Cuilin Zhang, M.D., Ph.D., MPH, *Senior Investigator*, NICHD Mentoring Award, National Institutes of Health, Bethesda, MD.

Yeyi Zhu, Ph.D., *Postdoctoral Fellow* (Mentors: Cuilin Zhang, M.D., Ph.D., MPH and Pauline Mendola, Ph.D.), Fellows Award for Research Excellence (FARE), NIH, Bethesda, MD.

Yeyi Zhu, Ph.D., *Postdoctoral Fellow* (Mentors: Cuilin Zhang, M.D., Ph.D., MPH and Pauline Mendola, Ph.D.), Early Investigator Travel Award, American Heart/Stroke Association, Phoenix, AZ.

Yeyi Zhu, Ph.D., *Postdoctoral Fellow* (Mentors: Cuilin Zhang, M.D., Ph.D., MPH and Pauline Mendola, Ph.D.), Russell Kirby Travel Scholarship, Epidemiology Congress of the Americas, Miami, FL.

Yeyi Zhu, Ph.D., *Postdoctoral Fellow* (Mentors: Cuilin Zhang, M.D., Ph.D., MPH and Pauline Mendola, Ph.D.), Travel Award, Society for Pediatric and Perinatal Epidemiology, Miami, FL.

Yeyi Zhu, Ph.D., *Postdoctoral Fellow* (Mentors: Cuilin Zhang, M.D., Ph.D., MPH and Pauline Mendola, Ph.D.), Poster Award, Epidemiology Congress of the Americas, Miami, FL.

The field of **reproductive health epidemiology** focuses on the many factors that affect human fecundity and fertility,

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

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

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) Study, 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.

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

Division Collaborators
- **Ellen Chaljub**, B.S.
- **Keewan Kim**, Ph.D.
- **Pauline Mendola**, Ph.D., M.S.
- **Kara Ann Michels**, Ph.D.
- **Neil J. Perkins**, Ph.D., M.S.
- **Torie Plowden**, M.D.
- **Rose Radin**, Ph.D., M.P.H.
- **Lindsey A. Sjaarda**, Ph.D., M.S.
- **Chandra Swanson**, B.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, almost 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 serum antioxidants (Mumford et al. *Journal of Nutrition* 2016), serum caffeine (Schliep et al. *American Journal of Clinical Nutrition* 2016), and dietary fat (Mumford et al. *American Journal of Clinical Nutrition* 2016). These findings have highlighted the important role of diet in reproductive function. Further research evaluating potential environmental factors, including urinary phenol and paraben metabolites, found that these markers were variable across two months in healthy women, highlighting that additional biospecimens may be needed to characterize exposure for

certain compounds (Pollack et al. *Environmental Research* 2016). In addition, it was also observed that medication use (Johnson et al. *Pharmacoepidemiology and Drug Safety* 2016) and protein intake (Gorczyca et al. *European Journal of Nutrition* 2016) vary across the menstrual cycle. 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.

2016 BioCycle Study Publications

Gorczyca AM, Sjaarda LA, Mitchell EM, Perkins NJ, Schliep KC, Wactawski-Wende J, Mumford SL. Changes in macronutrient, micronutrient, and food group intake throughout the menstrual cycle in healthy, premenopausal women. *European Journal of Nutrition* 2016;55(3):1181-1188. PMID: 26043860

Johnson KA, Sjaarda LA, Mumford SL, Garbose RA, Schliep KC, Mattison D, Perkins NJ, Wactawski-Wende J, Schisterman EF. Patterns and prevalence of medication use across the menstrual cycle among healthy, reproductive aged women. *Pharmacoepidemiology and Drug Safety* 2016;25(6):618-627. PMID: 26954695

Mumford SL, Browne RW, Schliep KC, Schmelzer J, Plowden TC, Michels KA, Sjaarda LA, Zarek SM, Perkins NJ, Messer LC, Radin RG, Wactawski-Wende J, Schisterman EF. Serum antioxidants are associated with serum reproductive hormones and ovulation among healthy women. *Journal of Nutrition* 2016;146(1):98-106. PMID: 26581679

Mumford SL, Chavarro JE, Zhang C, Perkins NJ, Sjaarda LA, Pollack AZ, Schliep KC, Michels KA, Zarek SM, Plowden TC, Radin RG, Messer LC, Frankel RA, Wactawski-Wende J. Dietary fat intake and reproductive hormone concentrations and ovulation in regularly menstruating women. *American Journal of Clinical Nutrition* 2016;103(3):868-877. PMID: 26843151

Pollack AZ, Perkins NJ, Sjaarda LA, Mumford SL, Kannan K, Philippat C, Wactawski-Wende J, Schisterman EF. Variability and exposure classification of urinary phenol and paraben metabolite concentrations in reproductive-aged women. *Environmental Research* 2016;151:513-520. PMID: 27567355

Schliep KC, Schisterman EF, Wactawski-Wende J, Perkins NJ, Radin RG, Zarek SM, Mitchell EM, Sjaarda LA, Mumford SL. Serum caffeine and paraxanthine concentrations and menstrual cycle function: correlations with beverage intakes and associations with race, reproductive hormones, and anovulation in the BioCycle Study. *American Journal of Clinical Nutrition* 2016;104(1):155-163. PMID: 27225433

Shimony MK, Schliep KC, Schisterman EF, Ahrens K, Sjaarda LA, Rotman Y, Perkins NJ, Pollack AZ, Wactawski-Wende J, Mumford SL. The relationship between sugar-sweetened beverages and liver enzymes among healthy premenopausal women: a prospective cohort study. *European Journal of Nutrition* 2016;55(2):569-576. PMID: 25801628

EAGER: EFFECTS OF ASPIRIN IN GESTATION AND REPRODUCTION (EAGER) STUDY

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

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

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 outcome. In this trial, 1,228 regularly menstruating women aged 18-40 years with a history of one or two miscarriages and trying to become pregnant again were block randomized to either the treatment group (daily aspirin [81mg] plus folic acid [0.4 mg]) or the placebo group (folic acid [0.4 mg]). Treatment or placebo administration began prior to conception and continued for 6 months of trying to conceive or through week 36 of pregnancy among women who became pregnant during the trial. 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 one or two prior pregnancy losses, regardless of gestational age of the loss or time since the loss occurred. Women used fertility monitors to help time intercourse relative to ovulation and used digital home pregnancy tests for detecting pregnancy. Urine was collected at clinic visits for detecting very early pregnancies and losses.

The primary outcomes of the EAGeR trial were published in 2014 (Schisterman et al. *Lancet* 2014), with additional findings regarding secondary outcomes published in 2015 and 2016. Overall, we found that a daily low dose of aspirin does not appear to prevent subsequent pregnancy loss among women with a history of one or two prior pregnancy losses (Schisterman et al. Lancet 2014; Mumford et al. *Human Reproduction* 2016). In addition, we found that preconception low-dose aspirin was well tolerated by women trying to conceive, and among women who became pregnant, and that rates of maternal, fetal, and neonatal complications were similar between treatment arms (Ahrens et al. *Obstetrics and Gynecology* 2016).

Principal Investigators

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

Division Collaborators

- **Ellen Chaljub**, B.S.
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- **Sarah Pugh**, Ph.D.
- **Rose Radin**, Ph.D., M.P.H.
- **Lindsey A. Sjaarda**, Ph.D., M.S.
- **Chandra Swanson**, B.S.
- **Edwina Yeung**, Ph.D., Sc.M.
- **Cuilin Zhang**, M.D., Ph.D., M.P.H.

We have also evaluated the utility of routine anti-Mullerian hormone (AMH) testing for prediction of pregnancy loss and preconception counseling in young, fecund women and have found that AMH levels were not associated with pregnancy loss (Zarek et al. *Fertility and Sterility* 2016). Thus, our data do not support routine AMH testing in fertile women. Moreover, our data also suggest that the current recommendations for delaying

pregnancy attempt after an early loss may be unwarranted (Schliep et al. *Obstetrics and Gynecology* 2016). We also evaluated the role of subclinical hypothyroidism and antithyroid antibodies and found no associations with time to pregnancy and pregnancy loss, which are reassuring findings for women with subclinical hypothyroidism (Plowden et al. *Journal of Clinical Endocrinology and Metabolism* 2016). Importantly, we found that nausea and vomiting were common very early in pregnancy and were associated with a reduced risk for pregnancy loss (Hinkle et al. *JAMA Internal Medicine* 2016). These findings overcome prior analytic and design limitations and represent the most definitive data available to date indicating the protective association of nausea and vomiting in early pregnancy and the risk for pregnancy loss. The team intends to build upon its current findings from the EAGeR Trial to fill critical research gaps in its quest to answer important public health questions for women of reproductive age.

2016 EAGeR Study Publications

Ahrens KA, Silver RM, Mumford SL, Sjaarda LA, Perkins NJ, Wactawski-Wende J, Galai N, Townsend JM, Lynch AM, Lesher LL, Faraggi D, Zarek S, Schisterman EF. Complications and safety of preconception low-dose aspirin among women with prior pregnancy loss. *Obstetrics and Gynecology* 2016;127(4):689-698. PMID: 26959198

Hinkle SN, Mumford SL, Grantz KL, Silver RM, Mitchell EM, Sjaarda LA, Radin RG, Perkins NJ, Galai N, Schisterman EF. Association of nausea and vomiting during pregnancy with pregnancy loss: a secondary analysis of a randomized clinical trial. *JAMA Internal Medicine* 2016;176(11):1621-1627. PMID: 27669539

Mumford SL, Silver RM, Sjaarda LA, Wactawski-Wende J, Townsend JM, Lynch AM, Galai N, Lesher LL, Faraggi D, Perkins NJ, Schliep KC, Zarek SM, Schisterman EF. Expanded findings from a randomized controlled trial of preconception low-dose aspirin and pregnancy loss. *Human Reproduction* 2016;31(3):657-565. PMID: 26759138

Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, Galai N, DeCherney AH, Mumford SL. Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss or live birth. *Journal of Clinical Endocrinology and Metabolism* 2016;101(6):2358-2365. PMID: 27023447 (With discussion)

Schliep KC, Mitchell EM, Mumford SL, Radin RG, Zarek SM, Sjaarda L, Schisterman EF. Trying to conceive after an early pregnancy loss: an assessment on how long couples should wait. *Obstetrics and Gynecology* 2016;127(2):204-212. PMID: 26942344 (With discussion)

Zarek SM, Mitchell EM, Sjaarda LA, Mumford SL, Silver RM, Stanford JB, Galai N, Schliep KC, Radin RG, Plowden TC, DeCherney AH, Schisterman EF. Antimüllerian hormone and pregnancy loss from the Effects of Aspirin in Gestation and Reproduction trial. *Fertility and Sterility* 2016;105(4):946-952.e2. PMID: 26707905

FOLIC ACID AND ZINC SUPPLEMENTATION TRIAL (FAZST)

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

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

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 is 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 is 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 are 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. The trial is ongoing and currently recruiting with expected completion of participant recruitment in December 2017. (See NCT Clinical Trials.gov Number: NCT01857310.)

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2016 FAZST Publications

Ongoing study; none to date.

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 dietary intake 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 (ART). The objective of the IDEAL study is to evaluate the impact of dietary and other modifiable 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.

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2016 IDEAL Publications

Ongoing study; none to date.

IDEAL participants will complete the same activities as female partners in FAZST (a baseline visit with a questionnaire and biospecimen collection; monthly questionnaires updating their pregnancy and fertility treatment status; and follow-up for pregnancy outcomes via medical record abstraction). The IDEAL study expands this follow-up to include additional biospecimen collection, as well as the addition of a fitness tracker to wear throughout the study follow-up. These women will also have scheduled follow-up questionnaires at two points during their fertility treatment, as well as at-home biospecimen collection. If they become pregnant during the follow-up period (up to 9 months post-randomization), they will have three additional pregnancy follow-up clinic visits. Data regarding diet, exercise, and lifestyle will be collected throughout the follow-up period. Recruitment began in early 2016 and is currently ongoing with expected completing in 2017.

EPIDEMIOLOGIC RESEARCH OF PREGNANCY FOCUSES ON THE HEALTH AND WELL-BEING OF PREGNANT WOMEN AND PREGNANCY OUTCOMES.

Branch investigators use a life course epidemiologic research paradigm. As such, pregnancy complications are understood in the context of pre- and peri-conceptional factors, as well as in relation to later onset diseases and inter-generational effects. 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) Consecutive Pregnancies Study [Biostatistics and Bioinformatics Branch]; 5) Diabetes and Women's Health Study; 6) Gestational Diabetes Mellitus: Epidemiology, Etiology and Health Consequences; and 7) NICHD Fetal Growth Studies. A brief description of each study follows.

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

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

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. More than 200 women were enrolled and more than 160 of them had delivered by the end of 2016.

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- **Yeyi Zhu**, Ph.D.

2016 B-WELL Mom Study Publications

Ongoing study; none to date.

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COLLABORATIVE PERINATAL PROJECT (CPP) MORTALITY LINKAGE

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. Children were followed up to 7 years of age.

The overarching goal of the CPP mortality linkage study is to link this pregnancy cohort with the National Death Index (NDI) to investigate the associations between a spectrum of pregnancy-related complications and overall and cause-specific mortality. This linkage study will facilitate assessment of hypotheses regarding the relationship between gravid health and overall and cause-specific mortality. Currently, the linkage is being readied for implementation.

Examples of specific hypotheses to be examined are listed below:

1. Pregnancy-induced hypertension and preeclampsia are significantly associated with total mortality and cause-specific mortality, in particular CVD mortality.

2. Asthma in pregnancy is significantly associated with total mortality and cause-specific mortality.

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2016 CPP Mortality Linkage Publications

Ongoing study; none to date.

3. Preterm delivery is significantly associated with total mortality and cause-specific mortality.

4. A longer-time-to-pregnancy is significantly 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 significantly associated with total mortality and cause specific mortality.

CONSORTIUM ON SAFE LABOR

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

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

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 2016, we explored pregnancy complications in obese women, because there is interest in whether obese, but metabolically healthy, subgroups exist. We found that women who were obese but without any pre-pregnancy chronic diseases were at significantly increased risk of a wide range of obstetric interventions and obstetric and neonatal complications compared with normal BMI women (Kim et al. Obstetrics & Gynecology 2016). Moreover, obese women who entered pregnancy without comorbidity, did not develop pregnancy complications such as gestational hypertensive disorders or gestational diabetes, and gained weight within recommended guidelines, still experienced elevated risk for obstetric and neonatal complications, indicating that optimizing maternal weight prior to pregnancy is important for all women. Additional work was conducted that addressed the ongoing debate for how to best define fetal growth abnormalities by assessing whether clinicians should be using a definition customized for maternal and fetal characteristics, such as maternal height and fetal sex. We completed rigorous investigations of the different customized definitions for defining abnormal birthweight including small-for-gestational age birthweight among obese women delivering at term (Hinkle et al. *British Journal of Obstetrics and Gynaecology* 2016). We found that customized definitions did not improve detection of neonates at risk for adverse perinatal outcomes. Importantly, small-for-gestational age neonates of obese women had a fivefold increased risk for mortality, highlighting the clinical importance of monitoring for SGA among obese women. In another analysis, we found that deliveries complicated by maternal psychiatric disorders, particularly when complicated by anxiety disorders, were associated with an increased risk of both spontaneous and indicated preterm delivery, even for earlier gestational ages less than 34 and 28 weeks' gestation (Männistö et al. *Annals of Epidemiology* 2016). These findings have important public health implications given that 7.3% of women in our study had a psychiatric diagnosis recorded in their medical record or discharge summary. Our work on social factors continued in 2016 where we found that state-level income inequality was associated with preterm birth rates (Wallace et al. *Maternal Child Health Journal* 2016).

We have also linked publicly available 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. The relationship between air pollutants and acute cardiac events

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- **Raji Sundaram**, Ph.D.
- **Cuilin Zhang**, M.D., Ph.D., M.P.H.

is well established in the general population, with the greatest effects seen in vulnerable populations. We found that ozone exposure in the week and hours prior to admission for delivery was associated with premature rupture of membranes (Wallace et al. *American Journal of Epidemiology* 2016) and that women with asthma had differentially higher risks for preterm birth and preeclampsia at the same level of exposure as non-asthmatics (Mendola et al. Journal of Allergy and Clinical Immunology 2016; *Mendola et al. Environmental Research* 2016).

Collectively, this body of research continues to provide data useful for the ongoing development of clinical guidance regarding the management of contemporary pregnant women. Another important undertaking was making this data publicly available via the NICHD DASH website, thereby, encouraging continued prolific publication from this cohort study.

2016 Consortium on Safe Labor Publications

Aliaga S, Zhang J, Long DL, Herring AH, Laughon M, Boggess K, Reddy UM, Grantz KL. Center variation in the delivery of indicated late preterm births. *American Journal of Perinatology* 2016;33(10):1008-16. PMID: 27120474

Hinkle SN, Sjaarda LA, Albert PS, Mendola P, Grantz KL. Comparison of methods for identifying small-for-gestational-age infants at risk of perinatal mortality among obese mothers: a hospital-based cohort study. British Journal of Obstetrics and Gynaecology, 2016;123(12):1983-1988. PMID: 26853429

Kim SS, Zhu Y, Grantz KL, Hinkle SN, Chen Z, Wallace M, Smarr MM, Epps NM, Mendola P. Obstetric and neonatal risks among obese women without chronic disease. *Obstetrics & Gynecology* 2016;128(1):104-112. PMID: 27275800

Männistö T, Mendola P, Kiely M, O'Loughlin J, Werder E, Chen Z, Ehrenthal DB, Grantz KL. Maternal psychiatric disorders and risk of preterm birth. *Annals of Epidemiology*, 2016;26(1):14-20. PMID: 26586549

Mendola P, Wallace M, Hwang BS, Liu D, Robledo C, Männistö T, Sundaram R, Sherman S, Ying Q, Grantz KL. Preterm birth and air pollution: Critical windows of exposure for women with asthma. *Journal of Allergy and Clinical Immunology* 2016;138(2):432-440.e5. PMID: 26944405

Mendola P, Wallace M, Liu D, Robledo C, Männistö T, Grantz KL. Air pollution exposure and preeclampsia among US women with and without asthma. *Environmental Research* 2016;148:248-255. PMID: 27085496

Wallace ME, Grantz KL, Liu D, Zhu Y, Kim SS, Mendola P. Exposure to ambient air pollution and premature rupture of membranes. *American Journal of Epidemiology* 2016;183(12):1114-1121. PMID: 27188941

Wallace ME, Mendola P, ChenZ, Hwang BS, Grantz KL. Preterm birth in the context of increasing income inequality. *Maternal Child Health Journal* 2016;20(1):164-171. PMID: 26450504

DIABETES & WOMEN'S HEALTH (DWH) STUDY

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

The DWH Study utilizes a hybrid design combining longitudinal collected historical data with prospective new data collection to further understand and discover novel pathways and determinants underlying the progression of gestational diabetes (GDM) to type 2 diabetes (T2DM) and related complications.

GDM is a common pregnancy complication. Women who develop impaired glucose tolerance in pregnancy and/or GDM are at substantially increased risk for T2DM and cardio-metabolic disorders in the years following pregnancy. Determinants underlying the transition from GDM to T2DM and co-morbidities are not well understood. There is limited information about the genetic and environmental factors that impact this transition. The overall goal of this 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 the women at high risk, as well as to understand the underlying molecular mechanisms of these relationships. A secondary goal of this study is to collect baseline information of children born from the pregnancies complicated by glucose intolerance.

Data collection for this study was leveraged from 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) that may predict T2DM risk. Biospecimens (blood, urine, saliva, and toenails) were collected from

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2016 Diabetes & Women's Health Publications

Bao W, Li S, Chavarro JE, Tobias K, Zhu Y, Zhang C. Low-carbohydrate-diet scores and long-term risk of type 2 diabetes among women with a history of gestational diabetes: a prospective cohort study. *Diabetes Care* 2016;39(1):43-9. PMID: 26577416

Bao W, Chavarro JE, Tobias K, Bowers K, Li S, Hu FB, Zhang C. Long-term risk of type 2 diabetes in relation to habitual iron intakes among women with a history of gestational diabetes: a prospective cohort study. *American Journal of Clinical Nutrition* 2016;103(2):375-81. PMID: 26762369

Li S, Zhu Y, Chavarro J, Bao W, Tobias D, Ley S, Forman J, Liu A, Mills J, Bowers K, Strøm M, Hansen S, Hu F, Zhang C. Healthful dietary patterns and the risk of hypertension among women with a history of gestational diabetes: a prospective cohort study. *Hypertension* 2016;67(6):1157-65. PMID: 27091899

Zhu Y and Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. *Current Diabetes Reports* 2016;16(1):7. PMID: 26742932

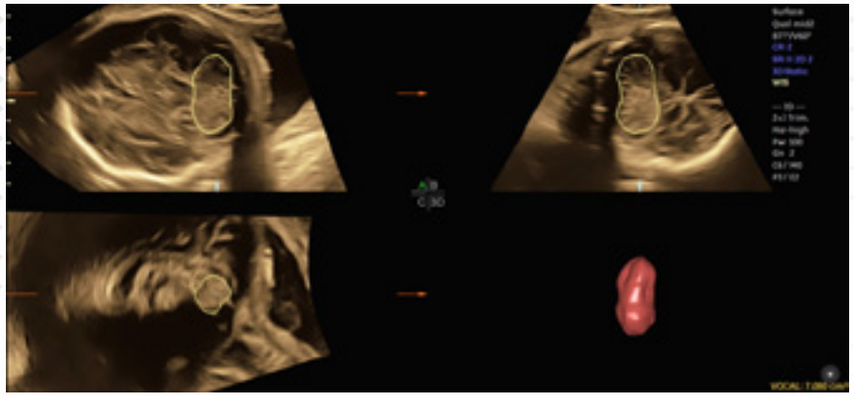
women for measurement of genetic and biochemical markers (both pathway specific and non-targeted) relevant to glucose metabolism. Key medical and environmental factors and covariates were collected using standardized questionnaires for both cohorts. The overall design paper was published in 2014 (Zhang et al. *Acta Obstetricia et Gynecologica Scandinavica* 2014). An invited review paper on a global perspective of the risk of progression from GDM to T2DM was published in 2016 (Zhu et al. *Current Diabetes Reports* 2016). Active data collection for the DWH study was just recently completed in September 2016.

In light of the study's unique design, data analysis was underway while the cohort was being followed. Examples of key findings to date include our observations that unhealthy dietary patterns such as a diet with a low-carbohydrate-diet score high in animal sources of protein and fat (Bao et al. *Diabetes Care* 2016) and greater intakes of total or dietary heme iron (Bao et al. *American Journal of Clinical Nutrition* 2016), were strongly and independently related to a higher risk of progression from GDM to T2DM. In addition, we found that adherence to a healthful dietary pattern was related to a lower subsequent risk of developing hypertension among women with a history of GDM (Li et al. *Hypertension* 2016). These findings identify potentially modifiable diet and lifestyle factors that may help lower the risk for T2DM and comorbidities among women with GDM, which composes a hopeful message to women at high risk.

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

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



Vocal (Virtual Organ Computer-Aided Analysis) tracing of fetal cerebellar volume.

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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- **Sarah Pugh**, Ph.D., M.P.H.
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- **Cuilin Zhang**, M.D., M.P.H., Ph.D.

2016 Fetal 3D Publications

Ongoing study; none to date.

GESTATIONAL DIABETES MELLITUS: EPIDEMIOLOGY, ETIOLOGY, AND HEALTH CONSEQUENCES

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

Gestational diabetes mellitus (GDM), one of the most common complications of pregnancy, 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 and targeted intervention strategies to prevent GDM and to interrupt the vicious cycle across generations involving maternal GDM, childhood obesity, impaired glucose metabolism, and adulthood-onset diabetes. Along this line of research, we are conducting studies to address the following topics:

1. Identification of risk factors (e.g., diet, lifestyle, reproductive history, and genetic factors) for the development of GDM and its recurrence. In collaboration with investigators at the Harvard T. H. Chan School of Public Health and other institutions, many novel risk factors have been identified and additional risk factors are currently under study based on data from the Nurses' Health Study II. Risk factors during pregnancy are also being investigated based on data from the NICHD Fetal Growth Studies and the Danish National Birth Cohort.

2. Investigation of the pathogenesis of GDM using prospectively and longitudinally collected biospecimens from pregnancy cohorts, such as the NICHD Fetal Growth Studies. Currently, this line of research focuses on a comprehensive panel of biochemical markers that are putatively implicated in glucose homeostasis, fetal growth, or both. Targeted and non-targeted metabolomics were analyzed for the discovery of new pathways and/or biochemical markers related to glucose intolerance and subsequent adverse fetal outcomes. Measurement of biomarkers in multiple pathways for glucose metabolism has been completed. Data analyses and manuscript preparations are underway.

3. Investigation of the impact and underlying mechanisms of how a hyperglycemic intrauterine environment affects short-term and long-term health outcomes in the offspring based on multiple datasets, for instance, the Diabetes & Women's Health (DWH) Study.

We have identified several factors before and during pregnancy that are significantly related to GDM risk, furthering our understanding of the etiology of GDM. For example, women with a younger age at menarche (Chen et al. *Diabetes Care* 2016) and women whose mother smoked during pregnancy (Bao et al. *International Journal of Epidemiology* 2016) have an increased risk for developing GDM. In addition, pre-pregnancy potato consumption was identified as an important modifiable risk factor for GDM (Bao et al. *British Medical*

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- **Edwina Yeung**, Ph.D., Sc.M.
- **Yeyi Zhu**, Ph.D.

Journal 2016). Furthermore, maternal depression (Hinkle et al. *Diabetologia* 2016) and sleep duration (Rawal et al. *American Journal of Obstetrics and Gynecology* 2016) early in pregnancy are also associated with an increased risk for developing GDM. We recently published an invited review on emerging diet, lifestyle, and other factors that may help to prevent GDM, and the challenges associated with prevention (Zhang et al. *Diabetologia* 2016). Overall the research is optimistic for GDM prevention, and while not all GDM events can be prevented, lifestyle interventions introduced early in pregnancy or before pregnancy have the potential of preventing GDM development, at least among some women.

We have also focused on understanding the pathophysiology of GDM by studying the role of maternal biomarkers, such as the insulin-like growth factor axis (Zhu et al. Diabetes 2016) or iron (Rawal et al. Diabetologia 2016), in the development and prediction of GDM. Specifically, biomarkers in the insulin growth factor axis in early pregnancy may be implicated in the pathogenesis of GDM and could improve GDM prediction, approximately 10-18 weeks earlier than typical GDM screening. The findings from this work will offer potential for GDM prediction and insights into the pathophysiology of the disease.

Findings from the GDM related research add to the accumulating evidence suggesting that adverse intrauterine exposures may lead to permanent fetal adaptations in anatomy and physiology, which may be beneficial for short term fetal survival, but result in an altered long-term risk of disease later in life. In particular, among women with GDM, maternal glucose concentrations during pregnancy were significantly and positively associated with offspring birth size and childhood overweight/obesity risk (Zhu et al. *American Journal of Clinical Nutrition* 2016).

2016 Gestational Diabetes Mellitus Publications

Bao W, Michels KB, Tobias DK, Li S, Chavarro JE, Gaskins AJ, Vaag A, Hu FB, Zhang C. Parental smoking during pregnancy and the risk of gestational diabetes in the daughter. International Journal of Epidemiology 2016;45(1):160-9. PMID: 26748845

Bao W, Tobias D, Hu FB, Chavarro JE, Zhang C. Pre-pregnancy potato consumption and risk of gestational diabetes mellitus: prospective cohort study. British Medical Journal 2016;352:h6898. PMID: 26759275

Bowers KA, Olsen SF, Bao W, Halldorsson TI, Strøm M, Zhang C. Plasma concentrations of ferritin in early pregnancy are associated with risk of gestational diabetes mellitus in women in the Danish National Birth Cohort. Journal of Nutrition 2016;146(9):1756-61 PMID: 27511926

Chen L, Li S, He C, Zhu Y, Buck Louis GM, Yeung E, Zhang C. Age at menarche and risk of gestational diabetes mellitus: a prospective cohort study among 27,482 women. Diabetes Care 2016;39(3):469-71. PMID: 26813668

Rawal S, Hinkle SN, Bao W, Zhu Y, Grewal J, Albert PS, Weir N, Tsai MY, Zhang C. A longitudinal study of iron status during pregnancy and the risk of gestational diabetes: findings from a prospective, multiracial cohort. Diabetologia, Epub Nov 10, 2016. PMID: 27830277

Zhang C, Rawal S, Chong Y. Risk Factors of diabetes in pregnancy: is prevention possible? Diabetologia 2016;59(7):1385-90. PMID: 27165093

Zhu Y, Mendola P, Albert PS, Bao W, Hinkle SN, Tsai MY, Zhang C. Insulin-like growth factor axis and gestational diabetes: A longitudinal study in a multiracial cohort. Diabetes 2016;65(11):3495-3504. PMID: 27468747

Zhu Y, Olsen SF, Mendola P, Yeung EH, Vaag A, Bowers K, Liu A, Bao W, Li S, Madsen C, Grunnet LG, Granström C, Hansen S, Martin K, Chavarro JE, Hu FB, Langhoff-Roos J, Damm P, Zhang C. Growth and obesity through the first 7 years of life in association with levels of maternal glycemia during pregnancy: A prospective cohort study. American Journal of Clinical Nutrition 2016;103(3):794-800. PMID: 26817507

NICHD FETAL GROWTH STUDY

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

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

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

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.

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 main paper on obesity and fetal growth trajectories was submitted and is currently under review.

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- **Melissa Smarr**, Ph.D.
- **Yeyi Zhu**, Ph.D.

2016 Fetal Growth Studies' Publications

Grantz KL, Grewal J, Albert PS, Wapner R, D'Alton ME, Sciscione A, Grobman WA, Wing DA, Owens J, Newman RB, Chien EK, Gore-Langton RE, Kim S, Zhang C, Buck Louis GM, Hediger ML. Dichorionic twin trajectories: the NICHD Fetal Growth Studies. *American Journal of Obstetrics & Gynecology* 2016;215(2):221.e1-221.e16. PMID: 27143399 (Featured as Editors' Choice)

Hediger ML, Fuchs KM, Grantz KL, Grewal J, Kim S, Gore-Langton RE, Buck Louis GM, D'Alton ME, Albert PS. Ultrasound quality assurance for singletons in the National Institute of Child Health and Human Development Fetal Growth Studies. *Journal of Ultrasound in Medicine* 2016;35(8):1725-33. PMID: 27353072

Hinkle SN, Buck Louis GM, Rawal S, Zhu Y, Albert PS, Zhang C. A longitudinal study of depression and gestational diabetes in pregnancy and the postpartum period. *Diabetologia* 2016;59(12):2594-2602. PMID: 27640810

Rawal S, Hinkle SN, Zhu Y, Albert PS, Zhang C. A longitudinal study of sleep duration in pregnancy and subsequent risk of gestational diabetes: findings from a prospective, multiracial cohort. *American Journal of Obstetrics and Gynecology*, Epub Dec 9, 2016. PMID: 27939328

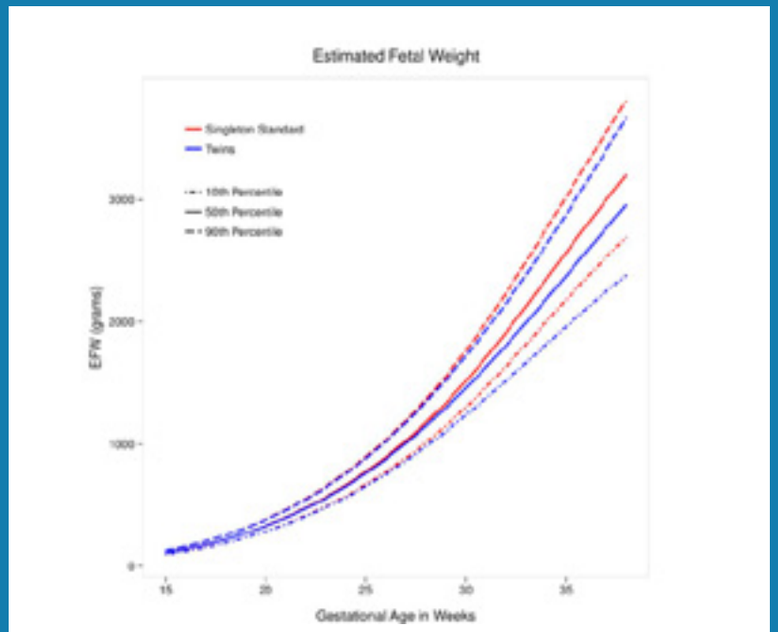
Rawal S, Hinkle SN, Bao W, Zhu Y, Grewal J, Albert PS, Weir N, Tsai MY, Zhang C. A longitudinal study of iron status during pregnancy and the risk of gestational diabetes: findings from a prospective, multiracial cohort. *Diabetologia*, Epub Nov 10, 2016. PMID: 27830277

Zhu Y, Mendola P, Albert PS, Bao W, Hinkle SN, Tsai MY, Zhang C. Insulin-like growth factor axis and gestational diabetes: A longitudinal study in a multiracial cohort. *Diabetes* 2016;65(11):3495-3504. PMID: 27468747

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. We found that compared with singleton fetuses, the mean abdominal circumference and estimated fetal weight trajectories of dichorionic twin fetuses diverged significantly beginning at 32 weeks (Figure; Grantz KL et al. *American Journal of Obstetrics & Gynecology*, 2016). The mean head circumference/ abdominal circumference ratio was progressively larger for twins compared with singletons beginning at 33 weeks', indicating a comparatively asymmetric growth pattern that is consistent with the concept that the intrauterine environment becomes constrained in its ability to sustain growth in twin fetuses. Near term, nearly 40% of twins would be classified as small for gestational age based on a singleton growth standard. The implications of these findings are that, in the short term, careful consideration should be given prior to intervening for dichorionic twin fetuses with a small estimated fetal weight percentile based on a singleton standard in otherwise uncomplicated pregnancies. Yet, future studies with long term follow up are needed.

Distribution of estimated fetal weight by number of fetuses and gestation, NICHD Fetal Growth Studies – Twin Gestations.



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

The NICHD Fetal Growth Studies is the basis for the study aimed at assessing the role of biomedical markers and metabolomics in the development of gestational diabetes (GDM) and in fetal growth. 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. Biomedical markers and metabolomics 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). The primary aim is to investigate the etiology of GDM and identify biomedical markers that can aid in the early prediction of GDM. Given the collection of serial 2D/3D ultrasounds from participating women, this study can also address questions regarding the interplay of cardio-metabolic biomarkers and metabolomics (both targeted and non-targeted) in relation to fetal growth based on biomarker data measured in the etiology study of GDM.In 2016, potentially

novel biomarkers in early pregnancy were identified being implicated in the pathogenesis of GDM, such as the insulin-like growth factor axis (Zhu et al. *Diabetes* 2016) and iron (Rawal et al. *Diabetologia* 2016). Findings related to iron metabolism in pregnancy are of important clinical and public health significance as they raise concerns on the universal recommendation of iron supplementation for all pregnant women in generally iron-replete populations. Analyses on additional biomarkers on both GDM and fetal growth are ongoing.

Infant and child health epidemiology focuses on the factors that affect the growth, development, and health of children from infancy up to adulthood.

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

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.

Principal Investigators

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

Division Collaborators

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- **Ruzong Fan**, Ph.D.
- **Aiyi Liu**, Ph.D.
- **Mehnaz Ali**, B.S.
- **Angela Dimopoulos**, M.D.
- **Edwina Yeung**, Ph.D., Sc.M.
- **Andreas Giannakou**, M.D.

BIRTH DEFECTS RESEARCH GROUP

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. These factors include folate, vitamin B12, and other B vitamins and their metabolites. The collaborating institutions are the NICHD and National Human Genome Research Institute, The Health Research Board of Ireland, The University of California, Berkeley and the Department of Biochemistry, 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) in order to explore the genetic and biochemical factors that relate to birth defects in depth. The Trinity Student Study quantitative traits genome wide association study (GWAS) has enabled us to collaborate with other institutions to search for genetic factors affecting metabolites of interest. We are currently collaborating with NHGRI and with Memorial University, Newfoundland, Canada to investigate biochemical pathways and genetic effects.

These data have also been valuable for research into statistical methods to examine genetic data. This work was led by Dr. Ruzong Fan in DIPHR. Before leaving NICHD, Dr. Fan

published his work comparing fixed and mixed effects for gene level association studies of complex traits (Fan et al. Genetic *Epidemiology* 2016). Our collaborators at NHGRI have also worked on methods for selecting relevant single nucleotide polymorphisms (SNPs). They expanded on the random forest approach of ranking SNPs for analysis by calculating an importance value relative to an observed minimal importance score (Szymczak et al. *BioData Mining* 2016).

In an investigation that took advantage of the extensive metabolic data collected by our Trinity Students Study, we examined how tryptophan metabolites are related to key immune system markers in healthy adults. We found strong positive associations between interleukin 10 and kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid. Neopterin was strongly positively associated with kynurenine and negatively associated with tryptophan. The strong (p=0.0002) association between interleukin 10 and kynurenine is unexpected and suggests that kynurenine related mechanisms may be involved in downregulation of inflammatory responses in healthy people (Deac et al. *Journal of Nutrition* 2016).

Our research continues to explore factors related to neural tube defects. Neural tube defects are known to have both a genetic and an environmental (dietary) component. The group has conducted extensive investigations into the role of folate enzyme genes and neural tube defects. The major gene responsible for folate uptake is the proton-coupled folate transporter (SLC46A1). We conducted a large collaborative study to examine the role of single nucleotide polymorphisms in this gene in cases of neural tube defects and oral clefts. Despite its key role in folate transfer, SLC46A1 variants were not significantly associated with the risk for either neural tube defects or clefts (VanderMeer et al. *American Journal of Medical Genetics* 2016).

In another example of the value of our quantitative traits GWAS for studying vitamin B12, we investigated the reason that methylmalonic acid (MMA), a commonly used measure of vitamin B12 status, sometimes does not predict status correctly. Investigation of single nucleotide polymorphisms (SNPs) in the HIBCH gene showed that a missense mutation (rs291466) increased expression of the HIBCH enzyme and the encoded protein. Homozygotes had an average of 46% higher MMA concentrations. HIBCH is related to valine catabolism. Therefore, elevated MMA concentrations due to this variant produce false positive tests for vitamin B12 deficiency. Testing for this SNP could resolve equivocal results when testing for vitamin B12 deficiency (Molloy et al. *American Journal of Human Genetics* 2016).

Other research involves examining quantitative traits in The Trinity Student Study 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.

Most recently we collaborated with investigators to follow up on our previous collaborative work showing how genetic variants affected the clotting system's von Willebrand factor (VWF). In this study, we showed that the genetic variants that affect VWF at ABO, VWF and chromosome 2 act primarily by altering VWF clearance, not production (Ozel et al. *Journal of Thrombosis and Haemostasis* 2016).

Preventing folate-related neural tube defects is an important mission. We have reported on the obstacles that are keeping many countries from instituting mandatory fortification,

the most effective preventive measure (Mills. *Birth Defects Research, Part A* 2016).

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 the NICHD, the National Human Genome Research Institute and the New York State Department of Health. Stanford University, the University of Iowa and the California Department of Public Health have joined the collaboration. Via a contract with NICHD, The New York State Congenital Malformations Registry has identified approximately 13,000 children who have major birth defects and suitable unaffected controls among all New York births. This information has been linked to blood spots retained after neonatal testing. DNA has been extracted from anonymous blood spots and used to test for genetic variants associated with these birth defects. We are now collaborating with the California State Department of Public Health Birth Defects Monitoring Program, The California Department of Public Health Genetic Disease Screening Program, the University of Iowa, The Statens Serum Institut in Denmark and the Center for Disease Control's National Birth Defects Prevention Study to search for genetic variants associated with birth defects.

Our recent research has moved from a candidate gene approach to examining copy number variants (CNVs) in birth defects.

Ebstein anomaly is an extremely uncommon defect in which the tricuspid valve is malformed and displaced. We performed a search for rare CNVs in 47 cases with isolated Ebstein anomaly identified in a population-based search of New York State births.

2016 Birth Defects Research Publications

Deac OM, Mills JL, Gardiner CM, Shane B, Quinn L, Midttun Ø, McCann A, Meyer K, Ueland PM, Fan R, Lu Z, Brody LC, Molloy AM. Serum immune system biomarkers neopterin and interleukin-10 are strongly related to tryptophan metabolism in healthy young adults. *Journal of Nutrition* 2016;146(9):1801-6. PMID: 27489009

Fan R, Chiu CY, Jung J, Weeks DE, Wilson AF, Bailey-Wilson JE, Amos CI, Chen Z, Mills JL, Xiong M. A comparison study of fixed and mixed effect models for gene level association studies of complex traits. *Genetic Epidemiology* 2016;40(8):702-721. PMID: 27374056

Hagen EM, Sicko RJ, Kay DM, Rigler SL, Dimopoulos A, Ahmad S, Doleman MH, Fan R, Romitti PA, Browne ML, Caggana M, Brody LC, Shaw GM, Jelliffe-Pawlowski LL, Mills JL. Copy-number variant analysis of classic heterotaxy highlights the importance of body patterning pathways. *Human Genetics* 2016;135(12):1355-1364. PMID: 27637763

Mills JL, Dimopoulos A, Bailey RL. What is standing in the way of complete prevention of folate preventable neural tube defects? *Birth Defects Research A Clinical and Molecular Teratology* 2016;106(7):517-9. PMID: 27418028

Molloy AM, Pangilinan F, Mills JL, Shane B, O'Neill MB, McGaughey DM, Velkova A, Abaan HO, Ueland PM, McNulty H, Ward M, Strain JJ, Cunningham C, Casey M, Cropp CD, Kim Y, Bailey-Wilson JE, Wilson AF, Brody LC. A common polymorphism in HIBCH influences methylmalonic acid concentrations in blood independently of cobalamin. *American Journal of Human Genetics* 2016;98(5):869-82. PMID: 27132595

Ozel AB, McGee B, Siemieniak D, Jacobi PM, Haberichter SL, Brody LC, Mills JL, Molloy AM, Ginsburg D, Li JZ, Desch KC. Genome-wide studies of von Willebrand factor propeptide identify loci contributing to variation in propeptide levels and von Willebrand factor clearance. *Journal of Thrombosis and Haemostasis* 2016;14(9):1888-98. PMID: 27359253

Sicko RJ, Browne ML, Rigler SL, Druschel CM, Liu G, Fan R, Romitti PA, Caggana M, Kay DM, Brody LC, Mills JL. Genetic variants in isolated Ebstein anomaly implicated in myocardial development pathways. *PLoS One* 2016;11(10):e0165174. PMID: 27788187

Szymczak S, Holzinger E, Dasgupta A, Malley JD, Molloy AM, Mills JL, Brody LC, Stambolian D, Bailey-Wilson JE. r2VIM: A new variable selection method for random forests in genome-wide association studies. *BioData Mining* 2016;9:7, 2016. PMID: 26839594

VanderMeer JE, Carter TC, Pangilinan F, Mitchell A, Kurnat-Thoma E, Kirke PN, Troendle JF, Molloy AM, Munger RG, Feldkamp ML, Mansilla MA, Mills JL, Murray JC, Brody LC. Evaluation of proton-coupled folate transporter (SLC46A1) polymorphisms as risk factors for neural tube defects and oral clefts. *American Journal of Medical Genetics A* 2016;170A(4):1007-16. PMID: 26789141

We found 35 rare CNVs in 24 (51%) of the 47 cases. Three cases had rare variants near the transcriptional repressor HEY1, a member of the NOTCH signaling pathway. Rare variants in genes related to cardiomyopathy were found in 23% of cases suggesting the importance of normal myocardial development in tricuspid valve formation (Sicko et al. *PLoS One* 2016).

We reported that heterotaxy, a defect of abnormal positioning of abdominal or thoracic organs, was associated with novel CNVs in a population-based study of cases identified from California births. We demonstrated that 56 rare CNVs were present in 69 cases of this uncommon defect. Moreover, many included genes involved in body patterning (NODAL, BMP, WNT pathways) and we found that similar CNVs were present in several cases. Our findings provide strong support for the concept that genetic factors are important in heterotaxy and provide leads for future mechanistic research in the body patterning area (Hagen et al. *Human Genetics* 2016).

We continue to be co-investigators as part of large birth defects consortiums. Previous studies have searched for genetic associations with oral facial clefts and craniosynostosis. We are conducting studies on several types of craniosynostosis (by affected suture). We are collaborating with the Department of Epidemiology Research at the

Statens Serum Institut in Denmark to examine genetic factors in hydrocephalus. Our group is also interested in exploring collaborations with investigators conducting such studies.

UPSTATE KIDS STUDY

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

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 the five boroughs 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 primary matched cohort comprises nearly 1,297 "exposed" infants (1,011 singletons and 286 twins) with reported infertility treatment and 3,692 "unexposed" infants (2,894 singletons and 789 twins) without reported treatment who were then matched for selection on maternal residence and plurality of birth irrespective of race/ethnicity. All co-twins of study participants and higher order multiples were enrolled in separate cohorts, and followed similarly.

Parental participation includes completion of: 1) a baseline questionnaire on reproductive and medical history, environmental exposures and infant characteristics; 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); and 3) children's longitudinal growth and medical history as recorded in journals. All infants or children who screen positive for developmental delays are referred to their primary health provider for clinical assessment. The Upstate KIDS cohort has been linked with the

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• **Hyojun Park**, Ph.D.
• **Rajeshwari Sundaram**, Ph.D.

Society for Assisted Reproductive Technologies' database for the capture of ART treatment. Additional linkages to New York State health registries for information such as immunizations, hospitalizations, lead screening, congenital malformations, and cancer diagnosis were completed or updated in 2014. With parental consent obtained at the 8-month screening, residual dried blood spots from Guthrie cards were used for the analysis of inflammatory and environmental chemical biomarkers, which are associated with alterations in child growth and development. 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. Analyses of immunoglobulins were also completed in 2014. 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.

2016 Upstate KIDS Study Publications

Ghassabian A, Sundaram R, Bell E, Bello SC, Kus C, Yeung E. Gross motor milestones and subsequent development. Pediatrics 2016;138(1): e20154372. PMID: 27354457

Ghassabian A, Sundaram R, Wylie A, Bell E, Bello SC, Yeung E. Maternal medical conditions during pregnancy and children's gross motor development up to age 24 months in the Upstate KIDS Study. Developmental Medicine and Child Neurology 2016;58(7):728-34. PMID: 26502927

Michels KA, Mumford SL, Sundaram R, Bell EM, Bello SC, Yeung EH. Differences in infant feeding practices by mode of conception among a United States cohort. Fertility & Sterility 2016;105(4):1014-1022. PMID: 26773191

Stern JE, Buck Louis GM, McLain AC, Luke B, Yeung E. Accuracy of self-reported survey data on assisted reproductive technology treatment parameters and reproductive history. American Journal Obstetrics Gynecology 2016;215(2):219. PMID: 26875948

Yeung E, Buck Louis G, Lawrence D, Kannan K, McLain AC, Caggana M, Druschel C, Bell E. Eliciting parental support for the use of newborn blood spots for pediatric research. BMC Medical Research Methodology 2016;16:14. PMID: 26846420

Yeung E, Sundaram R, Bell EM, Druschel C, Kus C, Ghassabian A, Bello S, Xie Y, Louis GM. Examining infertility treatment and early childhood development in the Upstate KIDS study. JAMA Pediatrics 2016;170(3):251-8. PMID: 26746435

Yeung E, Sundaram R, Bell EM, Druschel C, Kus C, Xie Y, Buck Louis GM. Infertility treatment and children's longitudinal growth between birth and 3 years of age. Human Reproduction 2016;31(7):1621-8. PMID: 27165624

UPSTATE KIDS CVD FOLLOW-UP STUDY

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

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. Home clinic visits are being conducted at 900 homes 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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- **Hyojun Park**, Ph.D.
- **Rajeshwari Sundaram**, Ph.D.
- **Jennifer Weck**, Ph.D

2016 Upstate KIDS CVD Follow-up Publications

Ongoing study; none to date.

WHOLE EXOME SEQUENCING IN PEDIATRIC ENDOCRINE DISEASE

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

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 Department of Laboratory Medicine and Pathology (Genetics Group), the New York State Department of Health Genetics Research Group, and The Santa Casa School or Medical Sciences of Sao Paolo, Brazil.

Principal Investigators

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- **Ruzong Fan**, Ph.D.
- **Andreas Giannakou**, M.D.

2016 Pediatric Endocrine Disease Publications

Ongoing study; none to date.

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, as described below.

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

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

BIOMARKER ANALYTICAL DEVELOPMENT

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 (Perkins et al. *Biometrical Journal* 2016; Mitchell et al. *Statistics in Medicine* 2016; Lyles et al. *Biometrics* 2016; McMahan et al. *Biometrical Journal* 2016). These methods were originally created for receiver operating characteristic (ROC) curves and recently expanded to estimate covariate-adjusted estimates of the ROC curve and summary measures. Division researchers continue to adapt these efficient designs and developed methods making pooling equally useful in the analysis of a broad spectrum of epidemiologic data through set-based logistic regression, log-linear calibration model and direct maximum likelihood to assess exposure outcome relations and gene-environment interactions.

Researchers here have diligently investigated the sources of laboratory measurement errors by gaining a laboratory perspective on the measurement process ranging from sample storage and preparation to the calibrations and measurement processes of assay equipment. This understanding has provided insight to data issues commonly present, yet largely ignored, in epidemiological research. 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

- **Emily M. Mitchell**, Ph.D.
- **Lindsey A. Sjaarda**, Ph.D., M.S.
- **Jennifer Weck**, Ph.D.

2016 Biomarker Analytical Development Publications

Danaher MR, Albert PS, Roy A, Schisterman EF. Estimation of interaction effects using pooled biospecimens in a case-control study. *Statistics in Medicine* 2016;35(9):1502-13. PMID: 26553532

Lyles, R.H., Mitchell, E.M., Weinberg, C., Umbach, D.M., Schisterman, E.F. An efficient design strategy for logistic regression using outcome- and covariate-dependent pooling of biospecimens prior to assay. *Biometrics* 2016;72(3):965-75. PMID: 26964741

McMahan CS, McLain AC, Gallagher CM, Schisterman EF. Estimating covariate-adjusted measures of diagnostic accuracy based on pooled biomarker assessments. *Biometrical Journal* 2016;58(4):944-61. PMID: 26927583

Mitchell EM, Plowden TC, Schisterman EF. Estimating relative risk of a log-transformed exposure measured in pools. *Statistics in Medicine* 2016;35(29):5477-5494. PMID: 27530506

Perkins NJ, Mitchell E, Lyles RH, Schisterman EF. Case-control data analysis for randomly pooled biomarkers. *Biometrical Journal* 2016;58(5):1007-20. PMID: 26824757

CAUSAL INFERENCE IN REPRODUCTIVE EPIDEMIOLOGY

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

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 time-varying confounding, and as applied to the role of gestational age (GA) in analysis of perinatal data. One method developed relies on a regression-based adjustment for GA to remove the correlation between gestational weight gain (GWG) and GA (Hinkle et al. *Paediatric and Perinatal Epidemiology* 2016). Compared to published weight-gain-for-gestational-age z-scores, this method provides an accessible alternative to the weight-gain-for-gestational-age z-scores without requiring assumptions concerning underlying population characteristics. A second method addresses analyzing the association between GWG and preterm delivery accounting for their mutual dependence on GA (Mitchell et al. *Epidemiology* 2016). Division researchers disentangle this inherent association by reframing preterm delivery as time to delivery and assessing the relationship through a survival framework.

Principal Investigators

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- **Emily M. Mitchell**, Ph.D.
- **Sunni L. Mumford**, Ph.D., M.S.
- **Neil J. Perkins**, Ph.D., M.S.

2016 Causal Inference in Reproductive Epidemiology Publications

Hinkle SN, Mitchell EM, Grantz KL, Ye A, Schisterman EF. Maternal weight gain during pregnancy: Comparing methods to address bias due to length of gestation in epidemiological studies. *Paediatric and Perinatal* Epidemiology 2016;30(3):294-304. PMID: 26916673

Mitchell EM, Hinkle SN, Schisterman EF. It's about time: A survival approach to gestational weight gain and preterm delivery. *Epidemiology* 2016;27(2):182-7. PMID: 26489043

Schisterman EF, Sjaarda LA. No right answers without knowing your question. *Paediatric and Perinatal Epidemiolog*. 2016;30(1):20-2. PMID: 2676805

The Health Behavior Branch's research identifies determinants of health and health-related behavior from the prenatal period to early childhood, adolescence, and young adulthood.

Stephen E. Gilman, Sc.D.

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. The Health Behavior Branch's research identifies determinants of health and health-related behavior from the prenatal period to early childhood, adolescence, and young adulthood, and tests the effectiveness of social, behavioral and environmental strategies to improve or 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 methodologies 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.

A defining feature of our branch's portfolio of 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.

Principal Investigators

- **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

Fellows

- **Katie Dempster**, B.A., Postbaccalaureate Fellow
- **Johnathan Ehsani**, Ph.D., Postdoctoral Fellow (departed in 2016)
- **Miriam Eisenberg**, Ph.D., Postdoctoral Fellow
- **Brian Fairman**, Ph.D., Postdoctoral Fellow
- **Pnina Gershon**, Ph.D., Postdoctoral Fellow
- **Matthew Grossman**, Postbaccalaureate Fellow
- **Chantal Guillaume**, Ph.D., Special Volunteer (departed in 2016)
- **Neha Trivedi**, Summer Intern
- **Indra Kar**, B.A., Postbaccalaureate Fellow
- **Liat Korn**, Ph.D., Special Volunteer
- **Awapuhi Lee**, B.A., Postbaccalaureate Fellow
- **Angela Lee-Winn**, Ph.D., Postdoctoral Fellow (departed in 2016)
- **Jeremy Luk**, Ph.D., Postdoctoral Fellow
- **Fearghal O'Brien**, Ph.D., Postdoctoral Fellow (departed in 2016)

2016 Awards

- **Jeremy Luk**, Junior Investigator Award, Research Society on Alcoholism

Adolescence is a critical period for the development of unhealthy patterns of behavior associated with subsequent morbidity and mortality.

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

Adolescence is also a critical period for physiological and behavioral changes associated with the onset of obesity and substance use. The influences of the social (peers and parents) and physical (e.g., place of residence, local programs, policies, and resources) environments may be particularly important during critical stages of development. As adolescents move from high school to post-secondary education and/or employment, their personal, social and physical environments change, with potential impacts on their health and behavior. Currently, we are conducting the NEXT Longitudinal Study of Adolescent Health Behavior (NEXT), which follows a nationally representative sample during the transition from high school to early adulthood.

NEXT GENERATION HEALTH STUDY

The NEXT Generation Health Study is a longitudinal survey of adolescent health and behavior. A nationally representative cohort of 2874 adolescents, approximately 16 years of age, was recruited in 2010 and is assessed annually up to age 22 years. The primary goals of the study are to examine trajectories of adolescent health status and behaviors from mid-adolescence through the post high school years. The NEXT Study assesses cardiovascular risk factors, adolescent problem behaviors including substance use, diet, physical activity, sleep, and driving. At the end of the recently completed Wave 7 survey data collection, we have a retention rate of 73% of the originally enrolled cohort of 10th graders. In addition to annual surveys conducted with the entire sample, a subsample of 560 study participants participated in the NEXT Plus Study and provided additional data on diet, physical activity, peer networks, and driving, while using accelerometers to measure activity and sleep. Blood samples were obtained to assess cardiovascular

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- **Jeremy Luk**, Ph.D.
- **Brian Fairman**, Ph.D.
- **Miriam Eisenberg**, PhD.
- **Joseph Bible**, Ph.D.
- **Benjamin Gee**, B.A.
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- **Awapuhi Lee**, B.A.
- **Matthew Grossman**, B.A.

risk, along with saliva for genetic analysis. The retention rate for this subsample for the Wave 7 assessments was 75%.

In the past year, we published a paper that describes the variability of a range of health behaviors varied by college status. Findings differed by health behavior (Simons-Morton, 2017). Relative to those attending a 4-year college, those in community college or technical school were less likely to binge drink, and more likely to speed and consume sugar sweetened beverages and to report physical (e.g. headache, stomach ache) and depressive symptoms. Those who did not attend school were more likely to drive while intoxicated and drink sugar-sweetened beverages compared to those attending 4-year colleges. We examined patterns over time of physical activity using both self-reported (Li, 2016a) and objectively measured (accelerometer) assessments (Li, 2016b). Regardless of the way physical activity is measured, we found that it declines over the high school years and continues to decline the first year after high school. Moreover, in the study using the accelerometer data, increased physical activity was found to be related to college attendance. Participants attending a 4-year college were more likely to engage in moderate to vigorous physical activity compared to those who did not attend college. Additionally, weight gain between 10th grade and the first year post high school was associated with decreased in physical activity over the same time period (Li et al., 2016a).

Analyses are underway examining sleep adequacy in relation to alcohol use, weight status and dietary intake. Additionally, we are developing a series of analyses regarding the impact of neighborhood environment, such as density of fast food retailers, green space, and economic indicators on health behaviors and outcomes. Earlier work on trajectories of health behaviors, including alcohol use, physical activity and dietary intake will be extended to include patterns of these behaviors during the four years post-high school.

2016 Adolescent Health Publications

Hingson R, Zha W, Simons-Morton B, White A. Alcohol-Induced Blackouts as Predictors of Other Drinking Related Harms Among Emerging Young Adults. *Alcoholism, Clinical and Experimental Research*. 2016;40(4):776-84. PMID: 27012148. PMCID: PMC4820355

Li K, Haynie D, Lipsky L, Iannotti RJ, Pratt C, Simons-Morton B. Changes in Moderate-to-Vigorous Physical Activity Among Older Adolescents. *Pediatrics*. 2016;138(4). PMID: 27669737. PMCID: PMC5051211

Li K, Haynie D, Palla H, Lipsky L, Iannotti RJ, Simons-Morton B. Assessment of adolescent weight status: Similarities and differences between CDC, IOTF, and WHO references. *Preventive Medicine*. 2016;87:151-4. PMID: 26921658. PMCID: PMC4884484

Li K, Liu D, Haynie D, Gee B, Chaurasia A, Seo DC, Iannotti RJ, Simons-Morton BG. Individual, social, and environmental influences on the transitions in physical activity among emerging adults. *BMC Public Health*. 2016;16:682. PMID: 27485724. PMCID: PMC4970300

Li K, Simons-Morton B, Gee B, Hingson R. Marijuana-, alcohol-, and drug-impaired driving among emerging adults: Changes from high school to one-year post-high school. *Journal of Safety Research*. 2016;58:15-20. PMID: 27620930. PMCID: PMC5022791

Lipsky LM, Nansel TR, Haynie DL, Liu D, Eisenberg MH, Simons-Morton B. Power of Food Scale in association with weight outcomes and dieting in a nationally representative cohort of U.S. young adults. *Appetite*. 2016;105:385-91. PMID: 27298083. PMCID: PMC4980265

Nansel TR, Lipsky LM, Eisenberg MH, Haynie DL, Liu D, Simons-Morton B. Greater Food Reward Sensitivity Is Associated with More Frequent Intake of Discretionary Foods in a Nationally Representative Sample of Young Adults. *Frontiers in Nutrition*. 2016;3:33. PMID: 27588287. PMCID: PMC4989129

Simons-Morton B, Haynie D, Liu D, Chaurasia A, Li K, Hingson R. The Effect of Residence, School Status, Work Status, and Social Influence on the Prevalence of Alcohol Use Among Emerging Adults. *Journal of Studies on Alcohol and Drugs*. 2016;77(1):121-32. PMID: 26751362. PMCID: PMC4711312

Simons-Morton B, Li K, Ehsani J, Vaca FE. Covariability in three dimensions of teenage driving risk behavior: impaired driving, risky and unsafe driving behavior, and secondary task engagement. *Traffic Injury Prevention*. 2016;17(5):441-6. PMID: 26514232. PMCID: PMC4851597

Our program of research on eating behaviors in children and families uses experimental and observational methods to investigate influences on, and interventions to improve, eating behaviors leading to optimal growth and development in clinical and general populations.


Tonja Nansel, Ph.D.

This work is of substantial public health importance. The poor diet quality of the U.S. population, characterized by excessive intake of total energy, added sugar, fat and sodium, and inadequate intake of fruits, vegetables and whole grains is well-documented. Poor diet (not including malnutrition) is now the largest contributor to early death globally, and is associated with numerous adverse health outcomes independent of obesity.

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.

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

A major focus of medical nutrition therapy in type 1 diabetes is on integrating the insulin regimen and carbohydrate estimation into the family's lifestyle, conforming to preferred meal routines, food choices, and physical activity patterns. 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. Additionally, a small body of evidence suggests that dietary intake, particularly carbohydrate quality (i.e., whole versus refined grains), may affect blood sugar control and insulin demand. 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.

Principal Investigator
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- **Katie Dempster**, B.A.

The 18-month CHEF randomized controlled trial tested the efficacy a family-based behavioral intervention designed to improve diet quality by promoting intake of fruit, vegetables, whole grains, legumes, nuts, and seeds (Nansel et al. 2015). Primary outcomes were dietary intake and glycemic control. Youth in the intervention group demonstrated greater intake of whole plant foods and improved diet quality as indicated by the Healthy Eating Index-2005 score, an index of conformance to U.S. dietary guidelines. However, glycemic control did not differ between intervention and control groups (Nansel et al. 2015).

Our work on the CHEF study in 2016 built on the successful primary outcomes of the intervention by examining four subsidiary research questions: diet costs as associated with diet quality; relationships between dietary intake and glycemic control; relationships among BMI, body composition, glycemic control, and cardiovascular risk factors; and psychosocial correlates of disordered eating behaviors. In contrast to the body of cross-sectional research reporting higher diet costs with greater diet quality, we found no association of diet cost with diet quality cross-sectionally or longitudinally, and no intervention effect on diet cost (Nansel et al. 2016a). These findings are consistent with a small body of intervention research finding no change in diet cost in association with dietary improvement, and challenge the prevailing assumption that improving diet quality necessitates greater cost. We examined longitudinally the association of dietary intake and glycemic control using two biomarkers and continuous glucose monitoring data obtained concurrently with diet records. Our findings indicated that greater diet quality and intake of fiber, carbohydrate, and natural sugars were associated with greater glycemic control and lower glycemic variability (Nansel et al., 2016b). We examined the longitudinal associations of BMI and body composition with glycemic control and cardiovascular risk factors, finding that BMI and adiposity were positively associated with indicators of hyperglycemic excursions assessed via masked continuous glucose monitoring (Lipsky et al. 2016a), as well as with several indicators of increased cardiometabolic risk including higher triglycerides and low density lipoprotein cholesterol, c-reactive protein, and blood pressure (Lipsky et al. 2016b). These findings contribute to our understanding of the impact of adiposity indicators on health outcomes in type 1 diabetes patients, who are at considerable risk for cardiovascular complications. We also examined theoretically-driven psychosocial correlates of disordered eating behaviors in this sample, and found that external motivation for healthful eating (i.e., behavior based on meeting others' expectations versus one's own values) was associated with greater disordered eating behaviors among youth with type 1 diabetes, particularly when self-efficacy for healthful eating was low (Eisenberg et al., 2016).

2016 CHEF Publications

Nansel TRa, Lipsky LM, Eisenberg MH, Liu A, Mehta SN, Laffel LM. Can Families Eat Better Without Spending More? Improving Diet Quality Does Not Increase Diet Cost in a Randomized Clinical Trial among Youth with Type 1 Diabetes and Their Parents. *Journal of the Academy of Nutrition and Dietetics*. 2016;116(11):1751-9 e1. PMID: 27597745. PMCID: PMC5085870

Nansel TRb, Lipsky LM, Liu A. Greater diet quality is associated with more optimal glycemic control in a longitudinal study of youth with type 1 diabetes. **American Journal of Clinical Nutrition**. 2016;104(1):81-7. PMID: 27194309. PMCID: PMC4919526

Lipsky LMa, Gee B, Liu A, Nansel TR. Glycemic control and variability in association with body mass index and body composition over 18 months in youth with type 1 diabetes. *Diabetes Research and Clinical Practice*. 2016;120:97-103. PMID: 27525365.

Lipsky LMb, 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* 2016 Jul 15. DOI: 10.1111/ijpo.12167. PMID: 27417272.

Eisenberg MH, Lipsky LM, Dempster KW, Liu A, Nansel TR. I Should but I Can't: Controlled Motivation and Self-Efficacy Are Related to Disordered Eating Behaviors in Adolescents With Type 1 Diabetes. *Journal of Adolescent Health*. 2016;59(5):537-42. PMID: 27567063. PMCID: PMC5077655

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.

2016 PEAS Publications

Nansel TR, Lipsky LM, Siega-Riz AM, Burger K, Faith M, Liu A. Pregnancy eating attributes study (PEAS): a cohort study examining behavioral and environmental influences on diet and weight change in pregnancy and postpartum. BMC Nutrition. 2016;2(1):45.

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.

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

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 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.

Principal Investigator

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- **Joe Bible**, Ph.D.
- **Johnathan Ehsani**, Ph.D.
- **Fearghal O'Brien**, Ph.D.
- **Pnina Gershon**, Ph.D.
- **Federico Vaca**, M.D.
- **Chantal Guillaume**, Ph.D.
- **Indra Kar**, B.A.

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

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.

2016 NTDS Publications

Klauer, S., Simons-Morton, B.G., Ehsani, J. (2016). Using Naturalistic Driving Methods to Study Novice Drivers. (Chapter 26 in Caird, J., Fisher, D, Editors, *Handbook of Young Driver Research: Research, Practice, Policy, and Directions*). CRC Press, New York, NY

O'Brien, F., Klauer, S.G., Ehsani, J., Simons-Morton, B.G. Changes over 12 months in eye glances during secondary task engagement among novice drivers. *Accident Analysis & Prevention*. 2016; 93, 48-54. PMID: 27177392. PMCID: PMC4907835

Shope JT, Zakrajsek JS, Finch S, Bingham CR, O'Neil J, Yano S, Wasserman R, Simons-Morton B. Translation to Primary Care of an Effective Teen Safe Driving Program for Parents. *Clinical Pediatrics*. 2016;55(11):1026-35. PMID: 27630004.

Simons-Morton, B.G. and Ouimet, M.C. (2016). What is the effect of passengers on teenage driving? (Chapter 16 in Caird, J., Fisher, D, Editors, *Handbook of Young Driver Research: Research, Practice, Policy, and Directions* Chapter 16). CRC Pres, New York, NY.

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

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).

2016 SPD Publications

Ehsani J, Li K, Grant B, Gershon P, Klauer S, Dingus T, Simons-Morton B. Factors Influencing Learner Permit Duration. *Safety*. 2016;3(1):2.

Simons-Morton B, Ehsani J. Learning to Drive Safely: Reasonable Expectations and Future Directions for the Learner Period. *Safety*. 2016;2(4):20.

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

The presence of teenage passengers has been shown to increase crash risk. However, in the NTDS 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. A series of simulation studies has been conducted to learn more about the nature of teen passenger influences in collaboration with the University of Michigan Transportation Research Institute.

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 variables measuring: failure to stop at yellow light intersections (Incident Rate Ratio (IRR)=2.16; 95% Confidence Interval [95CI]=1.06, 4.43); higher probability of overtaking (IRR=10.17; 95CI=1.43, 73.35); shorter left turn latency (IRR=0.43; 95CI=0.31,0.60); and, failure to stop at an intersection with an occluded stop sign (IRR=7.90; 95CI=2.06,30.35). 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)

Study participants attended an fMRI lab the week prior to driving the similar so that neuro-images of their brains could be obtained in association with psychological tasks. We tested whether neural regions previously shown to be involved in susceptibility to social influence on recommendation behavior also predicted social influence on driving risk one week later in a full-cab driving simulator. Results demonstrated that neural activity functionally defined by conformity in the fMRI recommendation task (VS+VMPFC) predicted risky behavior in the presence of a risky peer, relative to solo driving and safe peers. In addition, results demonstrated that individual differences in rTPJ activity, a region commonly associated with mentalizing, was significantly associated with safer behavior in the presence of a safe peer (relative to solo driving and risky peers) during the driving simulator session. (Cascio et al. 2016).

2016 Teen Passenger Study Publications

Bingham CR, Simons-Morton BG, Pradhan AK, Li K, Almani F, Falk EB, Shope JT, Buckley L, Ouimet MC, Albert PS. Peer Passenger Norms and Pressure: Experimental Effects on Simulated Driving Among Teenage Males. *Transportation Research Part F: Traffic Psychology and Behaviour*. 2016;41(A):124-37. PubMed PMID: 27818610; PMCID: PMC5094360

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 and Supervised Practice Driving Study. 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 NTDS, and in many cases to combine the UNTDS, NTDS, and SPD 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 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. Future analyses will examine this question with other age groups. One analyses examined the extent to which young drivers reduced risky driving behavior after a crash. 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).

2016 UNTDS Publications

O'Brien F, Klauer SG, Ehsani J, Simons-Morton BG. Changes over 12 months in eye glances during secondary task engagement among novice drivers. *Accident Analysis and Prevention*. 2016;93:48-54. PubMed PMID: 27177392; PMCID: PMC4907835

NEXT GENERATION HEALTH STUDY - DRIVING RESEARCH

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 while intoxicated by alcohol or drugs (DWI) that these aspects of driving risk co-vary over time (Simons-Morton et al., 2016b). In analyses of the changes and predictors of change in riding an impaired driver (RWI) using transitional regression models 33% of adolescents reported RWI in the past 12 months in W1, and slightly declined in W2 (24%), W3 (27%), and W4 (26%). Across time, transition models with generalized estimating equations showed that RWI was more likely among those who previously reported RWI (ORs from 3.62 to 3.66, $p < .001$), substance use (ORs from 1.81 to 1.82, $p < .001$), and heavy episodic drinking (ORs from 1.85 to 1.86, $p < .001$). Those living on college campuses were somewhat more likely to engage in RWI (OR = 1.38, $.05 < p < .10$) than those living at home (Vaca et al., 2016). 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 ($\beta = -2.02$, $p < 0.0001$) or on their own ($\beta = -1.29$, $p < 0.0001$) engaged in significantly less TPA. However, licensure interaction contrasts showed a significant difference by licensure for those living at home ($\beta = 1.06$, $p < 0.0001$). Compared to four-year university students, non-students ($\beta = -1.47$, $p < 0.0001$) and technical school/community college students ($\beta = -1.66$, $p < 0.0001$) showed significantly less TPA engagement. The interaction contrasts indicated a significant difference by licensure among non-students ($\beta = 0.74$, $p < 0.0001$) and technical school/community college students ($\beta = 1.13$, $p < 0.0001$). Compared to non-workers, those who worked 1-30 hours/week ($\beta = -0.58$, $p < 0.0001$) or 30+ hours/week ($\beta = -1.23$, $p < 0.0001$) engaged in significantly less TPA. The interaction contrasts indicated a significant difference by licensure among people who worked 1-30 hours/week ($\beta = 0.69$, $p < 0.0001$) or 30+ hours/week ($\beta = 1.12$, $p < 0.0001$) (Kar et al., 2016).

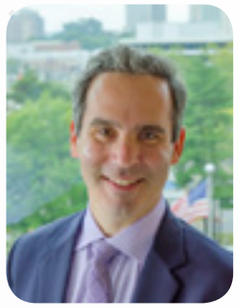
2016 NEXT Generation Study Publications

Simons-Morton B, Li K, Ehsani J, Vaca FE. Covariability in three dimensions of teenage driving risk behavior: impaired driving, risky and unsafe driving behavior, and secondary task engagement. *Traffic Injury Prevention*. 2016;17(5):441-6. PMID: 26514232. PMCID: PMC4851597

Vaca FE, Li K, Hingson R, Simons-Morton BG. Transitions in Riding With an Alcohol/Drug-Impaired Driver From Adolescence to Emerging Adulthood in the United States. *Journal of Studies on Alcohol and Drugs*. 2016;77(1):77-85. PMID: 26751357. PMCID: PMC4711323

Mental disorders, and health disparities more broadly, have significant developmental origins.

Risë B. Goldstein, Ph.D.



Stephen E. Gilman, ScD

This work is ideally situated within a 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. 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 early-onset subtype of depression, an elevated risk for recurrent episodes in adulthood, and a decreased likelihood of subsequent recovery.

In 2016, contributions to the field focusing focused on the early origins of adult mental health. We examined the involvement of biomarkers of maternal immune activity during pregnancy in the offspring's risk of major depression. Motivated by ecological evidence showing that exposures associated with immune disruption (e.g., natural disaster, influenza epidemics) during pregnancy can lead to an increased risk of mood disorders in offspring, and by preclinical studies,

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we examined the involvement of pro- and anti-inflammatory cytokines in offspring's risk of major depression. We reported in Translational Psychiatry that concentrations of the pro-inflammatory cytokine TNF-□ in mid-gestation maternal serum was associated with offspring risk of depression – and that this association varied in direction between male and female offspring (Gilman et al. 2016). We have also focused attention on the role of children's development in long-term risk of mental health, finding, for example, that cognitive development at 7 years of life is strongly related to the chronicity of adult mood disorders as well as suicide risk (Hung et al., 2016, B*ritish Journal of Psychiatry*). Additional findings of interest from our program's staff and fellows in 2016 cover the areas of anxiety and substance use disorders and social determinants of health from childhood throughout the life course.

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 attention-deficit/hyperactivity disorder (ADHD), the co-occurrence of ADHD with alcohol and illicit substance use, and receipt of treatment for ADHD. 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.

DEVELOPMENTAL ORIGINS OF SUICIDE MORTALITY

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.

2016 Publications on Mental Health and Health Disparities

Gilman SE, Cherkerzian S, Buka SL, Hahn J, Hornig M, Goldstein JM. Prenatal immune programming of the sex-dependent risk for major depression. *Translational Psychiatry*. 2016;6(5):e822. PMID: 27244231.

Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, Pickering RP, Ruan WJ, Huang B, Grant BF. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Social Psychiatry and Psychiatric Epidemiology*. 2016;51(8):1137-48. PMID: 27106853. PMCID: PMC4980174

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Nguyen TT, Tchetgen EJ, Kawachi I, Gilman SE, Walter S, Glymour MM. Comparing Alternative Effect Decomposition Methods: The Role of Literacy in Mediating Educational Effects on Mortality. *Epidemiology*. 2016;27(5):670-6. PMID: 27280331. PMCID: PMC5051696

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Ransome Y, Gilman SE. The Role of Religious Involvement in Black-White Differences in Alcohol Use Disorders. *Journal of Studies on Alcohol and Drugs*. 2016;77(5):792-801. PMID: 27588538. PMCID: PMC5015471