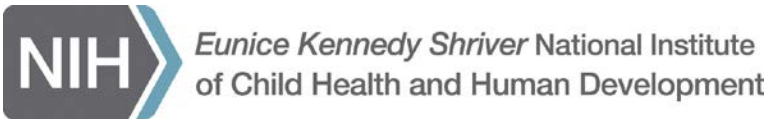
Division of Intramural Population Health Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development

2015 Annual Report



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

The Division of Intramural Population Health Research is dedicated to promoting the health and wellbeing of populations through novel research, including the development of methods for our discipline, and training future generations of population scientists. We are actively involved in research with the overarching goal of working to ensure the health of all, including vulnerable subgroups of the population such as pregnant women, infants and children. The Division traces its origin to 1967 when it first appeared on the Institute's organizational chart, and only five years after the establishment of the Institute. Next year, we will be celebrating our 50th Anniversary! Currently, the Division comprises the Office of the Director and three intramural research branches – Biostatistics and Bioinformatics Branch, Epidemiology Branch and Health Behavior Branch. Division scientists remain committed to the completion of etiologic and interventional research. Examples of our work include identifying behaviors that help couples conceive and have a healthy infant born at term, identifying lifestyles and behaviors associated with optimal fetal growth, identifying safe driving behaviors for young drivers, and developing guidance for healthy eating commencing in childhood to maximize the health of individuals living with chronic diseases such as diabetes. We are very excited to be planning research that will allow us to better understand health across the lifespan and future generations. An example of our commitment to generations includes the launching of a bold initiative to understand early life stressors that impact adult onset diseases. We are linking information from pregnant women who participated in the U.S. Collaborative and Perinatal Project from 1959 to 1965 with the National Death Index to identify patterns between pregnancy complications or health and cause-specific mortality.

In addition to our currently ongoing research (B-WELL-MOM Study, FAZST Trial, NEXT Study, PEAS Study) described in various Branch reports, two new studies were implemented in 2015. The IDEAL Study will characterize healthy lifestyles (e.g., diet, sleep, stress) associated with fertility, inclusive of couples receiving infertility treatment. Our second new study - Fetal Body Composition and Volumes Study – will measure (2D and 3D) obstetrical ultrasound images from the NICHD Fetal Growth Studies to develop a catalogue that characterizes fetal body composition (fat mass) and organ size from the earliest stages of development through delivery. I encourage you to read the report to learn more about some of our discoveries published this past year. A few examples of our research findings published in the last year that might peek your interest include:

- Male partners' benzophenone type-UV filters (sunscreens) are associated with a longer-time-to-pregnancy (Buck Louis et al. 2015)
- Persistent endocrine disrupting chemicals were associated with poorer semen quality (Mumford et al. 2015)
- Low dose aspirin restores the expected number of male to female live born infants (Radin et al. 2015)

- Air pollution increases blood pressure of women admitted to labor and delivery Männistö et al. 2015)
- Early life adversity is associated with abnormal neurologic abnormalities in infant and children (Gilman et al. 2015)
- Family- and child-based behavioral interventions improves glycemic control in youth with type 1 diabetes irrespective of family income, and also increases adherence to dietary guidelines including the intake of plant foods (Nansel et al. 2015)
- Motor vehicle crashes were associated with secondary task engagement, elevated g-force events and stress response insensitivity (Simons-Morton et al. 2015)

More information about the Division's media coverage and press releases can be found at: https://www.nichd.nih.gov/news/releases/Pages/news.aspx.

Training and mentoring is another critical component of our mission, and in 2015 the Division was home to 48 fellows representing over 40 academic institutions. Our mentees' diversity, with regard to professional stature and academic discipline, is one reason why the Division's research is made better by their involvement. We are proud of our fellows' accomplishments and placements, as they establish their careers. And we do not hesitate to tap them for additional help and service long after they transition from us.

In reflecting about the past year, I remain proud of the Division's notable service for our many constituents. This includes service to our Institute and the National Institutes of Health more globally, service to other governmental agencies and research entities, and to our professional societies. Our internationally recognized scientists continue to hold leadership positions in professional societies and serve on various editorial boards.

In closing, we remain committed to maximizing health across the lifespan and we do so by being good stewards of the populations we serve. Our work is not possible without the continued support of our Scientific Director, Dr. Constantine A. Stratakis, our former Institute Director, Dr. Alan E. Guttmacher, and our Acting Institute Director, Catherine Y. Spong. Please visit our website [https://www.nichd.nih.gov/about/org/diphr/Pages/default.aspx] to learn more about the Division's exciting and unique research, opportunities for training and professional careers, and possible collaborations including the leveraging of resources. And as always, we welcome your comments or questions about the Division [louisg@mail.nih.gov].

Appreciatively,

/Germaine M. Buck Louis/

Germaine M. Buck Louis, Ph.D., M.S.
Director and Senior Investigator

Office of the Director

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


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

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 the environmental influences of successful human reproduction and development. She is the Principal Investigator for the LIFE Study, ENDO Study, NICHD Fetal Growth Studies, and the Pregnancy Exposome Study.


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

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.


Jennifer Weck, Ph.D.

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 highly relevant for many of the Division's research initiatives underscoring her role as a valuable collaborator. Dr. Weck also administers 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 on a host of health and disease outcomes. Dr. Weck also manages the Division and Institute's Biospecimen Repository.

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.

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

Environmental Influences on Human Reproduction and Development

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

In response to these data gaps, 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. With the completion of the LIFE and ENDO Studies, several recent publications have identified environmental chemicals and lifestyles that are associated with untoward health outcomes.

Longitudinal Investigation of Fertility and the Environment (LIFE Study)

The goal of the LIFE Study is to determine whether ubiquitous environmental chemicals 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. A spectrum of reproductive endpoints have been captured in the LIFE Study, allowing for research focusing on their interrelatedness in keeping with the highly timed and conditional nature of human reproduction and development (i.e., hormonal profiles, menstruation and ovulation, semen quality, time-to-pregnancy, pregnancy loss, gestation, and infant birth size). The LIFE Study recruited a cohort comprising 501 couples who were discontinuing contraception for purpose of becoming pregnant. Both partners of the couple completed daily journals while trying for pregnancy until they were pregnant or up to 12 months. Women achieving pregnancy completed daily then monthly journals through delivery. Blood samples were taken to quantify metals and persistent environmental chemical, including organochlorine pesticides (OCPs), polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and perfluoroalkyl and polyfluoroalkyl (PFASs). Urine samples were used to quantify short-lived chemicals such as bisphenol A (BPA), benzophenone-type UV filter chemicals, phthalates, parabens, and trace elements. Men provided semen samples during the women's first two menstrual cycles, while women provided two saliva samples for the measurement of stress biomarkers - cortisol and alpha amylase. Women were instructed in the use of the Clearblue® Easy Fertility Monitor to help time intercourse relative to ovulation along with the use of Clearblue® (digital) home pregnancy test kits for the detection of pregnancy.

Among some of the notable discoveries in 2015, were findings suggesting that couples tend to repeat how long it takes to become pregnant each trying attempt (Sapra et al. 2015) and evidence suggesting that specific environmental chemicals are associated with a longer time-to-pregnancy (Buck Louis et al., 2015, gravid diseases such as gestational diabetes (Zhang et al. 2015), changes in semen quality (Bloom et al. 2015; Buck Louis et al. 2015), diminished birth size (Robledo et al. 2015; Smarr et al. 2015), and changes in the ratio of male to female births (Bae et al. 2015). Important methodologic advances also arose from the LIFE Study for the analysis of human fecundity and fertility endpoints, such as the development of Bayesian (Lum et al. 2015) and joint modeling approaches (McLain et al. 2015). In the coming year, LIFE Study investigators will seek to better understand the impact of chemical mixtures on human reproduction, and how healthy lifestyles might minimize untoward chemical effects.

Principal Investigator

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

Collaborators

- Zhen Chen, Ph.D.

- Sung Duk Kim, Ph.D.
- Sunni Mumford, Ph.D., M.P.H.
- Rajeshwari Sundaram, Ph.D.
- Iris Bae, Ph.D.
- Melissa Smarr, Ph.D.
- Katherine Sapra, Ph.D., M.Phil., M.P.H.

2015 LIFE Study Publications

- Goldstone AE, Chen Z, Perry MJ, Kannan K, Buck Louis GM. Urinary bisphenol A and semen quality, the LIFE Study. *Reproductive Toxicology* 2015; 51:7-13. PMID: 25462789

- Zhang C, Sundaram R, Maisog J, Calafat AM, Barr DB, Buck Louis GM. A prospective study of pre-pregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. *Fertility and Sterility* 2015; 103(1):184-189. PMID: 25450302

- Bae J, Kim S, Kannan K, Buck Louis GM. Couples' urinary bisphenol A and phthalate metabolite concentrations and the secondary sex ratio. *Reproductive Toxicology* 2015; 137:450-445. PMID: 26575635

- Eisenberg ML, Chen Z, Ye A, Buck Louis GM**.** The relationship between physical occupational exposures and health on semen quality: Data from the LIFE Study. *Fertility and Sterility* 2015;103(5):1271-1277. PMID: 25765658

- Bloom MS, Buck Louis GM, Sundaram R, Maisog J, Steuerwald AJ, Parson PJ. Metals and birth outcomes and background exposures to select elements, the Longitudinal Investigation of Fertility and the Environment. *Environmental Research* 2015; 138C:118-129. doi: 10.1016/j.envres.2015.01.008.

- Robledo CA, Yeung E, Mendola P, Sundaram R, Maisog J, Sweeney A, Barr D, Buck Louis GM. Preconception maternal and paternal exposure to persistent organic pollutants and birth size. *Environmental Health Perspectives* 2015; 123(1):88-94. PMID: 25095280

- Buck Louis GM**,** Chen Z, Schisterman EF, Kim S, Sweeney AM, Sundaram R, Lynch CD, Gore-Langton RE, Barr DB. Perflurochemicals and Human Semen Quality, the LIFE Study. *Environmental Health Perspectives* 2015; 123(1):57-63. PMID: 25127343

- Bae J, Kim S, Kannan K, Buck Louis GM. Couples' urinary bisphenol A and phthalate metabolite concentrations and the secondary sex ratio. *Environmental Research* 2015; 137:450-457. PMID: 25677702

- McLain AC, Sundaram R, Buck Louis GM. Joint analysis of longitudinal and survival data measured on nested time-scales using shared parameter models: an application to fecundity data. *Journal of the Royal Statistical Society* 2015;64(Part 2):339-357.

- Eisenberg ML, Chen Z, Ye A, Buck Louis GM. The relationship between physical occupational exposures and health on semen quality: Data from the LIFE Study. *Fertility and Sterility* 2015;103:1271-1277. PMID: 25516559

- Bloom MS, Buck Louis GM, Sundaram R, Maisog J, Steuerwald AJ, Parson PJ. Birth outcomes and background exposures to select elements, the Longitudinal Investigation of Fertility and the Environment. *Environmental Research* 2015; 138C:118-129. http://dx.doi.org/10.1016/j.envres.2015.01.008. PMID: 25707016

- Bae J, Kim S, Schisterman EF, Barr DB, Buck Louis GM. Maternal and paternal serum concentrations of perfluoroalkyl and polyfluoroalkyl substances and the secondary sex ratio. *Chemosphere* 2015;133:31-40. PMID: 25863705

- Sapra KJ, McLain AC, Maisog JM, Sundaram R, Buck Louis GM. Clustering of retrospectively reported and prospectively observed time-to-pregnancy. *Annals of Epidemiology* 2015; 2015 Dec;25(12):959-63. PMID: 26033375

- Buck Louis GM, Chen Z, Kim S, Sapra KJ, Bae J, Kannan K. Urinary concentrations of benzophenone-type ultra violet light filters and semen quality. *Fertility and Sterility* 2015;104(4):989-996. PMID: 26253817

- Lum KJ, Sundaram R, Buck Louis GM, Louis TA. A Bayesian approach to joint modeling of menstrual cycle length and fecundity. *Biometrics* 2015; Aug 21. DOI: 10.1111/biom.12379. PMID: 26295923

- Bloom MS, Whitcomb BW, Chen Z, Ye A, Kannan K, Buck Louis GM. Associations between urinary phthalate concentration and semen quality parameters in a general population. *Human Reproduction* 2015;30(11): 2645-2657. PMID: 26350610

- Smarr MM, Grantz KL, Sundaram R, Maisog JM, Kannan K, Buck Louis GM. Parental urinary biomarkers of preconception exposure to bisphenol A and phthalates in relation to birth outcomes: the LIFE Study. *Environmental Health* 2015; 14:73. PMID: 26362861

- Mumford SL, Kim S, Chen Z, Barr DB, Buck Louis GM. Urinary phytoestrogens associated with subtle effects on semen quality among male partners of couples desiring pregnancy: The LIFE Study. *Journal of Nutrition* 2015;145(11):2535-2541. PMID: 26423741

- 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* 2015;543(Pt A):28-36. PMID: 26575635

- Mumford SL, Kim S, Chen Z, Gore-Langton R, Barr DB, Buck Louis GM. Persistent organic pollutants and semen quality: the LIFE study. *Chemosphere* 2015;135:427-435. PMID: 25441930

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 environmental chemicals 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. The goals of the ENDO Study were to assess the association between environmental chemicals and odds of an endometriosis diagnosis, and 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 bisphenol A (BPA), metals, organochlorine pesticides (OCPs), parabens, perfluoroalkyl and polyfluoroalkyl (PFASs), phthalates, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), trace elements and UV-type BP filters. Other biologic specimens were collected from women undergoing surgery and included endometrium (normal and ectopic, omentum fat, and peritoneal fluid). Additional research is ongoing within the ENDO Study to explore the relation between these classes of environmental chemicals and fibroids.

One of the key discoveries this year was the finding that over 30% of reproductive age women reported experiencing chronic or cyclic pain, with the highest prevalence for women diagnosed with endometriosis (Schliep et al., 2015). Other important discoveries from the ENDO Study include evidence supporting that surgeons are able to reliability diagnosis endometriosis when compared with experts (Schliep et al., 2015, BJOG). With regard to fibroids, specific environmental chemicals were associated with fibroids in the absence of other gynecologic disorders such as endometriosis (Trabert et al., 2015; Pollack et al. 2015).

Principal Investigator

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

Collaborators

- Zhen Chen, Ph.D.
- Sunni Mumford, Ph.D., M.S.
- Karen Schliep, Ph.D., M.P.H.

2015 ENDO Study Publications

- Schliep KC, Mumford SL, Peterson CM, Chen Z, Sharp HT, Johnstone EB, Hammoud AO, Stanford JB, Sun L, Buck Louis GM. Pain typology and incident endometriosis. Pain characterization among women with and without endometriosis using operative and non-operative diagnostic methodologies. *Human Reproduction* 2015; 30(10):2427-38 PMID: 26269527

- Trabert B, Chen Z, Kannan K, Peterson CM, Pollack A, Sun L, Buck Louis GM. Persistent organic pollutants (POPs) and fibroids: Results from the ENDO study. *Journal of Exposure Science and Environmental Epidemiology* 2015;25:278-285 PMID: 24802554

- Pollack AZ, Buck Louis GM, Chen Z, Sun L, Trabert B, Guo Y, Kannan K. Bisphenol A, benzophenonetype ultraviolet filters, and phthalates in relation to uterine leiomyoma. *Environmental Research* 2015; 137:101-107. PMID: 25531814

NICHD Fetal Growth Studies

Environmental Chemicals and Fetal Growth

The NICHD Fetal Growth Studies (*c.f.* Epidemiology Branch report) is the basis for the follow on study aimed at assessing persistent environmental chemicals and fetal growth. This project leverages the NICHD Fetal Growth Studies to address questions about lifestyle and environmental chemicals in relation to fetal growth and birth size. Given the collection of serial 2D/3D ultrasounds from participating women representing four racial/ethnic groups of pregnant U.S. women recruited from 12 clinical sites, we will be able to assess the relation between lifestyle and environmental chemicals and fetal anthropometric measurements (e.g., abdominal circumference, bi-parietal diameter, head circumference, humerus and femur length) in addition to birth weight and gestation. This work is grounded within an evolving body of research suggestive of an adverse association between environmental exposures, such as air pollution and pregnancy outcomes. Moreover, lipophilic chemicals such as organochlorine pesticides, polybrominated diethyl ethers and polychlorinated biphenyls may expose the developing organism via placental or lactational transfer. In this follow-on research, we are measuring four classes of chemicals in 2,694 plasma samples obtained from women upon enrollment into the study: 1) persistent lipophilic pollutants (e.g., organochlorine pesticides, polybrominated biphenyl congeners, polybrominated diphenyl ethers, and polychlorinated biphenyl congeners); 2) persistent non-lipophilic chemicals (e.g.,

perflurochemicals); 3) lifestyle exposures (e.g., caffeine and metabolites, constituents of tobacco smoke, serum lipids); and 4) trace elements (essential and nonessential). For 120 randomly selected women stratified by race/ethnicity, we are measuring these compounds in each trimester. Laboratory analyses are underway and expected to be completed in early 2016. Of note is that parallel and complimentary work that is focusing on the metabolome, with Dr. Cuilin Zhang as principal investigator (*c.f.* Epidemiology Branch).

Another novel aspect of the study is the assessment of thermal indices obtained from serial ultrasounds and prenatal medications use relative to pregnancy outcomes. This avenue of research will answer questions on the safety of obstetrical ultrasounds and commonly taken medications and fetal growth. This work is being led by Dr. Melissa Smarr.

Principal Investigator

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

Collaborators

- Paul Albert, Ph.D.
- Katherine Laughon Grantz, M.D., M.S.
- Una Grewal, Ph.D., M.P.H.
- Sung Duk Kim, Ph.D.
- Melissa Smarr, Ph.D.
- Jennifer Weck, Ph.D.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

2015 Fetal Growth Studies' Publications

- Buck Louis GM, Grewal J, Albert P, Sciscione A, Wing DA, Grobman W, Newman R, Wapner R, D'Alton ME, Skupski D, Nageotte NP, Ranzini A, Owen J, Chien EK, Craigo S, Hediger ML, Kim S, Zhang C, Grantz KL. Racial/ethnic differences in fetal growth, the NICHD Fetal Growth Studies. *American Journal of Obstetrics and Gynecology* 2015; 449.e1–449.e41. PMID: 26410205

Exposome of Normal Pregnancy

Christopher Wild published a landmark paper in 2005 that introduced the concept of the exposome, which he defined as the totality of environmental exposures from conception onward. Successful human reproduction and development involves completion of a series of highly integrated and timed events during sensitive windows such as folliculogenesis, spermatogenesis, fertilization, implantation, and pregnancy. Building upon the Division's expertise in the modeling of environmental exposures including lifestyle and leveraging existing

cohort studies and their biospecimen repositories, we designed this proof-of-concept study as an initial foray into the exposome research. This work has two research aims: 1) to characterize and quantify the "normal" pregnancy exposome using an existing pregnancy cohort study (Trial of Calcium for Preeclampsia Prevention), and 2) to determine its utility and feasibility for design and implementation on a larger scale. We first selected women with low risk pregnancies and healthy outcomes so that we can quantify normal variation from exposome-related changes (Buck Louis, PI). In addition, we selected women whose infants were born at the extremes of birth size for comparison with 'normal' pregnant women (Laughon Grantz, PI). Laboratory analyses are underway in which a mixture of persistent (i.e., metals and trace elements, OCPs, OPPs, PBBs, PBDEs, PCBs, PFCs) and non-persistent chemicals (e.g., benzophenone type UV-filters, parabens, pesticides, phenols, phthalates) are being quantified in blood and urine, respectively, during each trimester of pregnancy. In addition, both untargeted and untargeted proteomic and metabolomics analyses along with targeted analysis of other biomarkers (e.g., adipokines, angiogenesis, glucose homeostasis, sex hormones, inflammation, oxidative stress) are underway. Statistical analysis is currently underway.

Co-Principal Investigators

- Germaine M. Buck Louis, Ph.D., M.S.
- Katherine Laughon Grantz, M.D., M.S.

Collaborators

- Melissa Smarr, Ph.D.
- Rajeshwari Sundaram, Ph.D.
- Edwina Yeung, Ph.D., Sc.M.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

Biostatistics and Bioinformatics Branch

Branch Chief: Paul S. Albert, Ph.D.


Paul Albert, 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 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 on identifying environmental, genetic, or behavioral factors that influence these durations. A major research focus during 2015 has been on developing new statistical methods for predicting the risk of preterm birth subject to a competing risk in subsequent pregnancies using information about the gestational age and adverse pregnancy outcomes from previous pregnancies. BBB investigators have proposed joint models for menstrual cycle length and time to pregnancy, and have developed new statistical methodology for analyzing time-to-pregnancy data that accounts for length-biased sampling and selection bias due to the difficulty of identifying very early pregnancy losses.

BBB investigators have developed new statistical methods for analyzing biomarker data. For example, in 2015 we have developed new methods for statistical inference when the population is selected with a biomarker measured with error, the efficient analysis of multiple endpoints in clinical trials, and the robust methods for estimating ROC curves with clustered data. In 2015, BBB investigators have collaborated with HBB scientists in developing new statistical methodology for analyzing kinematic events in longitudinal natural driving studies in teenagers.

BBB investigators have also developed prediction models that use kinematic events to predict subsequent crashes. BBB investigators have developed new approaches for using longitudinal fetal ultrasound measurements to accurately predict subsequent neonatal morbidity. Also, BBB investigators have developed new statistical methodology for identifying subgroups of individuals that have enhanced predictive accuracy when using longitudinal biomarker data for predicting a subsequent poor outcome. BBB investigators have developed new methodology for assessing agreement from longitudinally collected ratings and scores. In addition to assessing agreement, BBB investigators have new approaches for assessing the accuracy of ratings or tests when no gold standard test is available.

During 2015, 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 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 *Fertility and Sterility*.

Staff

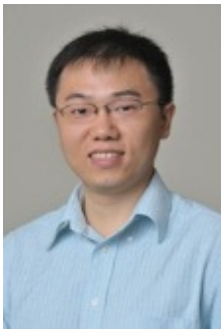
- Paul S. Albert, Ph.D., Senior Investigator and Chief
- Aiyi Liu, Ph.D., Senior Investigator
- Rajeshwari Sundaram, Ph.D., Senior Investigator
- Zhen Chen, Ph.D., Investigator
- Ruzong Fan, Ph.D., Investigator
- Danping Liu, Ph.D., Investigator

- Sung Duk Kim, Ph.D., Staff Scientist

Fellows

- Joe Bible, Ph.D., Postdoctoral Fellow
- Olive Buhule, Ph.D., Postdoctoral Fellow
- Ashok Chaurasia, Ph.D., Postdoctoral Fellow (departed 2015)
- Chi-yang Chiu, Ph.D., Postdoctoral Fellow
- Jared Foster, Ph.D., Postdoctoral Fellow (departed 2015)
- Beom Seuk Hwang, Ph.D., Postdoctoral Fellow
- Ling Ma Ph.D., Postdoctoral Fellow
- Wondwosen Yimer, Ph.D., Postdoctoral Fellow

Longitudinal and Correlated Data Analysis



Danping Liu, Ph.D.

Sung Duk Kim, Ph.D.

A majority of the Division's studies are longitudinal and involve sampling frameworks such as schools, families (parent-child triads), couples, maternal/fetal pairs, and individuals. Longitudinal studies have inherent methodological challenges over time, including the problem of attrition, difficulties in making statistical inference when data are correlated, and difficulties in characterizing complex longitudinal patterns. Many of the Branch's independent research projects address one or more of these issues in the context of substantive problems related to one or more of the Division's studies. Particular methodological problems that have been addressed include: 1) the joint modeling of longitudinal data and time-to-event for understanding the association of longitudinal profiles and an outcome of interest. Branch Investigators have proposed approaches for inference and prediction with applications to the Longitudinal Investigation of Fertility and the Environment (LIFE) Study as well as to the NICHD Fetal Growth Studies; 2) characterizing longitudinal relapsing-remitting and circadian rhythm patterns in longitudinal data with applications to the studying bacterial vaginosis in women and the NEXT Study; and 3) development of new modeling approaches for predicting crashes from longitudinal kinematic (g-force) events.

Examples of recently developed methods include Kim and Albert's (2015) proposed new methods for predicting poor pregnancy outcomes from multivariate longitudinal biomarker data, and Fulton and colleagues' (2015) new regression model for dealing with zero-inflation in clustered binary data that was developed to study factors associated with dating violence in the NEXT study.

2015 Longitudinal and Correlated Data Publications

- Fan RZ, Chen V, Xie YL, Yin LL, Kim S, Albert P, and Simons-Morton B. A functional data analysis approach to analyze circadian rhythm patterns in activity counts for teenage girls. *Journal of Circadian Rhythms* 13(3):1-13, 2015.

- Fulton KA, Liu D, Haynie DL, and Albert PS. Mixed model and estimating equation approaches for zero-inflation in clustered binary response data with application to a dating violence study. *Annals of Applied Statistics*, 9, 275-299, 2015. PMID: 26937263

- Hwang, B and Chen Z. An integrated Bayesian nonparametric approach for stochastic and variability orders in ROC curve estimation. An application to Endometriosis Diagnosis. *Journal of the American Statistical Association,* 110:923-934, 2015. PMID: 26839441

- Jackson, JC, Albert PS, and Zhang Z. A two-state mixed hidden Markov model for risky teenage driving behavior. *Annals of Applied Statistics,* 9,849-865, 2015.

- Shih JH, Albert PS, Mendola P, and Grantz SK. Risk prediction in consecutive time-to-event outcomes subject to a competing event: application to predicting preterm birth in repeated pregnancies. *Journal of the Royal Statistical Society,* Series C, 65:711-730, 2015.

- Tran V, Liu D, Pradhan AK, Li K, Bingham CR, Simons-Morton BG, and Albert PS. Assessing risk-taking in a driving simulator study: modeling longitudinal semicontinuous driving data using a two part regression model with correlated random effects. *Analytic Methods in Accident Research,* 5: 17–27, 2015. PMID: 26894036

- Yao H, Kim S, Chen M-H, Ibrahim JG, Shah, AK, and Lin J. Bayesian inference for multivariate meta-regression with partially observed within-study sample covariance matrix. *Journal of the American Statistical Association,* 110:528-544, 2015. PMID: 26257452.

Analyzing Time-to-Event Data

Rajeshwari Sundaram, Ph.D.

An important analytical issue for many Division studies is the characterization of time to an event. In many studies, correlated event-times are measured (e.g., repeated time-to pregnancy, gestation at birth in consecutive pregnancies, 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.

2015 Time-to-Event Publications

- Feng, Y., Ma, L., and Sun, J. Regression Analysis of Current Status Data Under the Additive Hazards Model with Auxiliary Covariates. *Scandinavian Journal of Statistics*, 42: 118—136, 2015.

- Katki HA, Cheung LC, Fetterman B, Castle PE, and Sundaram R. A joint model of persistent human papillomavirus infection and cervical cancer risk: implications for cervical cancer guidelines. *Journal of the Royal Statistical Society*, Series A, 178:903-923, 2015. PMID: 26556961

- Lum KJ, Sundaram R, and Louis TA. Accounting for length-bias and selection effects in estimating the effects of menstrual cycle length. *Biostatistics,* 16:113-128, 2015. PMID: 25027273

- Ma L, Hu T, and Sun J. Sieve Maximum Likelihood Regression Analysis of Dependent Current Status Data. *Biometrika*, 102:731-738, 2015.

- Mclain AC, Sundaram R, and Buck Louis GM. Joint analysis of longitudinal and survival data measured on nested time-scales using shared parameter models: an application to fecundity data. *Journal of the Royal Statistical Society-Series C*, 64:339-357, 2015.

Analysis of Biomarker Data

Most of the studies within the Division collect biomarkers as either measures of exposure or outcome, with these biomarker measurements often being measured repeatedly. Often, these biomarkers are subject to large biological and technical errors as well as issues pertaining to detection limits. BBB investigators have developed optimal design strategies for reducing

Aiyi Liu, Ph.D.

Zhen Chen, Ph.D.

measurement error when multiple assays are subject to detection limits, and on optimal pooling strategies for reducing the expense of assay measurements in large studies. BBB investigators have also developed supervised latent-class models for examining the effects of a large number of biomarkers on the incidence of disease, an area of research which will have increased importance as the number of assays that can be examined with a single biospecimen will increase substantially.

BBB investigators have made major contributions to the area of group testing, where groups of samples are tested together as compared with testing each sample individually. Recently, BBB investigators have proposed optimal group testing designs for disease screening (Malinovsky and Albert, 2015).

We have an active research program in assessing inter-rater agreement and diagnostic accuracy. BBB investigators have developed new methodology for assessing agreement from longitudinally collected ratings and scores. In addition to assessing agreement, researchers are often interested in assessing the accuracy of ratings or tests when there is no gold standard test available. Many of the methods developed for assessing agreement and diagnostic accuracy were developed from collaborative research in the Endometriosis: National History, Diagnosis, and Outcome (ENDO) Study, which focuses on comparing and evaluating different measures for diagnosing endometriosis in the absence of a gold standard.

2015 Analysis of Biomarkers Publications

- Hwang, B and Chen Z. An integrated Bayesian nonparametric approach for stochastic and variability orders in ROC curve estimation: An application to Endometriosis Diagnosis. *Journal of the American Statistical Association*, 110:923-934, 2015. PMID: 26839441

- Malinovsky Y and Albert PS. A note on the minimax solution for the two-stage testing problem. *The American Statistician*, 69: 45-52, 2015.

Analysis of Genetic Data

Ruzong Fan, Ph.D.

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 2015, BBB investigators developed functional regression models for gene-based association analysis of complex traits by jointly analyzing large number of genetic variants, such as single nucleotide

polymorphisms (SNPs) and next generation sequence (NGS) data adjusting for covariates. We focus on meta-analysis, survival analysis, and pleiotropy analysis of complex traits. To facilitate translation of our methods, eleven sets of R-codes are publically available: http://www.nichd.nih.gov/about/org/diphr/bbb/software/fan/Pages/default.aspx

2015 Analysis of Genetic Data Publications

- Fan RZ, Wang YF, Chiu CY, Chen W, Ren HB, Li Y, Boehnke M, Amos CI, Moore J, and Xiong MM. Meta-analysis of complex diseases at gene level with generalized functional linear models. *Genetics* 202(2):457-70, 2015. PMID: 26715663

- Fan RZ, Wang YF, Qi Y, Ding Y, Weeks DE, Lu ZH, Ren HB, Cook RJ, Xiong MM and Chen W. Gene-based association analysis for censored traits via functional regressions. *Genetic Epidemiology* 40(2):133-43, 2015. PMID: 26782979

- Fan RZ, Wang YF, Boehnke M, Chen W, Li Y, Ren HB, Lobach I, and Xiong MM (2015) Gene level meta-analysis of quantitative traits by functional linear models. *Genetics,* 200(4):1089-104. PMID: 26058849

- Wang YF, Liu AY, Mills JL, Boehnke M, Wilson AF, Bailey-Wilson JE, Xiong MM, Wu CO, and Fan RZ (2015) Pleiotropy analysis of quantitative traits at gene level by multivariate functional linear models. *Genetic Epidemiology,* 39(4):259-75. PMID: 25809955

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), 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. Further, the study objectives include developing predictors of poor pregnancy outcomes using previous pregnancy outcomes.

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.

2015 Collaborative Publications

- Bae J, Kim S, Kannan K, and Buck Louis GM. Couples' Urinary Bisphenol A and Phthalate Metabolite Concentrations and the Secondary Sex Ratio. *Environmental Research,* 137: 450-457, 2015. PMID: 25677702

- Bae J, Kim S, Schisterman EF, Barr DB, and Buck Louis GM. Maternal and Paternal Serum Concentrations of Perfluoroalkyl and Polyfluoroalkyl Substances and the Secondary Sex Ratio. *Chemosphere*, 133: 31-40, 2015. PMID: 25863705

- Bae, J, Kim, S, Kannan, K, and Buck Louis, GM. Couples' Urinary Concentrations of Benzophenone-Type Ultraviolet Filters and the Secondary Sex Ratio. *Science of the Total Environment*, 543:28-36, 2015. PMID: 26575635

- Bailey RL, Looker AC, Lu ZH, Fan RZ, Eicher-Miller HA, Fakhouri TH, Gahche JJ, Weaver CM, and Mills JL. B-vitamins and bone mineral density and risk of lumbar osteoporosis in older females in the U.S. *The American Journal of Clinical Nutrition*, 102 (3):687-694, 2015. PMID: 26224297

- Bloom MS, Buck Louis GM, Sundaram R, Maisog JM, Steuerwald AJ, and Parsons PJ. Birth outcomes and background exposures to select elements, the Longitudinal Investigation of Fertility and Environment (LIFE). *Environmental Research*, 138:118-129, 2015. PMID: 25707016

- Bloom MS, Whitcomb BW, Chen Z, Ye A, Kannan K, and Buck Louis GM. Associations between urinary phthalate concentrations and semen quality parameters in a general population. *Human Reproduction*, 30(11):2645-57, 2015. PMID: 26350610

- Boghossian NS, Sicko RJ, Kay DM, Rigler SL, Caggana M, Tsai M, Yeung EH, Pankratz N, Cole BR, Druschel CM, Romitti PA, Browne ML, Fan RZ, Liu A, Brody LC, and Mills JM. Rare copy number variants implicated in posterior urethral valves. *American Journal of Medical Genetics,* 170: 622-633, 2015. PMID: 26663319

- Boghossian NS, Albert PS, Mendola P, Grantz KL, and Young E. Delivery blood pressure and other first pregnancy risk factors in relation to hypertensive disorders in second pregnancies. *American Journal of Hypertension*, 28(9):1172-1179, 2015. PMID: 25673041

- Brooks-Russell A, Conway KP, Liu D, Xie Y, Vullob GC, Li K, Iannotti RJ, Compton W, and Simons-Morton BG. Dynamic patterns of adolescent substance use: results from a nationally representative sample of high school students. *Journal of Studies on Alcohol and Drugs*, 76:962–970, 2015. PMID: 26562606

- Buck Louis GM, Chen Z, Schisterman E, Kim S, Sweeney AM, Sundaram R, Schisterman E, Lynch C, Gore-Langton R and Barr DB. Perfluorochemicals and human semen quality, the LIFE Study. *Environmental Health Perspective,* 123(1):57-63, 2015. PMID: 25127343

- Buck Louis GM, Chen Z, Kim S, Sapra K, Bae J, and Kannan K. Urinary concentrations of Benzophenone-type ultraviolet light filters and semen quality. *Fertility & Sterility*, 104(4):989-96, 2015. PMID: 26253817

- Buck Louis GM, Grewal J, Albert PS, Sciscione A, Nageotte MP, Grobman W, Newman R, Wapner R, D'Alton ME, Skupski D, Wing DA, Ranzini A, Owen J, Chien EK, Craigo S, Hediger ML, Kim S, Zhang C, and Grantz KL. Racial/Ethnic Standards for Fetal Growth: the NICHD Fetal Growth Studies. *American Journal of Obstetrics & Gynecology*, 213: 449.e1-449.e41, 2015. PMID: 26410205

- Buck Louis GM, Druschel C, Bell E, Stern JE, Luke B, McLain A, Sundaram R, and
- Yeung E. Use of assisted reproductive technology treatment as reported by mothers in comparison with registry data: the Upstate KIDS Study. *Fertility and Sterility*, 103:1461-68, 2015. PMID: 25813287

- Carter TC, Pangilinan F, Molloy AM, Fan RZ, Wang YF, Shane B, Gibney ER, Midttun O, Ueland PM, Cropp CD, Kim Y, Wilson AF, Bailey-Wilson JE, Brody LC, and Mills JL. Common variants at putative regulatory sites nonspecific alkaline phosphatase gene influence circulating pyridoxal 5'-phosphate concentration in healthy adults. *Journal of Nutrition,* 145:1386-93, 2015. PMID: 25972531

- Deac O, Mills JL, Shane B, Midttun O, Ueland PM, Brosnan JT, Brosnan ME, Laird E, Gibney ER, Fan RZ, Wang YF, Brody LC, and Molloy AM. Tryptophan catabolism and vitamin B6 status are affected by gender and lifestyle factors in healthy young adults. *Journal of Nutrition*, 145 (4):701-7, 2015. PMID: 25833774

- Downes KL, Hinkle SN, Sjaarda LA, Albert PS, and Grantz KL. Prior prelabor or intrapartum cesarean delivery and risk of placenta previa. *American Journal of Obstetrics and Gynecology*, 212: 669.e1-e6, 2015.

- Eisenberg, M, Kim, S, Chen, Z, Sundaram, R, Schisterman, E and Buck Louis, G. The relationship between male body mass index and waist circumference on semen quality: Data from the LIFE Study. *Human Reproduction*, 30(2):493-4, 2015. PMID: 24306102

- Eisenberg, M, Chen, Z, Ye, A and Buck Louis, G. The relationship between physical occupational exposures and health on semen quality: Data from the LIFE Study. *Fertility and Sterility*. 103:1271-7, 2015. PMID: 25765658

- Gee BT, Nansel TN, and Liu A**.** The reduction of hypoglycemic events with a behavioral intervention: A randomized clinical trial for pediatric patients with Type I diabetes mellitus. *Diabetic Medicine*, doi: 10.1111/dme.12744, 2015.

- Goldstone, AE, Chen Z, Perry MJ, Kannan K and Buck Louis, GM. Urinary Bisphenol A and Semen Quality, The LIFE Study. *Reproductive Toxicology*, 51(1):7-13, 2015. PMID: 25462789

- Grantz KL, Hinkle SN, Mendola P, Sjaarda LA, Leishear K, and Albert PS. Differences in risk factors for recurrent versus incident preterm delivery. *American Journal of Epidemiology*, 182:157-67, 2015. PMID: 26033931

- Hinkle SN, Johns AM, Albert PS, Kim S, and Laughon Grantz K. Longitudinal changes in gestational weight gain and the association with intrauterine fetal growth. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 190:41-7, 2015. PMID: 25978857

- Männistö T, Mendola P, Liu D, Leishear K, Sherman S, and Laughon SK. Acute air pollution exposure and blood pressure at delivery among women with and without hypertension. *American Journal of Hypertension*, 28:58–72, 2015. PMID: 24795401

- Männistö T, Mendola P, Liu D, Leishear K, Ying Q, and Sundaram R. Temporal variation in the acute effects of air pollution on blood pressure measured at admission to labor/delivery. *Air Quality, Atmosphere and Health*, 8:13–28, 2015.

- Mumford S, Kim S, Chen Z, Barr DB, and Buck Louis GM. Urinary Phytoestrogens Are Associated with Subtle Indicators of Semen Quality among Male Partners of Couples Desiring Pregnancy. *Journal of Nutrition,* 145(11):2535-41, 2015. PMID: 26423741

- Mumford SL, Kim S, Chen Z, Gore-Langton R, Barr DB and Buck Louis GM. Persistent Organic Pollutants and Semen Quality: The LIFE study. *Chemosphere*, 135:427-35, 2015. PMID: 25441930

- Nansel TR, Laffel LMB, Haynie DL, Mehta SN, Lipsky LM, Volkening LK, Butler DA, Higgins LA, and Liu A. Improving dietary quality in youth with type 1 diabetes: randomized clinical trial of a family-based behavioral intervention. *International Journal of Behavioral Nutrition and Physical Activity,* 12(1):58, 2015. PMID: 25952160

- Nansel TR, Thomas DM, and Liu A. Efficacy of a behavioral intervention across income in pediatric type 1 diabetes. *American Journal of Preventive Medicine,* 49: 930-4, 2015. PMID: 26231856

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- Pollack AZ, Buck Louis GM, Chen Z, Sun L, Trabert B, Guo Y and Kannan K. Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma. *Environmental Research*, 137:101-7, 2015. PMID: 25531814

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- Robledo CA, Yeung E, Mendola P, Sundaram R, Sweeney AM, Barr DB, and Buck Louis GM. Preconception maternal and paternal exposure to persistent organic pollutants and birth size, the LIFE study. *Environmental Health Perspectives*, 123:88-94, 2015. PMID: 25095280

- Sadeghi N, Nayak A, Walker L, Irfanoghula, MO, Albert PS, Pierpaoli CB, and the Brain Development Cooperation Group. Analysis of the contribution of experimental bias, experimental noise, and inter-subject biological variability on the assessment of developmental trajectories in diffusion MRI studies of the brain. *Neuroimaging*, 109: 480-92, 2015. PMID: 25583609

- Sapra KJ, McLain AC, Maisog JM, Sundaram R, and Buck Louis GM. Clustering of retrospectively reported and prospectively observed time-to-pregnancy. *Annals of Epidemiology*, doi:10.1016/j.annepidem. 25:959-962, 2015. PMID: 26033375

- Schisterman EF, Mumford SL, Schliep KC, Sjaarda LA, Stanford JB, Lesher LL, Wactawski-Wende J, Lynch AM, Townsend JM, Perkins NJ, Zarek SM, Tsai MY, Chen Z, Faraggi D, Galai N, and Silver RM. Preconception low dose aspirin and time to pregnancy: findings from the effects of aspirin in gestation and reproduction randomized trial. *Journal of Clinical Endocrinology & Metabolism*, 100(5):1785-91, 2015. PMID: 25710565

- Schliep KC, Mumford SL, Peterson CM, Chen Z, Johnstone EB, Sharp HT, Stanford JB, Hammoud AO, Sun L, and Buck Louis GM. Pain typology and incident endometriosis. *Human Reproduction*, 30:2427-38, 2015. PMID: 26269529

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- Smarr MM, Grantz KL, Sundaram R, Maisog J, Kannan K, and Buck Louis GM. Parental urinary biomarkers of preconception exposure to bisphenol A, phthalates in relation to birth outcomes. *Environmental Health*, 14:1-11, 2015. PMID: 26362861

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- Wallace ME, Mendola P, Liu D, and Grantz KL. The joint effects of structural racism and income inequality on small for gestational age birth. *American Journal of Public Health*, 105:1681–88, 2015. PMID: 26066964

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- Wylie A, Sundaram R, Kus C, Ghassabian A, and Yeung EH. Maternal pre-pregnancy obesity and achievement of infant motor development milestones in the Upstate KIDS Study. *Obesity*, 23:907-13, 2015. PMID: 25755075

- Zhang C, Sundaram R, Maisog J, Calafat A, Barr DB, and Buck Louis GM. A prospective study of pre-pregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. *Fertility and Sterility*, 103:184-89, 2015. PMID: 25450302

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Epidemiology Branch

Branch Chief: Enrique F. Schisterman, Ph.D., M.A.


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

The Epidemiology Branch's mission is threefold: 1) to plan and conduct investigator-initiated original epidemiologic research focusing on reproductive, perinatal, and pediatric 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 research including reproductive, perinatal, pediatric, and methodologic epidemiologic 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 from the etiology, determinants, and health consequences of gestational diabetes to the genetic and lifestyle determinants of birth defects through important international collaborations. Moreover, the Epidemiology Branch is focused on clinical trials designed to evaluate inexpensive interventions to improve reproductive health in men and women, allowing for substantial possible public health impact. The Branch is committed to providing evidence to help inform clinical guidance and public policy regarding pregnant woman, particularly in light of the many changes in the characteristics of obstetrical populations over time. The Branch also focuses on abnormal fetal growth in relation to pregnancy complications, the effects of nutrition and the environment on reproduction and pregnancy, lifestyle determinants that impact reproduction, and the impact of air pollution on pregnant women and their offspring. High quality scientific investigation in these domains will aid in the design of effective interventions and preventive strategies to improve the health of many population subgroups.

The Epidemiology Branch has an ambitious research agenda and is strongly committed to improving population health. 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 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
- 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
- Ji Suk Bae, M.D., Visiting Fellow (departed in 2015)
- Wei Bao, M.D., Ph.D., Postdoctoral Fellow (departed in 2015)
- Nikhita Chahal, B.S., Postbaccalaureate Fellow
- Ellen Chaljub, B.S. , Postbaccalaureate Fellow
- Sharon Dar, M.P.H., Special Volunteer
- Katheryne Downes, M.P.H., Special Volunteer Predoctoral Fellow (departed in 2015)
- Angela Dimopoulos, M.D., Postdoctoral Fellow
- Nikira Epps, B.A., Postbaccalaureate Fellow (departed in 2015)
- Akhgar Ghassabian, Ph.D., Postdoctoral Fellow
- Sandie Ha, Ph.D., Postdoctoral Fellow
- Erin Hagen, B.S., Postbaccalaureate Fellow (departed in 2015)
- Stefanie Hinkle, Ph.D., Postdoctoral Fellow (departed in 2015)
- Robyn Kalwerisky, B.S., Postbaccalaureate Fellow (departed in 2015)
- Keewan Kim, Ph.D. , Postdoctoral Fellow
- Sung Soo Kim, Ph.D., Visiting Fellow
- Shanshan Li, Ph.D., Postdoctoral Fellow (departed in 2015)
- Kara A. Michels, Ph.D., M.P.H., Postdoctoral Fellow
- Emily M. Mitchell, Ph.D., Postdoctoral Fellow (departed in 2015)
- Torie Plowden, M.D., Clinical 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
- Karen C. Schliep, Ph.D., M.S.P.H., Postdoctoral Fellow (departed in 2015)
- Melissa Smarr, Ph.D., Postdoctoral Fellow
- Chandra Swanson, B.S., Postbaccalaureate Fellow
- Maeve Wallace, Ph.D., Postdoctoral Fellow (departed in 2015)
- Shvetha Zarek, M.D., Clinical Fellow (departed in 2015)
- Yeyi Zhu, Ph.D., Postdoctoral Fellow

2015 Awards

- Angela Dimopoulos, M.D., *Postdoctoral Fellow* (Mentor: James Mills, M.D., M.S.), Postdoctoral Fellow and Student Travel Award (Research), Teratology Society, Montreal, PQ, Canada

- Shanshan Li, Ph.D., *Postdoctoral Fellow* (Mentor: Cuilin Zhang, M.D., Ph.D., M.P.H.), Fellows Award for Research Excellence (FARE), NIH, Bethesda, MD.

- Pauline Mendola, Ph.D., *Investigator,* Society for Pediatric and Perinatal Epidemiology, President's Award, Denver, CO.

- Emily Mitchell, Ph.D., *Postdoctoral Fellow* (Mentor: Enrique Schisterman, Ph.D.), ASA Section on Statistics in Epidemiology Young investigators Award, Joint Statistical Meetings, Travel Scholarship, Seattle, WA.

- Sunni L. Mumford, Ph.D., *Earl Stadtman Investigator*, Society for Epidemiologic Research, Brian MacMahon Early Career Epidemiologist Award, Denver, CO.

- Enrique F. Schisterman, Ph.D., *Chief and Senior Investigator*, Society for Epidemiologic Research, Excellence in Education, Denver, CO.

- Karen Schliep, Ph.D., *Postdoctoral Fellow* (Mentor: Sunni L. Mumford, Ph.D.), Society for Epidemiologic Research, Lilienfeld Postdoctoral Prize Paper Award Finalist, Denver, CO.

- Maeve Wallace, Ph.D., *Postdoctoral Fellow* (Mentor: Pauline Mendola, Ph.D.), Fellows Award for Research Excellence, National Institutes of Health, Bethesda, MD.

- Edwina H. Yeung, Ph.D., *Investigator*, Society for Pediatric and Perinatal Epidemiologic Research, Rising Star Award, Denver, CO.

- Cuilin Zhang, M.D., Ph.D., MPH, *Senior Investigator*, American Epidemiology Society (AES) elected member (elected 2015), Berkeley, California.

- 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.

Reproductive Epidemiology

The field of reproductive epidemiology focuses on the many factors that affect human fecundity and fertility, which are defined as the biologic capacity of men and women for

reproduction irrespective of pregnancy intentions and the ability to have a live birth, respectively. The discipline also investigates impairments and disorders such as conception delay, anovulation, infertility, and semen quality in relation to environmental, nutritional, and genetic factors. The Epidemiology Branch conducts important reproductive epidemiologic research studies, such as the BioCycle Study, Effects of Aspirin in Gestation and Reproduction (EAGeR) Study, and the Folic Acid and Zinc Supplementation Trial (FAZST). A brief description of each study and its key components follows.

The BioCycle Study: Longitudinal Study of Hormone Effects on Biomarkers of Oxidative Stress and Antioxidant Status During the Menstrual Cycle

Principal Investigators

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

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

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

Division Collaborators

- Ellen Chaljub, B.S.
- Robyn Kalwerisky, B.S.
- Keewan Kim, Ph.D.
- Pauline Mendola, Ph.D., M.S.
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The BioCycle Study is a prospective longitudinal cohort study comprising 259 women aged 18 to 44 years (98% follow-up rate) followed for two menstrual cycles (2005-2007). The study was designed to better understand menstrual cycle function and the intricate relationships between reproductive hormone levels and oxidative stress. Since completion of the study, much progress has been made in the analysis of the BioCycle Study data. To date, over 70 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, including sugar-sweetened beverages

(Shimony et al. *European Journal of Nutrition* 2015), carbohydrate intake (Sjaarda et al. *The Journal of Clinical Endocrinology and Metabolism* 2015), alcohol (Schliep et al. *American Journal of Clinical Nutrition* 2015), and dietary fat (Mumford et al. *American Journal of Clinical Nutrition* 2015). These findings have highlighted the important role of diet on reproductive function. Further research evaluating potential environmental factors, such as cadmium, lead, and mercury levels suggested associations between these factors and elevations in biomarkers of kidney and liver function (Pollack et al *Journal of Toxicology and Environmental Health, Part A: Current Issues* 2015). In addition, it was also observed that medication use (Matyas et al. *Human Reproduction* 2015; Johnson et al. *Pharmacoepidemiology and Drug Safety* 2015) and stress (Schliep et al. *Epidemiology* 2015) may impact ovulatory function. Further research into the mechanisms driving these associations is needed to understand the potential implications for women's health.

Overall, these papers have been influential in describing not only the short-term impact of a healthy 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.

2015 BioCycle Study Publications

- Andrews MA, Schliep KC, Wactawski-Wende J, Stanford JB, Zarek SM, Radin RG, Sjaarda LA, Perkins NJ, Kalwerisky RA, Hammoud AO, Mumford SL. Dietary factors and luteal phase deficiency in healthy eumenorrheic women. *Human Reproduction* 2015; 30(8):1942-1951. PMID: 26082480

- Matyas RA, Mumford SL, Schliep KC, Ahrens KA, Sjaarda LA, Perkins NJ, Filiberto AC, Mattison D, Zarek SM, Wactawski-Wende J, and Schisterman EF. Effects of over-the-counter analgesic use on reproductive hormones and ovulation in healthy, premenopausal women. *Human Reproduction,* 30(7):1714-1723, 2015. PMID: 25954035

- Pollack AZ, Mumford SL, Mendola P, Perkins NJ, Rotman Y, Wactawski-Wende J, and Schisterman EF. Kidney biomarkers associated with blood lead, mercury, and cadmium in premenopausal women: a prospective cohort study. *Journal of Toxicology and Environmental Health, Part A: Current Issues,* 78(2):119-31, 2015. PMID: 25424620

- Schliep KC , Mumford SL, Vladutiu CJ, Ahrens KA, Perkins NJ, Sjaarda LA, Kissell KA, Prasad A, Wactawski-Wende J, and Schisterman EF. Perceived stress, reproductive hormones, and ovulatory function: a prospective cohort study. *Epidemiology,* 26(2):177-184, 2015. PMID: 25643098

- Schliep KC, Zarek SM, Schisterman EF, Wactawski-Wende J, Trevisan M, Sjaarda LA, Perkins NJ, and Mumford SL. Alcohol intake, reproductive hormones, and menstrual

cycle function: a prospective cohort study. *American Journal of Clinical Nutrition,* 102(4):933-942, 2015. PMID: 26289438

- Sjaarda LA, Schisterman EF, Schliep KC, Plowden T, Zarek SM, Yeung E, Wactawski-Wende J, and Mumford SL. Dietary carbohydrate intake does not impact insulin resistance or androgens in healthy, eumenorrheic women. *Journal of Clinical Endocrinology and Metabolism*, 100(8):2979-2986, 2015. PMID: 26066675

EAGeR: Effects of Aspirin in Gestation and Reproduction (EAGeR) Study

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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 ≤2 miscarriages and planning 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 1 documented pregnancy loss at <20 weeks' gestation during the past 12 months; and 2) expanded: women with 1 or 2 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 EAGeR trial was recently completed and the key study results were published in 2014 (Schisterman et al. *Lancet* 2014), with additional findings regarding secondary outcomes published in 2015. 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* 2015). However, in a smaller group of women who had experienced a single recent pregnancy loss, aspirin increased the likelihood of becoming pregnant and having a live birth, and was associated with a shorter time to pregnancy (Schisterman et al. *The Journal of Clinical Endocrinology and Metabolism* 2015) and a lower risk of preterm birth (Silver et al. *Obstetrics and Gynecology* 2015). We have also found that initiation of low-dose aspirin prior to conception was associated with the sex ratio among live born infants, and specifically that low-dose aspirin restored the numbers of male live births and pregnancy with male offspring among women with 1 to 2 prior pregnancy losses (Radin et al. *Journal of Clinical Investigation* 2015). These results suggest that low-dose aspirin modulates inflammation that would otherwise reduce the conception or survival of male embryos.

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 fecundability or pregnancy loss (Zarek et al. *Fertility and Sterility* 2015; Zarek et al. *The Journal of Clinical Endocrinology and Metabolism* 2015). Thus, our data do not support routine AMH testing. 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* 2015). 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.

2015 EAGeR Study Publications

- Lesher LL, Matyas RA, Sjaarda LA, Newman SL, Silver RM, Galai N, Hovey KM, Wactawski-Wende J, Emerick L, Lynch AM, Mead B, Townsend JM, Perkins NJ, Mumford SL, Stanford J, and Schisterman EF. Recruitment for longitudinal, randomised pregnancy trials initiated preconception: lessons learned from the effects of aspirin in gestation and reproduction trial. *Paediatric and Perinatal Epidemiology*, 29(2):162-67, 2015. PMID: 25682951

- Radin RG, Mumford SL, Silver RM, Lesher LL, Galai N, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Simhan HN, Sjaarda LA, Perkins NJ, Zarek SM, Schliep KC,

Schisterman EF. Sex ratio following preconception low-dose aspirin in women with prior pregnancy loss. *Journal of Clinical Investigation*, 125(9):3619-626, 2015. PMID: 26280577

- Schisterman EF, Mumford SL, Schliep KC, Sjaarda LA, Stanford JB, Lesher LL, Wactawski-Wende J, Lynch AM, Townsend JM, Perkins NJ, Zarek SM, Tsai MY, Chen Z, Faraggi D, Galai N, and Silver RM. Preconception low dose aspirin and time to pregnancy: findings from the effects of aspirin in gestation and reproduction randomized trial. *Journal of Clinical Endocrinology and Metabolism*, 100(5):1785-1791, 2015. PMID: 25710565

- Silver RM, Ahrens K, Wong LF, Perkins NJ, Galai N, Lesher LL, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Mumford SL, Sjaarda L, and Schisterman EF. Low-dose aspirin and preterm birth: a randomized controlled trial. *Obstetrics and Gynecology,* 125(4):876-884, 2015. PMID: 25751215

- Wong LF, Schliep KC, Silver RM, Mumford SL, Perkins NJ, Ye A, Galai N, Wactawski-Wende J, Lynch AM, Townsend JM, Faraggi D, and Schisterman EF. The effect of a very short interpregnancy interval and pregnancy outcomes following a previous pregnancy loss. *American Journal of Obstetrics and Gynecology,* 212(3); 375.e1-375.e11, 2015. PMID: 25246378

- Zarek SM, Mitchell EM, Sjaarda LA, Mumford SL, Silver RM, Stanford JB, Galai N, White MV, Schliep KC, DeCherney AH, and Schisterman EF. Is anti-müllerian hormone associated with fecundability? Findings from the EAGeR trial. *The Journal of Clinical Endocrinology and Metabolism,* 100(11):4215-21, 2015. PMID: 26406293

Folic Acid and Zinc Supplementation Trial (FAZST)

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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, assisted reproductive technology outcomes. In response to these emerging data, we designed the FAZST Trial.

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

2015 FAZST Publications
Ongoing study; none to date.

IDEAL Fertility Study: Impact of Diet, Exercise and Lifestyle on Fertility

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Infertility affects approximately 16% of couples in the United States. Roughly one third of infertility is caused by male disorders, one third by female disorders, and one third by combined male and female disorders. 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 regards 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.

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 is anticipated to begin in early 2016.

Perinatal Epidemiology

Perinatal epidemiology 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 trans-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) Collaborative Perinatal Project Mortality Linkage; 2) Consortium on Safe Labor; 3) Consecutive Pregnancies Study [Biostatistics and Bioinformatics Branch]; 4) Diabetes and Women's Health Study; 5) Gestational Diabetes Mellitus: Epidemiology, Etiology and Health Consequences; 6) NICHD Fetal Growth Studies; and 7) the *breathe*-Wellbeing, Environment, Lifestyle and Lung Function Study. A brief description of each study follows.

Collaborative Perinatal Project (CPP) Mortality Linkage

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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.
3. Preterm delivery is significantly associated with total mortality and cause-specific mortality.
4. 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.
6. Dysfunctional labor and cesarean delivery are significantly associated with total mortality and cause specific mortality

Consortium on Safe Labor

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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 2015, we compared spontaneous and induced labor characteristics for women with normal neonatal outcomes undergoing trial of labor after cesarean (TOLAC) who had one prior cesarean and no vaginal deliveries to nulliparous women in labor, and also compared women who achieved vaginal delivery (e.g. having a successful vaginal birth after cesarean (VBAC)). There has been a national interest in increasing the VBAC rate in women with a prior low transverse cesarean delivery to decrease the overall cesarean rate. Duration of labor for women with one prior cesarean and no prior vaginal births undergoing TOLAC was slightly slower than nulliparous women in spontaneous labor (Grantz KL et al. *American Journal of Obstetrics and Gynecology* 2015). For all women undergoing TOLAC, women who spontaneously entered labor had slightly slower progress prior to 7 cm cervical dilation and women who were induced had slower progress prior to 8 cm compared to nulliparous women. Subsequently, labor progressed similarly after 7 cm and 8 cm, respectively, for both spontaneous and induced laboring women undergoing a trial of labor compared to nulliparous women. For the subgroup of women presenting in spontaneous labor who achieved vaginal delivery, the duration of labor was similar for VBAC and nulliparous women. By improved understanding of the appropriate rates of progress at different points in labor, this new information on labor curves in women undergoing TOLAC, particularly for induced labor, should help physicians when managing labor. Other areas of ongoing research include determining the optimal duration for the second stage of labor and continuing to explore how the sociodemographic changes in the current obstetrical population have affected pregnancy complications, maternal and neonatal morbidity, and implications for clinical management, including delivery timing and route.

We have also linked publically 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 is well established in the general population, with the greatest effects seen in vulnerable populations. We found that acute cardiovascular events during labor/delivery (cardiac arrest/failure, stroke, etc.) were also more common after air pollution exposure in the week prior to delivery (Männistö et al. *Heart* 2015). Our novel exploration of preconception exposures continue to show that chronic exposures to air pollution are important for perinatal health as well as the acute effects often studied. We found that preconception exposure contributed to oral cleft risk, in addition to early pregnancy exposures during organogenesis (Zhu et al. *Environmental Research* 2015).

Collectively, this body of research is providing data to develop clinical guidance regarding the management of contemporary pregnant women.

2015 Consortium on Safe Labor Publications

- Mendola P, Mumford SL, Männistö TI, Holston A, Reddy UM, and Laughon SK. Controlled direct effects of preeclampsia on neonatal health after accounting for mediation by preterm birth. *Epidemiology* 2015; 26(1):17-26. PMID: 25437315

- Männistö T, Mendola P, Liu D, Leishear K, Sherman S, and Laughon SK. Acute air pollution exposure and blood pressure at delivery among women with and without hypertension. *American Journal of Hypertension* 2015; 28(1):58-72. PMID: 24795401

- Männistö T, Mendola P, Liu D, Leishear K, Ying Q, and Sundaram R. Evaluating time windows for acute effects of air pollution on blood pressure measured at admission to labor/delivery. *Air Quality, Atmosphere and Health* 2015; 8(1):13-28.

- Robledo CA, Mendola P, Yeung E, Mannisto T, Sundaram R, Liu D, Ying Q, Sherman S, Lipsky L, and Grantz KL. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. *Environment Research* 2015; 137:316-22. PMID: 25601734

- Flores KF, Robledo CA, Hwang BS, Leishear K, Grantz KL, and Mendola P. Does maternal asthma contribute to racial/ethnic disparities in obstetric and neonatal complications? *Annals of Epidemiology* 2015; 25(6):392-7. PMID: 25724829

- Zhu Y, Zhang C, Liu D, Grantz KL, Wallace M, and Mendola P. Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects. *Environmental Research* 2015; 140:714-20. PMID: 26099933

- Wallace M, Mendola P, and Grantz KL. Joint effects of structural racism and income inequality on small-for-gestational-age birth. *American Journal of Public Health* 2015; 105(8):1681-8. PMID: 26066964

- Grantz KL, Gonzalez-Quintero V, Troendle J, Reddy UM, Hinkle SN, Kominiarek MA, Lu Z, and Zhang J. Labor patterns in women attempting vaginal birth after cesarean with normal neonatal outcomes. *American Journal of Obstetrics & Gynecology* 2015; 213(2):226.e1-6. PMID: 25935774

- Männistö T, Mendola P, Grantz KL, Leishear K, Sundaram R, Sherman S, Ying Q, and Liu D. Acute and recent air pollution exposure and cardiovascular events at labor and delivery. *Heart* 2015; 101(18):1491-8. PMID: 26105036

- Clark-Ganheart CA, Reddy UM, Kominiarek M, Huang CJ, Landy HJ, and Grantz KL. Pregnancy outcomes among obese women and their offspring by attempted mode of

delivery. *Obstetrics & Gynecology* 2015; 126(5):987-93. PMID: 26444123

- Coviello L, Grantz KL, Huang C, Kelly TE, and Landy HJ. Risk factors for retained placenta. *American Journal of Obstetrics & Gynecology* 2015; 213(6):864.e1-864.e11. PMID: 26226556

- Halscott T, Reddy UM, Landy H, Ramsey P, Iqbal S, Huang J, and Grantz KL. Maternal and Neonatal Outcomes by Attempted Mode of Operative Delivery From a Low Station in the Second Stage of Labor. *Obstetrics & Gynecology* 2015; 126(6):1265-72. PMID: 26551186

Consecutive Pregnancies Study

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An adverse outcome in one pregnancy is often associated with the same or other adverse outcomes in subsequent pregnancies. However, despite this knowledge, our understanding of why some women have a recurrence of complications and adverse outcomes while others do not remains very limited, including whether there are modifiable risk factors for recurrence. Of great interest is whether we can predict when a complication would recur. The longitudinal data available from the Consecutive Pregnancies Study also present an opportunity to develop clinically relevant statistical methods for prediction and risk assessment.

The Consecutive Pregnancies Study was a unique collaborative effort between the Biostatistics and Bioinformatics and the Epidemiology Branches designed to: 1) estimate the association between the occurrence and timing of pregnancy complications among consecutive pregnancies in women; 2) examine the demographic and environmental factors which may influence these associations; and 3) further develop statistical methodology that will be important in studying associations among multiple pregnancy outcomes. Repeat pregnancy data in Utah were collected on 114,679 pregnancies from 51,086 women, from 2002 to 2010.

With this novel dataset, we have been able to investigate how prior pregnancy history can serve as indicators for subsequent pregnancy complications and neonatal outcomes. Some

highlights from 2015 include: Prior term delivery did not necessarily confer protection from preterm delivery risk factors in a second pregnancy (Grantz KL et al. *American Journal of Epidemiology* 2015). In addition, in the setting of a prior preterm delivery, many risk factors did not persist. These findings indicate that it is important to take prior pregnancy delivery timing into account when assessing risk factors for subsequent preterm delivery risk. We also found that first pregnancy prelabor cesarean delivery was associated with more than a two-fold increased risk of placenta previa in the second pregnancy (Downes et al. *American Journal of Obstetrics & Gynecology.* 2015). In contrast, prior intrapartum cesarean delivery was associated with a non-significant 20% increased risk of placenta previa. Timing of cesarean delivery relative to labor onset is an important distinction, especially given the high percentages of primary and repeat cesarean delivery that occur in the U.S. These findings highlight the importance of labor in relation to cesarean delivery for the development of future placenta previa and, therefore, may inform clinical decision-making related to primary cesarean delivery especially in cases of maternal request or non-medically indicated cesarean delivery.

2015 Consecutive Pregnancies Study Publications

- Boghossian N, Yeung E, Mendola P, Grantz KL, and Albert PS. Delivery blood pressure and other first pregnancy risk factors in relation to hypertensive disorders in second pregnancies. *American Journal of Hypertension* 2015; 28(9):1172-9. PMID: 25673041

- Downes KL, Hinkle SN, Sjaarda LA, Albert PS, and Grantz KL. Previous prelabor or intrapartum cesarean delivery and risk of placenta previa. *American Journal of Obstetrics & Gynecology* 2015; 212(5):669.e1-6. PMID: 25576818

- Grantz KL, Hinkle SN, Mendola P, Sjaarda LA, Leishear K, and Albert PS. Differences in risk factors for recurrent versus incident preterm delivery. *American Journal of Epidemiology* 2015; 182(2): 157-167. PMID: 26033931

Diabetes & Women's Health (DWH) Study

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- Yeyi Zhu, Ph.D.

The DWH Study utilizes a retrospective cohort design 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, 4,000 women with a history of GDM were enrolled and are being followed for 3 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) are collected from 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 have been collected using standardized questionnaires for both cohorts. Data collection is expected to be completed by September 2016; the first cycle of data collection was completed in 2014 and the second cycle is currently ongoing. The overall design paper was published in 2014 (Zhang et al. *Acta Obstetricia et Gynecologica Scandinavica* 2014).

In light of the study's unique design, data analysis is underway while the cohort is being followed. Examples of key findings to date include our observations that unhealthy dietary patterns such a diet with a low-carbohydrate-diet score that is high in animal sources of protein and fat (Bao et al. *Diabetes Care* 2015), greater intakes of total or dietary heme iron (Bao et al. *American Journal of Clinical Nutrition* 2015), or obesity and excess weight gain after GDM (Bao et al. *Diabetologia* 2015) were strongly and independently related to a higher risk of progression from GDM to T2DM. These findings identify potentially modifiable diet and lifestyle factors that contribute to an excess risk for T2DM among women with GDM.

2015 Diabetes & Women's Health Publications

- Bao W, Yeung E, Tobias DK, Hu FB, Vaag AA, Chavarro JE, Mills JL, Grunnet LG, Bowers K, Ley SH, Kiely M, Olsen SF, and Zhang C. Long-term risk of type 2 diabetes mellitus in relation to body mass index and weight change among women with a history of gestational diabetes mellitus: a prospective cohort study with up to 18 years of follow up. *Diabetologia* 2015; 58(6):1212-9. PMID: 25796371

- Tobias DK, Gaskins AJ, Missmer SA, Hu FB, Manson JE, Buck Louis GM, Zhang C, and Chavarro JE. History of infertility and risk of type 2 diabetes mellitus: a prospective cohort study. *Diabetologia* 2015; 58(4):707-15. PMID: 25596853

Gestational Diabetes Mellitus: Epidemiology, Etiology, and Health Consequences

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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, a number of 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, such as depression and sleep duration and quality, are being investigated based on data from the NICHD Fetal Growth Studies.

2. Investigation of the pathogenesis of GDM using prospectively and longitudinally collected biospecimens from pregnancy cohorts, such as the CPEP Study and 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 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* 2015) and women whose mother smoked during pregnancy (Bao et al. *International Journal of Epidemiology* 2015) 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 Journal* 2015). Research based on data from the LIFE Study has identified pre-pregnancy serum levels of perfluorooctanoic acid as being significantly and positively associated with GDM risk (Zhang et al. *Fertility and Sterility* 2015). We have also focused on understanding the role of maternal cardio-metabolic biomarkers, such as adipokines (Bao et al. *Metabolism* 2015), in the development and prediction of GDM, laying the ground for areas for future research related to the dynamic associations of cardio- metabolic factors and GDM risk. Taken together, findings from our research highlight the importance of exposures in the pre-gravid time window in the development of GDM.

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* 2015).

2015 Gestational Diabetes Mellitus Publications

- Zhang C, Sundaram R, Maisog J, Calafat A, Barr DB, and Buck Louis GM. A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. *Fertility and Sterility* 2015; 103(1):184-9. PMID: 25450302

- Bao W, Baecker A, Song Y, Kiely M, Liu S, and Zhang C. Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: a systematic review. *Metabolism* 2015; 64(6):756-64. PMID: 25749468

NICHD Fetal Growth Studies: Singletons and Twins

Fetal Growth Study
NICHD

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

In 2015, we found that by the second trimester in uncomplicated pregnancies, there were already significant differences in the size of individual fetal dimensions (biparietal diameter, head circumference, abdominal circumference, humerus length, and femur length) by categories of maternal self-identified race/ethnicity, and trajectories are established that continue to diverge throughout gestation (Buck Louis et al. *American Journal of Obstetrics and Gynecology* 2015). These findings suggest that assessment of fetal growth by ultrasound needs to be evaluated clinically using racial/ethnic-specific standards for early identification of potential abnormalities and to preclude overdiagnosis of intrauterine growth restriction and unnecessary intervention.

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. Data analysis and manuscript preparation are underway.

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. Data analysis and manuscript preparation are underway.

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. Assay measurement was completed. Data analysis and manuscript preparation are underway.

2015 Fetal Growth Studies' Publications

- Buck Louis GM, Grewal J, Albert P, Sciscione A, Wing DA, Grobman W, Newman R, Wapner R, D'Alton ME, Skupski D, Nageotte NP, Ranzini A, Owen J, Chien EK, Craigo S, Hediger ML, Kim S, Zhang C, and Grantz KL. Racial/ethnic differences in fetal growth, the NICHD Fetal Growth Studies. *American Journal of Obstetrics and Gynecology* 2015, 213(4);449.e1–449.e41. PMID: 26410205

Fetal 3D Study

Principal Investigator

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

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

The overarching research aim of the Fetal 3D Study is to both establish standards for fetal body composition and organ volumes by race/ethnicity and to understand the relationship between gravid diseases and longitudinal changes in fetal body composition (subcutaneous fat, lean mass) and organ measurements (in singletons) over the course of pregnancy, thereby, complementing available data for the Cohort. A second aim is to investigate potentially modifiable factors including maternal BMI, weight gain, longitudinal changes in maternal body composition, nutrition and lifestyle factors with changes in fetal body composition and organ volumes with the goal of helping to identify exposures or susceptibility that may be associated with adverse outcomes among women and the fetuses they carry. A third aim is to explore the association of biomarkers with longitudinal changes in fetal body composition and organ volumes. A collection of measurements of lean and fat body composition and volume data as proposed in the present study offers great potential of investigating associations of a wide spectrum of pregnancy complications and longitudinal changes in fetal body composition as well as visceral organ size.

Breathe-Wellbeing, Environment, Lifestyle and Lung Function (B-WELL-Mom) Study

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

Division Collaborators

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- Katherine Laughon Grantz, M.D., M.S.
- Sandie Ha, Ph.D.
- Sung Soo Kim, Ph.D.
- Leah Lipsky, Ph.D.
- Sunni Mumford, Ph.D., M.S.
- Neil Perkins, Ph.D., M.S.
- Lindsey A. Sjaarda, Ph.D., M.S.
- Jennifer Weck, Ph.D.
- Yeyi Zhu, Ph.D.

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 150 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 100 women were enrolled in 2015 and 21 of them had delivered by the end of the year.

Pediatric Epidemiology

Pediatric epidemiology focuses on the factors that affect the growth, development, and health of children from infancy through adulthood. In 1962, NICHD was established to understand human development throughout the lifecourse, including developmental disabilities and important events during pregnancy. To continue this mission, the pediatric epidemiology 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 infant feeding and childhood obesity. 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 pediatric research areas, including the Birth Defects Research Group, Genetic Factors in Birth Defects Research Group, and the Upstate KIDS Study. A brief summary of each study follows.

Birth Defects Research Group

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

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

Division Collaborators

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- Ruzong Fan, Ph.D.
- Aiyi Liu, Ph.D.

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. This work was led by Dr. Ruzong Fan in DIPHR and will be discussed in his report (Wang et al. *Genetic Epidemiology* 2015 ;39:259-75).

In an investigation that took advantage of the extensive metabolic data collected by our Trinity Students Study, we examined how tryptophan catabolism and vitamin B6 status are influenced by life style factors and gender (Deac et al. *Journal of Nutrition* 2015 ;145(4):701-7).. Vitamin B6, which is important in folate metabolism, is also critical in tryptophan metabolism. Tryptophan is noteworthy because its metabolism is altered in numerous diseases including diabetes, cancer and Alzheimer's disease. Moreover, tryptophan metabolism is affected by pro-inflammatory markers such as interleukins and TNF-alpha. Unfortunately, little was known about how to take into account factors such as gender and smoking when interpreting tryptophan data. This investigation demonstrated that gender was the most important factor to consider in evaluating tryptophan metabolites and that protein intake also influenced their concentrations.

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. We have recently explored the effect of an enzyme gene variant in the gene that reduces synthetic folate (folic acid) to natural folates, dihydrofolate reductase (DHR). If the variant of interest affected folate status, it would be a potential marker for neural tube defect risk. Although it had been suggested that the 19 base pair insertion/deletion variant influenced folate concentrations, we found that it was not related to serum or red cell folate or to total homocysteine concentrations in the Trinity Student Study cohort. Because of the large population studied, we can almost rule out an effect. This also makes it very unlikely that this DHR variant would be a useful predictor of neural tube defect risk (Ozaki M, et al. *Journal of Nutrition* 2015; 145(10):2207-11).

In another attempt to identify genetic/nutritional factors that could be related to neural tube defects, we investigated the role of genetic variants in the genes that influence the

interconversion of different forms of vitamin B6, an important factor in folate metabolism. This investigation showed that variants in one of the genes involved in interconversion, tissue nonspecific alkaline phosphatase (ALPL) is an important factor in determining concentrations of pyridoxal 5'-phosphate (PLP), the co-enzyme form that delivers vitamin B6 to tissues. In all, 19 single nucleotide polymorphisms were associated with altered PLP concentrations. These findings suggest that variants in vitamin B6 enzyme genes are worth additional consideration as neural tube defect risk factors (Carter et al. *Journal of Nutrition* 2015; 145(7):1386-93).

Ongoing 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.

2015 Birth Defects Research Group Publications

- Wang Y, Liu A, Mills JL, Boehnke M, Wilson AF, Bailey-Wilson JE, Xiong M, Wu CO, and Fan R. Pleiotropy analysis of quantitative traits at gene level by multivariate functional linear models. *Genetic Epidemiology* 2015; 39:259-75. PMID: 25809955

- Deac OM, Mills JL, Shane B, Midttun Ø, Ueland PM, Brosnan JT, Brosnan ME, Laird E, Gibney ER, Fan R, Wang Y, Brody LC, and Molloy AM. Tryptophan catabolism and vitamin B-6 status are affected by gender and lifestyle factors in healthy young adults. *Journal of Nutrition* 2015; 145(4):701-7. PMID: 25833774

- Ozaki M, Molloy AM, Mills JL, Fan R, Wang Y, Gibney ER, Shane B, Brody LC, and Parle-McDermott A. The dihydrofolate reductase 19 bp polymorphism is not associated with biomarkers of folate status in healthy young adults, irrespective of folic acid intake. *Journal of Nutrition* 2015; 145(10):2207-11. PMID: 26269242

- Carter TC, Pangilinan F, Molloy AM, Fan R, Wang Y, Shane B, Gibney ER, Midttun Ø, Ueland PM, Cropp CD, Kim Y, Wilson AF, Bailey-Wilson JE, Brody LC, and Mills JL. Common variants at putative regulatory sites of the tissue nonspecific alkaline phosphatase gene influence circulating pyridoxal 5'-phosphate concentration in healthy adults. *Journal of Nutrition* 2015; 145(7):1386-93. PMID: 25972531

Genetic Factors in Birth Defects Study

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- Ruzong Fan, Ph.D.
- Erin Hagen, B.S.
- Aiyi Liu, Ph.D.
- Edwina Yeung, Ph.D., Sc.M.

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, National Human Genome Research Institute and the New York State Department of Health. Stanford University and the California Department of Public Health have joined the collaboration. 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, and the Center for Disease Control's National Birth Defects Prevention Study to receive de-identified samples and data from infants with birth defects. This follow-on work will allow us to search for genetic variants associated with birth defects.

A variety of defects have been analyzed in the past using a candidate gene approach including omphalocele, Hirschsprung's disease, limb defects, and ano-rectal atresia. Our recent research has moved from a candidate gene approach to examining copy number variants in other birth defects. Analysis is ongoing for several uncommon defects. Our first copy number variant study of heterotaxy appeared in print in 2015.

Posterior urethral valves are a very serious congenital malformation resulting in renal insufficiency in a quarter to a half of all affected children. The contribution of genetic factors to causation of posterior urethral valves has received little attention. In this first population based genome-wide investigation of copy number variants, we genotyped cases from New York State using the Illumina HumanOmni 2.5 microarray. Copy number variants were found in more than half the cases. Some involved genes that have been associated with similar defects in animals; some have been seen previously in other urinary tract anomalies; and some have never been reported. These results suggest that genetic factors may play a larger role in posterior urethral valves than was previously appreciated and provide some potential areas for future

investigation (Boghossian et al. *American Journal of Medical Genetics Part A* e published Dec 14, 2015).

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 have recently started a collaboration with the Department of Epidemiology Research at the Statens Serum Institut in Denmark. Our group is also interested in exploring collaborations with investigators conducting such studies.

2015 Genetic Factors in Birth Defects Study Publications

- Rigler SL, Kay DM, Sicko RJ, Fan R, Liu A, Caggana M, Browne ML, Druschel CM, Romitti PA, Brody LC, and Mills JL. Novel copy-number variants in a population-based investigation of classic heterotaxy. *Genetic Medicine* 2015; 17(5):348-57. PMID: 25232849

Whole Exome Sequencing in Pediatric Endocrine Disease

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- Ruzong Fan, Ph.D.


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 is being performed through DIPHR via a contract with the University of Minnesota. Laboratory follow up studies will be 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.

Upstate KIDS Study

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- Candace Robledo, Ph.D., M.P.H.
- Rajeshwari Sundaram, Ph.D.

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. (Buck Louis et al. *Paediatric and Perinatal Epidemiology* 2014)

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 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 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.

2015 Upstate KIDS Study Publications

- Wylie A, Sundaram R, Kus C, Ghassabian A, and Yeung EH. Maternal pre-pregnancy obesity and achievement of infant motor developmental milestones in the Upstate KIDS Study. *Obesity 2015*; 23(4):907-13. PMID: 25755075

- Buck Louis GM, Druschel C, Bell E, Stern JE, Luke B, McLain A, Sundaram R, and Yeung E. Use of assisted reproductive technologies treatment as reported by mothers in comparison to registry data, Upstate KIDS Study. *Fertility & Sterility* 2015; 103(6):1461-8. PMID: 25813287

- Yeung E, McLain AC, Anderson N, Lawrence D, Boghossian N, Druschel C, and Bell E. Newborn adipokines and birth outcomes. *Paediatric and Perinatal Epidemiology* 2015; 29(4):317-325. PMID: 26111443

Upstate KIDS CVD Follow-Up Study

Principal Investigator
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- Rajeshwari Sundaram, Ph.D.
- Jennifer Weck, Ph.D.

The Upstate KIDS cohort described above will be followed to age 8 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 will re-enroll 3200 children from the original cohort at age 5-6 years and follow them for an additional three years by annual questionnaires. Home clinic visits will be conducted at 900 homes for measures of anthropometry, body fat, and blood pressure 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.

Methodologic Research in Epidemiology

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

Biomarker Analytical Development

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.

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

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

Biomarkers are, and will continue to be, an integral part of epidemiological research, making substantial contributions to our understanding of disease pathways and processes. New and emerging biomarkers are essential to this continued understanding. Biomarkers vary greatly in their relation to human disease etiology, but also in measurement techniques and analytic methods. Measurement error can occur in a variety of measurement-specific or more general ways including intra-individual variability and instrument sensitivity, among other causes. Acknowledging, evaluating, and adjusting for these errors is crucial for the correct assessment of individual, as well as population, risk, as measurement error is a consideration for

measurement of all biomarkers(Lyles et al. *International Journal of Environmental Research and Public Health* 2015). Division researchers continue to inform the epidemiologic community of sources and effects of measurement error, but also with developing and implementing methodologies that maximize statistical efficiency while properly accounting for measurement error.

Novel study designs that reduce cost and leverage statistical efficiency are also a major focus of Division researchers (Danaher et al. *Statistics in Medicine* 2015; Mitchell et al. *American Journal of Epidemiology* 2015; Lyles et al. *Biometrics* 2015; Perkins et al*. Biometrical Journal* 2015; Mitchell et al. *Statistics in Medicine* 2015). These methods, originally created for receiver operating characteristic (ROC) curves, have been adapted and found to have equally useful in the analysis of a broad spectrum of epidemiologic data including binary and right-skewed outcomes 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.

2015 Biomarker Analytical Development Publications

- Mitchell EM, Lyles RH, Manatunga AK, and Schisterman EF. Semi-parametric regression models for a right-skewed outcome subject to pooling. *American Journal of Epidemiology* 2015; 181(7):541-8.

- Mitchell EM, Lyles RH, and Schisterman EF. Positing, fitting, and selecting regression models for pooled biomarker data. *Statistics in Medicine* 2015; 34(17):2544-58. PMID: 25846980

- Lyles RH, Van Domelen D, Mitchell EM, and Schisterman EF. A discriminant function approach to adjust for processing and measurement error when a biomarker is assayed in pooled samples*. International Journal of Environmental Research and Public Health*. 2015; 12(11):14723-40. PMID: 26593934

- Danaher MR, Albert PS, Roy A, Schisterman EF. Estimation of interaction effects using pooled biospecimens in a case-control study. *Statistics in Medicine*. doi: 10.1002/sim.6798, 2015. PMID: 26553532

Causal Inference in Reproductive Epidemiology

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

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

Division Collaborators

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

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 confounding and colliders, and as applied to the birth weight paradox and the role of birth weight in analysis of perinatal data (Schisterman et al. *Epidemiology* 2015, In press). In addition, our objective is to apply the same tools to better understand the role of history of prior outcomes as well as potential outcomes in appropriate modeling (Westreich et al. *International Journal of Epidemiology* 2015). Moreover, our work has shed light on the problem of selection bias as an issue of truncation. Both fixed left and variable left truncation may result in loss of precision underscoring the need to properly account for time, especially in time-to-pregnancy studies. Our team of researchers has made significant contributions to this literature in a variety of areas.

Division researchers have also made important contributions regarding the role of exposure-enriched designs in which a cohort study is enriched for a primary exposure of interest to improve cost-effectiveness (Ahrens et al. *American Journal of Epidemiology* 2015). These designs present analytical challenges not commonly discussed in epidemiology when interested in conducting secondary analyses. We have shown that caution should be employed when analyzing studies that have already been enriched, intentionally or unintentionally, for a primary exposure of interest. Specifically, causal diagrams can help identify scenarios in which secondary analyses may be biased, and specific analytical methods can be used to remove the bias (e.g., inverse probability weights).

Furthermore, investigators developed an alternative regression-based adjustment for gestational age (GA) to the z-score method used to mitigate bias in studies examining total gestational weight gain (GWG) and outcomes associated with GA (Hinkle et al. *Paediatric and Perinatal Epidemiology* 2015, In Press). Removing the correlation between GWG and GA in this manner achieves unbiased estimates of the association between total GWG and neonatal mortality, providing an accessible alternative to the weight-gain-for-gestational-age z-scores without requiring assumptions concerning underlying population characteristics.

In addition, the standard recommendation in epidemiological studies is to exclude person-time not at risk (i.e., time during which the outcome could not have occurred) from the denominators of disease rates. However, we have shown that there are scenarios where person-time not at risk should be included (Mumford et al. *Epidemiology* 2015). When interested in estimating treatment effects that allow and account for potential noncompliance, or where the exposure may be associated with the time at risk, we argue that person-time not at risk should be included. In the case of time to pregnancy, although the ITT-type analysis may underestimate the biological fecundity of the population, it may also yield an answer to a question that is of more interest to couples trying to become pregnant.

2015 Causal Inference in Reproductive Epidemiology Publications

- Ahrens KA, Cole SR, Westreich D, Platt RW, and Schisterman EF. A cautionary note about estimating effect of secondary exposures in cohort studies. *American Journal of Epidemiology*. 2015; 181(3):198-203. PMID: 25589243

- Mumford SL, Schisterman EF, Cole SR, Westreich D, and Platt RW. Time at risk and intention to treat analyses: parallels and implications for inference. *Epidemiology* 2015; 26(1):112-118. PMID: 25275571

- Westreich DW, Edwards JK, Cole SR, Platt RW, Mumford SL, and Schisterman EF. Imputation approaches for potential outcomes in causal inference. *International Journal of Epidemiol*ogy 2015; 44(5):1731-7. PMID: 26210611

Health Behavior Branch

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


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.

Staff

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

Fellows

- Katie Dempster, B.A., Postbaccalaureate Fellow
- Johnathan Ehsani, Ph.D., Postdoctoral Fellow
- Miriam Eisenberg, Ph.D., Postdoctoral Fellow
- Benjamin Gee, B.A., Postbaccalaureate Fellow (departed in 2015)
- Pnina Gershon, Ph.D., Special Volunteer
- Chantal Guillaume, Ph.D., Special Volunteer
- Kiana Harris, Summer Intern
- Indra Kar, B.A., Postbaccalaureate Fellow
- Awapuhi Lee, B.A., Postbaccalaureate Fellow
- Angela Lee-Winn, Ph.D., Postdoctoral Fellow
- Kaigang Li, Ph.D., Research Fellow (departed in 2015)
- Fearghal O'Brien, Ph.D., Postdoctoral Fellow
- Hira Palla, B.S., Postbaccalaureate Fellow (departed in 2015)
- Cheyenne Fox Tree-McGrath, B.A., Postbaccalaureate Fellow (departed in 2015)
- Federico Vaca, M.D., Special Volunteer
- Wynette Williams, B.A., Postbaccalaureate Fellow (departed in 2015)

2015 Awards

- Benjamin Gee, Student Paper Award, Society of Behavioral Medicine
- Miriam Eisenberg, NIH Summer Mentor Award, Office of Intramural Training and Education

Adolescent Health Behavior

Principal Investigator

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

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

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- Leah Lipsky, Ph.D.
- Risë B. Goldstein, Ph.D., M.P.H.
- Kaigang Li, Ph.D.
- Johnathan Ehsani, Ph.D.
- Fearghal O'Brien, PhD.
- Miriam Eisenberg, PhD.
- Angela Lee-Winn, Ph.D.
- Ashok Chaurasia, Ph.D.
- Joseph Bible, Ph.D.
- Cheyenne FoxTree-McGrath, B.A.
- Benjamin Gee, B.A.
- Hira Pilla, B.S.
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- Indra Kar, B.A.
- Kathleen Dempster, B.S.
- Awapuhi Lee, B.A.

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

The 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 6 survey, we have a retention rate of 82% 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 risk, along with saliva for genetic analysis. The retention rate for this subsample was 82%.

In the past year, we have examined on the patterns over time of substance use (Simons-Morton, 2016) and dietary intake (Lipsky, et al, 2015). Not surprisingly, alcohol use increases over time, and previous use and having friends who use alcohol were the strongest predictors of alcohol use the first year after high school. Moreover, analysis showed college attendance, particularly living on campus, is associated with higher use whereas employment status was not. Dietary intake was found to be relatively stable across high school and into the first year after. This is concerning, because reported intake was inconsistent with recommendations for a healthful diet. In addition, we report that young adults are likely to see a physician in the past year, and most of those will be asked about substance abuse (Hingston, 2015). However, few receive advice about health risks or information on reducing alcohol, tobacco or drug use. With regard to alcohol use among those in the first year after high school, those who report drinking until they black out also report other consequences of excessive drinking, such as work or school absence and relationship problems (Hingston, in press).

Analysis have been conducted regarding trajectories of physical activity, with publications forthcoming. As with dietary intake, levels of physical activity were stable through high school and the first year after, and far below levels recommended to obtain health benefits. Analyses are underway examining trajectories of marijuana and other substance use and patterns of sleep. We are conducting analysis using objective measures of diet and physical activity in relation to weight status and cardiovascular risk in the NEXT Plus sample. 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.

2015 Adolescent Health Publications

- Brooks-Russell A, Conway KP, Liu D, Xie U, Vullo GC, Li K, Iannotti RJ, Compton W, and Simons-Morton B. (2015). Dynamic patterns of adolescent substance use: results from a nationally representative sample of high school students. *Journal of Studies of Alcohol and Drugs*. 76, 6, 962-970. PMID: 26562606. PMCID: PMC4712666.
- Fan R, Chen V, Yin L, Kim SD, Albert PS, and Simons-Morton B.G (2015). A functional data analysis approach to analyze circadian rhythm patterns in activity counts for teenage girls. *Journal of Circadian Rhythms*, 13, 13. doi: http://dx.doi.org/10.5334/jcr.ac
- Fulton KA, Liu D, Haynie DL, and Albert PS. (2015). Mixed model and estimating equation approaches for zero inflation in clustered binary response data with application to a dating violence study. *Annals of Applied Statistics*, 9, 275-299. doi: 10.1214/14-AOAS791. Report number: IMS-AOAS-AOAS791 PMID: 26937263
- Hingson R, Zha W, White A, and Simons-Morton, BG. (2015). Screening and brief alcohol counselling of college students and person not in school. *JAMA Pediatrics*, 169(11), 1068-1070. doi:10.1001/jamapediatrics.2015.2231. PMID: 26414397. PMCID: PMC4709036.
- Lipsky L, Haynie D, Liu D, Chaurasia A, Gee B, Li K, Iannotti R, and Simons-Morton BG. (2015). Trajectories of eating behaviors in a nationally representative cohort of U.S. adolescents during the transition to young adulthood. *International Journal of Behavioral Nutrition and Physical Activity,* 12:138. PMID: 26537771. PMCID:4632654.

Behavioral Intervention in Health Care

Principal Investigator

- Tonja R. Nansel, Ph.D.

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Division Collaborators

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Chronic disease and other behavior-related or behavior-managed conditions account for the majority of morbidity, mortality, and health care costs; yet, the health care system is based on

an acute care model that cannot adequately assist individuals to engage in the health behaviors required to prevent or manage these conditions. The behavioral sciences offer a substantial knowledge base in mechanisms of promoting behavior change. Thus, integration of the behavioral and medical sciences in clinical practice offers great potential for improving health and decreasing the burden of illness. Our research in this area includes a series of studies involving children and adolescents with type 1 diabetes, including the Family Management of Childhood Diabetes study and the Cultivating Healthy Eating in Families of Youth with Type 1 Diabetes or the CHEF Study, and a recently launched observational study on pregnant women's diet (PEAS Study).

Family Management of Type 1 Diabetes in Youth

Achieving good glycemic control is critical for preventing short- and long-term complications of type 1 diabetes. However, disease management is complex and intensive, involving multiple daily insulin injections or use of an insulin pump, multiple daily blood glucose testing, daily regulation of carbohydrate intake, regular physical exercise, and problem-solving to correct excessive blood glucose fluctuations. Successful management of diabetes in youth is heavily dependent upon family adaptation to the affective, behavioral, and cognitive demands imposed by the disease, and deterioration in management is commonly observed during adolescence. Poor management of diabetes during adolescence is likely to persist into early adulthood, accelerating the risks of both long-term medical complications and psychiatric sequelae. An optimal chronic illness model for care would involve the integration of behavioral management principles into routine clinical care, including assessment and specification of target behaviors, identification of barriers and motivators, collaborative setting of goals, facilitation of problem-solving and coping skills, and provision of follow-up and support. Integration of these components into medical management of diabetes is likely to enhance disease in a practical, cost-effective and lasting manner.

Families receiving care at one of four geographically disperse clinical sites were randomized to receive either standard care or a clinic-integrated behavioral intervention, in which a trained non-professionals delivered the semi-structured approach based on applied problem-solving at each routine clinic visit. A sample of 390 families was followed for two years. Biomedical and self-report data were collected during clinic visits, as well as in-home and by telephone. The intervention tested in this study was based on both individual and family system theoretical perspectives, including social cognitive theory, self-regulation, and authoritative parenting. It was designed to provide experiential training for families in the use of a problem solving approach (represented by the acronym "WE*CAN") to improve parent-child teamwork and more effective problem-solving skills for diabetes management. The intervention was designed to be applicable to the broad population of youth with diabetes and their families, flexibly implemented and tailored to the varying needs of families, and delivered at a low intensity over

time to meet the changing families' needs and roles during the period in which responsibility for diabetes management typically undergoes transition. Intervention components included a preparation telephone contact prior to clinic visits, an action session during clinic visits designed to assist the family in setting specific goals for diabetes management and problem-solving to facilitate goal attainment, and follow-up telephone contacts to reinforce effort and further assist progress. The intervention was effective in improving glycemic control relative to the standard care control group at the two-year follow-up.

Major research findings from 2015.

- Secondary analyses indicated a reduction in hypoglycemia during the second year of the study – the same time frame in which improvement in glycemic control was observed relative to the control group (Gee et al., 2015). As efforts to improve glycemic control through intensive insulin therapy can unintentionally increase the risk of hypoglycemia, findings suggest the clinical utility of using behavioral intervention as an effective means for enhancing diseases management.

- Additionally, we determined that the intervention was similarly effective in improving glycemic control across family income groups (Nansel, Thomas, et al., 2015). Previous research suggests that families of higher income may be better equipped to benefit from behavior interventions, inadvertently exacerbating health disparities. Our findings indicate that low income may not necessarily impede benefits of health behavior interventions.

Additional information is available at:
https://www.nichd.nih.gov/about/org/diphr/hbb/research/Pages/family-management.aspx

Cultivating Healthful Eating 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 the many barriers to healthful eating.

Our program of research includes a cross-sectional study to investigate individual and family factors related to eating behaviors in this population, followed by a behavioral nutrition efficacy trial. The cross-sectional study enrolled 291 parent-youth dyads and obtained data using medical record abstraction, parent-youth interview, youth self-report surveys, parent self-report surveys, and youth three-day diet records. The 18-month CHEF 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. A sample of 139 families was randomized to the behavioral nutrition intervention including continuous glucose monitoring feedback or to continuous glucose monitoring feedback only. The intervention approach, which is grounded in social cognitive theory, self-regulation, and self-determination theory, integrates motivational interviewing, active learning, and applied problem-solving to target increased dietary intake of fruits, vegetables, whole grains, legumes, nuts, and seeds. The intervention sessions, delivered by trained non-professionals, are structured such that concepts and activities are subsequently applied to each meal of the day. The semi-structured approach allows for flexibility in delivery to accommodate differences in youth age as well as family cultural and socioeconomic differences. Data were collected from medical records, parent-youth interviews, youth self-report surveys, parent self-report surveys, youth three-day diet records, parent three-day diet records, youth continuous glucose monitoring, youth body composition (DXA), and youth biomarkers including lipids, carotenoids, and markers of inflammation and oxidative stress. Primary outcomes were dietary intake and glycemic control.

Major research findings from 2015. The CHEF intervention was successful in improving diet quality of youth receiving the behavioral intervention (Nansel, Laffel, et al., 2015). 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. This effect remained through 18-month follow-up. However, glycemic control did not differ between intervention and control groups. Findings indicate the potential utility of incorporating such strategies into clinical care to improve the poor diet quality currently observed in this population. An important secondary research aim was to examine the association of diet quality with diet cost. In the cross-sectional study, we found that differences in diet cost across tertiles of diet quality indicators were very modest, with none reaching statistical significance (Nansel, Haynie, et al., 2015). Further, in the efficacy trial, there was no intervention effect on diet cost, and change in diet cost was not associated in change in diet quality among youth. Among parents, greater intake of whole plant foods was associated with lower diet cost (Nansel et al, findings presented at the 2015 International Society of Behavioral Nutrition and Physical Activity). Findings refute the prevailing assumption that improving diet quality necessitates greater cost.

Additional information is available at:

https://www.nichd.nih.gov/about/org/diphr/hbb/research/Pages/dietary-intake.aspx

Pregnancy Eating Attributes Study (PEAS)

The rising prevalence of obesity in the U.S. over the past several decades and the accompanying spread of adverse long-ranging health effects pose serious public health and economic consequences. Approximately half of women of reproductive age now enter pregnancy at a high body mass index, and approximately half of pregnant women experience pregnancy-associated weight gains in excess of Institute of Medicine (IOM) guidelines, leading to increased maternal and child perinatal and chronic health risks. Sparse intervention research indicates moderate improvement in short-term maternal diet and gestational weight gain, with little evidence of long-term adherence. The well-documented inadequacies of these and traditional weight-loss interventions relying on existing paradigms suggest the need for innovations that allow for a shift in the theoretical framework underlying the determinants of eating behavior. Recent findings from basic research in neuroscience suggest that the brain reward response to food is a critical element that is currently absent in this theoretical framework. However to date, this quickly expanding body of work has not been incorporated into population-based research. The Pregnancy Eating Attributes Study addresses this knowledge gap by examining the implications of findings on the importance of the food reward response for understanding and influencing maternal diet and weight change, as well as infant feeding practices. The overarching goal of this research is to advance understanding of the determinants of eating behavior in order to develop and test novel interventions for improving dietary intake during pregnancy and early childhood, leading to improved maternal and child health trajectories.

PEAS is an observational cohort study examining the role of food reward sensitivity and food reward value 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 genetics, physical activity, stress, sleep and depression. Four hundred and fifty women of varying baseline weight status are enrolled early in pregnancy (before 12 weeks postpartum) and followed until 1 year postpartum. Measures include assessments of food reward and other eating-related constructs, behavioral control, home food environment, dietary intake, other health behaviors, and anthropometrics. Clinical data and biological specimens are obtained. Infant anthropometrics and feeding practices are also assessed. Primary exposures include aspects of food reward and behavioral control, which are assessed in multiple ways to maximize information and utility. Primary outcomes include gestational weight gain, postpartum weight retention and dietary quality. Recruitment for the study was launched in Fall 2014 with an expected completion in 2016.

2015 Behavioral Intervention in Health Care Publications

- Nansel TR, Thomas DM, and Liu A. Efficacy of a behavioral intervention for pediatric type 1 diabetes across income. *American Journal of Preventive Medicine* 2015; 49(6): 930-934. PMID: 26231856. PMCID: PMC4706073.

- Nansel TR, Laffel L, Haynie D, Mehta S, Lipsky L, Volkening L, Butler D, Higgins L, and Liu A. Improving dietary quality in youth with type 1 diabetes: randomized clinical trial of a family-based behavioral intervention. *International Journal of Behavioral Nutrition and Physical Activity* 2015; 12:58. PMID: 25952160. PMCID: PMC4436744.

- Gee BT, Nansel TR, and Liu A. Reduction of hypoglycemic events with a behavioral intervention: a randomized clinical trial for pediatric patients with type 1 diabetes mellitus. *Diabetic Medicine* 2015. doi: 10.111/dme.12744. PMID: 25763988

- Mehta SN, Nansel TR, Volkening LK, Butler DA, Haynie DL, and Laffel LM. Validation of a contemporary adherence measure for youth with type 1 diabetes: the Diabetes Management Questionnaire. *Diabetic Medicine* 2015; 32(9): 1232-8. PMID: 26280463. PMCID: PMC4802856.

- Nansel TR, Haynie D, Lipsky L, Mehta S, and Laffel L. Little variation in diet cost across wide ranges of overall dietary quality among youth with type 1 diabetes. *Journal of the Academy of Nutrition and Dietetics* 2015; 115(3): 433-39. PMID: 25266245. PMC4344866.

- Caccavale LJ, Nansel TR, Quick, V., Lipsky, L., Laffel L, Mehta S. Associations of disordered eating behaviors with the family diabetes environment in adolescents with type 1 diabetes. *Journal of Developmental and Behavioral Pediatrics* 2015; 36(1): 8-13. PMID: 25493461. PMCID: PMC4276537.

Research on Young Drivers

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- Chantal Guillaume, Ph.D.
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Crash risk is highest early in licensure, declining rapidly for a period of months, then slowly over a period of years, reaching adult levels when young adults are in their mid-twenties. Compared with older drivers, teenagers and young adults are more likely to speed, drive in a risky and illegal manner, and engage in distracting secondary tasks, characteristics that contribute to their increased crash rates. However, little is known about how teenage driving behavior varies over time. Research questions of compelling interest to our research team include the following: How and what do novices learn that contributes to safe driving behavior? What is the variability in teen driving risk 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 has included surveys, 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 and executive functioning integrated into this research. Thus, we employ sophisticated methodology to answer key research questions about teenage driving.

The 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. Some 20 papers have been published and analyses are still underway.

The study is already a landmark in driving research. We have published papers on methods, driving exposure, crash risk, and dangerous driving (Simons-Morton et al., 2015a). Separate papers documented high crash rates and elevated gravitational force event rates among teens

relative to their parents driving the same vehicles. However, the association between kinematic risky driving among parents and their teenage children was modest and moderated by shared personality characteristics (Ehsani, et al., 2015). Moreover, perceived risk was only weakly associated with crash and kinematic risky driving rates (Simons-Morton, et al., 2015b). Distraction due to secondary task engagement increased crash risk among novice drivers and longer glances away from the forward roadway increased crash risk more than shorter glances. In interviews conducted at the end of the study, participants reported that the vehicle instrumentation had little effect on their driving. However, consistent with other research (Ouimet et al., 2015; Simons-Morton et al., in press), the presence of passengers affected the way they drove, with some passengers increasing and others decreasing their tendencies to take risks (Ehsani et al., 2015).

The 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 December, 2014; data reduction and coding are proceeding. 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.

The Effect of Teenage Passengers on Teenage Simulated Driving Performance (Teen Passenger Study)

The presence of teenage passengers has been shown to increase crash risk (Ouimet et al., 2015; Simons-Morton et al., in press). 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 1 (TPS1) was designed to ascertain the effect of a risk-accepting or risk-averse teenage passenger on teenage risky driving. We recruited 66 newly licensed male teenage drivers and randomized them to risk-accepting or risk-averse passenger conditions. The passenger was a trained male confederate. We were interested in the effect of social norms on driving behavior, so we employed a pre-drive priming task in which the participant and confederate passenger watched a video of risky driving and the confederate passenger verbalized that he would or would not, depending on the role he was playing, ever ride with that driver. A randomized block design included 2 conditions (passenger: risk-accepting vs. risk-averse) X 2 drive orders (driving alone first vs. driving with the passenger first). Analyses published in 2014 indicated a main effect of passenger presence and an interaction by group, indicating greater driving risk in the risk-accepting passenger group. We concluded that teenage drivers exposed to a risk-accepting teenage passenger were less likely to stop at red lights while driving in a simulator and this risky behavior was greater in the presence of a risk-accepting than a risk-averse peer passenger. Tran et al. (2015) re-evaluated these analyses using a 2-part regression model with correlated random effects.

In collaboration with Emily Falk, a neuro-cognitive researcher then at the University of Michigan, we recruited the TPS1 study participants to attend an fMRI lab the week or so prior to driving the similar so that neuro-images of their brains could be obtained in association with psychological tasks. While they were in the scanner they played “cyberball”, a social exclusion computer task in which the participant is gradually excluded from receiving the cyberball. Theoretically, when a person is socially excluded he or she tends to conform in social context to avoid exclusion and gain acceptance. We found that participants who were sensitive to social exclusion according to neuroimaging data were also sensitive to passenger presence when driving the simulator a week later. Relatedly, those with lower response inhibition (greater impulsivity) assessed in the standard “Go No Go” exercise prior to being imaged were more susceptible to teen passengers’ influences on risky simulated driving (Cascio, 2015).

TPS2 tested the effect of male teenage peer pressure on male teenage risky driving performance. The study design was similar to TPS1, except we put the drivers under pressure by instructing them to reach 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).

TPS3 evaluated the effect of pre-drive mood on risky simulated driving in the presence of a peer passenger. Participants were randomized to play a mood enhancing guitar game with the confederate passenger prior to driving in the simulator, or to sit with a confederate peer listening to quiet music. The association between pre-drive passenger mood and driving performance was in the expected direction, but not significant (Simons-Morton, et al., 2015c).

The 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 will analyze 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 previous possible. The large combined database will allow subgroup analyses and will allow us to answer key questions such as: (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 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.

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 ongoing analyses we focus on self-reported risky driving behavior, secondary task engagement, and self-reported driving while intoxicated by alcohol or drugs (DWI). We demonstrated that these aspects of driving risk co-vary over time (Simons-Morton et al., 2015d). In other analyses we demonstrated reciprocal prospective associations between parental monitoring knowledge (PMK) and DWI (Li et al., 2015), with greater PMK associated with less risk of DWI the following year and DWI associated with increased PMK the following year. In other analyses we found that riding with an intoxicated driver was associated with increased likelihood in the following year of both RWI and DWI (Vaca et al., 2015). Another part of the NEXT Generation Health

includes a unique naturalistic driving study of a subsample of NEXT participants designed to examine how driving behavior varies over time. The DriveCam device was installed in the vehicles of 84 licensed drivers and maintained for a period of 3 years. The device records the video footage of the driver and forward roadway the seconds before and after an elevated g-force event. Analyses are ongoing to examine the variability in elevated g-force event rates (1) over time; and (2) according to individual characteristics and driving conditions.

2015 Publications: Research on Young Drivers

- Cascio CN, Carp J, O'Donnell MB, Tinney FJ Jr, Bingham CR, Shope JT, Ouimet MC, Pradhan AK, Simons-Morton BG, and Falk EB. (2015). Buffering Social Influence: Neural Correlates of Response Inhibition Predict Driving Safety in the Presence of a Peer. *J Cogn Neurosci*, 27(1), 83-95. PMID: 25100217. PMCID: PMC4719161.

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- Ehsani JP, Haynie D, Klauer S, Perlus J, Gerber E, Ouimet MC, Klauer SG, and Simons-Morton B.G. (2015). Teen drivers' perceptions of their peer passengers: qualitative study. *Transportation Research Record No. 2516,* 22-26.

- Li K, Simons-Morton BG, Vaca FE, and Hingson R. (2015). Reciprocal Associations between Parental Monitoring Knowledge and Impaired Driving in Adolescent Novice Drivers. *Traffic Injury Prevention* 16(7):645-51. PMID: 25941751. PMCID: PMC4692247.

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- Simons-Morton BG, Klauer S, Ehsani JP, Guo F, Ouimet MC, Lee S, Albert P, and Dingus T. (2015). Naturalistic Teenage Driving Study: Finding and Lessons Learned. *Journal of Safety Research*. 54:41-44. PMID: 26403899. PMCID: PMC4583651.

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Research Program on Mental Health and Health Disparities

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The research program on mental health and health disparities is new to the Health Behavior Branch in 2015. Because mental disorders, and health disparities more broadly, have significant developmental origins, 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 2015, we had several important contributions to the field underscoring the importance of the early childhood environment on adult mental health. First, with colleagues at Stockholm University and the Harvard TH Chan School of Public Health, we used a quasi-experimental design to investigate the long-term mental health consequences of the World War II-era evacuation of Finnish children to Sweden. Published in the *British Medical Journal*, this study showed that girls evacuated to Sweden were significantly more likely to be hospitalized for depression as adults than their siblings who remained in Finland during the war (Santavirta, Santavirta, Betancourt, and Gilman, 2015). Second, we conducted one of the largest studies to date on the role of childhood and adulthood stressors in the risk of first-time and recurrent bipolar disorder. Published in *Molecular Psychiatry*, the top-ranked journal in the field of psychiatry, this study demonstrated that not only did children who were exposed to adversity have higher lifetime risks of bipolar disorder, but they were also more prone to bipolar disorder when exposed to stressors in adulthood. We interpreted these findings as evidence supporting the importance of the childhood environment for developing capacity to stress adaptation.

Our work linking childhood environments to mental health over the life course has led us to pursue the underlying mechanisms. One potential mechanism focuses on neurodevelopment. A 2015 study directed by Dr. Galen Hung, collaborator at Taipei City Psychiatric Center and the National Yang Ming University in Taiwan, reported that children in socioeconomically disadvantaged households were more likely to exhibit neurological abnormalities as early as 4 months of age, and continuing through 7 years. That study, published in the *International Journal of Epidemiology* (Hung et al., 2015), used data from the landmark Collaborative Perinatal Perinatal project, which conducted intensive neurological examinations of a national cohort of children born in the United States in the early 1960's. Relatedly, our team has also pursued the biological pathways impacted by childhood adversity, focusing largely on immune and inflammatory systems. That pursuit led to a discovery in 2015 that adverse environments experienced during pregnancy were linked with systemic inflammation in their adult offspring (Slopen et al., 2015, *Psychoneuroendocrinology*).

One of the major public health consequences of mental illness is suicide, a leading cause of death among young people. Our own studies have shown that suicide risk within the context of mental illness is also developmental in nature. Children's cognitive development was strongly related to adult suicide risk in a 40-year follow-up study of children in the Collaborative Perinatal Project (Hung et al., In Press, *British Journal of Psychiatry*). In addition, through collaborations with the Army "STARRS" Study (Army Study to Assess Risk and Resilience in Servicemembers), we published 6 reports in 2015 detailing the sociodemographic (gender, occupation) and clinical correlates of suicide among soldiers, leading to methodologic studies aiming to improve suicide risk prediction.

Our prior work on suicide set the stage for a major new effort that was approved by the Institute in 2015 that will go forward in the upcoming year. That study, *The Developmental Origins of Suicide Mortality*, will conduct 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.

Finally, the integration of this research on mental health and health disparities within the Branch and Division has opened the door to new collaborations with NIH investigators on the questions of development and mental health. Of particular note is a new initiative involving collaborators on the **NEXT Generation Health Study** to investigate the neighborhood influences on adolescent health status, including mood and behaviors. Analyses of associations of neighborhood "green space," particularly accessibility of parks, with depressive symptoms are currently underway. Other work in progress involves examination of neighborhood factors with diagnoses 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. In addition, we embarked on a new collaboration in 2015 with investigators on the **Upstate KIDS** study to investigate the role of prenatal, social, and developmental factors in maternal depressive symptoms during the post-partum period and extending through the first 3 years of a child's life. Our team looks forward to building on the progress made in 2015 to advance our understanding the developmental determinants of mental illness and health disparities and to reduce their impact on public health.

2015 Publications on Mental Health and Health Disparities

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DIHPR NICHD FELLOW PUBLICATIONS

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- Buck Louis GM, Chen Z, Kim S, **Sapra KJ**, Bae J, Kannan K. (2015). Urinary concentrations of benzophenone-type UV filters and semen quality. *Fertility and Sterility*; 104(4):989-96. PMID: 26253817

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Biostatistics and Bioinformatics Branch

- **Hwang, BS** and Chen, Z. (2015) An integrated Bayesian nonparametric approach for stochastic and variability orders in ROC curve estimation: An application to endometriosis diagnosis. *Journal of the American Statistical Association*; 110(511):923-34. doi: 10.1534/genetics.115.180869. Epub 2015 Dec 29. PMID: 26839441

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Epidemiology Branch

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- Yang Y, Chen R, Xu J, Li Q, Xu X, **Ha S**, Song W, Tan J, Xu F, and Kan H. (2015) The effects of ambient temperature on outpatient visits for varicella and herpes zoster in Shanghai, China: A time-series study. *J Am Acad Dermatol*;73(4):660-5. PMID: 26277211

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