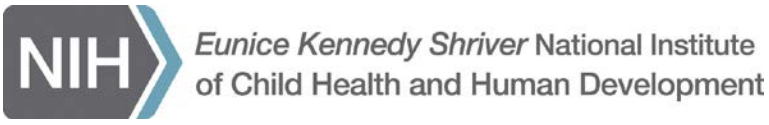
Division of Intramural Population Health Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development

2014 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 well being of populations through novel research, including the development of methods, and training future generations of population scientists. 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. Following its strategic planning process and reorganization in September 2013, the Division now comprises the Office of the Director and three intramural research branches: 1) Biostatistics and Bioinformatics Branch, 2) Epidemiology Branch and 3) Health Behavior Branch. As we continued to design and conduct etiologic and interventional research as described throughout this report, Division scientists are increasingly focusing on understanding health to better inform us about disease processes. Examples of our health oriented research include: identifying the fertile window and day specific conception probabilities for contemporary cohorts of reproductive aged couples, identifying the predictors of male fecundity for achieving pregnancy and birth, defining optimal standards for fetal growth, tailoring children's growth and development trajectories by mode of conception, and discovering interventions that establish long-term healthy eating and safe driving behaviors. In addition, the Division is launching a number of new initiatives aimed at understanding gynecologic and urologic health in relation to health and disease across the lifespan. One such initiative is linking information on pregnant women who participated in the U.S. Collaborative and Perinatal Project between 1959-1965 with the National Death Index to assess patterns between women's gravid health and cause-specific mortality.

The Division had a number of noteworthy accomplishments this year, including the implementation of two new population health studies aimed at maximizing the health of pregnant women with asthma (B-WELL-Mom Study), and in promoting the nutritional status of pregnant women through the postpartum period (PEAS Study), as led by investigators in the Epidemiology Branch and Health Behavior Branch, respectively. Another notable accomplishment is the successful completion of recruitment of women for the Epidemiology Branch's Diabetes and Women Health's Study. This longitudinal study seeks to identify lifestyle factors and their interaction with genetic factors that prevent the onset of type 2 diabetes among high-risk women, or those with a previous history of gestational diabetes. The NICHD Fetal Growth Studies also were successfully completed allowing investigators to develop standards for optimal fetal growth in four racial/ethnic groups of U.S. women along with trajectories for the growth of twins. These studies will be utilized to develop prediction tools that clinicians can use to monitor fetal growth and to aid in the clinical management of growth restricted fetuses. One notable resource built by this study is the 2D/3D imaging database, which comprises approximately 2 million images for future research focusing on the longitudinal growth of organs and bones over the course of pregnancy. These novel studies along with other recently completed studies have stimulated new methods development as described in the Biostatistics and Bioinformatics Branch's report.

In 2014, the Division was home to 16 (Senior) Investigators, 7 Staff Scientists, 1 Laboratory Health Specialist, 2 Research Fellows, 10 Visiting Fellows, and 2 Clinical Fellows. This is in addition to 19 post-doctoral, 2 pre-doctoral and 13 post-baccalaureate Intramural Research Fellows and our annual compliment of approximately 10 summer interns. Division scientists also mentor (under)graduate students from various academic institutions and serve on thesis and dissertation committees. Collectively, our mentees represent various academic institutions across the U.S. Also, we continue to mentor our fellows as they transition to early stage careers in research and academic institutions, and 'tap' them for continued service to the Institution and NIH.

In reflecting upon the 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.

I would like to highlight a few of the Division's key discoveries selected from many excellent papers published this year. I encourage you to read about other discoveries as further described in individual Branch reports.

Key Discoveries

Biostatistics and Bioinformatics Branch

- A mixture modeling approach was developed to predict adverse pregnancy outcomes such as growth restriction using longitudinal fetal ultrasound data. This method overcomes past methodologic limitations by achieving efficiency and robust prediction (Liu and Albert *Biostatistics* 2014).

- An innovative study design was developed for use in precision medicine including clinical trials and observational designs when enrolling study participants based upon a biomarker subject to measurement error (Albert et al. *Biometrics* 2014).

Epidemiology Branch

- Using data from over 223,000 pregnancies, infants born to mothers with asthma were found to experience more respiratory complications and hyper-bilirubinemia in the neonatal period and were more likely to be admitted to neonatal intensive care units than infants whose mothers did not have asthma (Mendola et al. *Journal Allergy and Clinical Immunology*, 2014).

- Serum copeptin, a biomarker of vasopressin, concentrations were higher in pregnant women who developed preeclampsia but not hypertension in comparison to unaffected women, suggesting this marker may be informative for preeclampsia (Yeung et al. *Hypertension* 2014).

- In the Effects of Aspirin in Gestation and Reproduction (EAGeR) Trial, women randomized to the low dose aspirin arm who had only one previous miscarriage before 4.5 months gestation were more likely to become pregnant and have a live birth in comparison to women not receiving aspirin (Schisterman et al. *Lancet* 2014).

- More than 40% of gestational diabetes could be prevented if mothers ate well, exercised regularly, stopped smoking, and maintained a healthy body weight before pregnancy (Zhang et al. *British Medical Journal* 2014).

Health Behavior Branch

- Drivers who glance away from the road for longer periods of time were at greater risk for a crash than drivers with shorter glances (Simons-Morton et al. *Journal of Adolescent Health*, 2014).

- Among youth with type 1 diabetes, the diet cost for consuming a healthier diet was not significantly greater than among those consuming a less healthy diet, suggesting that healthier diets may be obtainable within families' existing food spending (Nansel et al. *Journal of the Academy of Nutrition and Dietetics*, 2014).

Office of the Director

- Among couples trying to become pregnant, those whose male partners had higher concentrations of benzophenone-type UV filters (sunscreens) or phthalates (plasticizers) required a longer time to become pregnant in comparison to couples whose male partners had lower concentrations (Buck Louis et al. *American Journal of Epidemiology*, 2014, *Fertility and Sterility,* 2014).

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 Institute Director, Dr. Alan E. Guttmacher, and Scientific Director, Dr. Constantine A. Stratakis.

Please visit our website 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. 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, both of which are described in the Epidemiology Branch's report.

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 reports for the general public.

A more complete description of the three intramural Branches and their investigators is provided in the individual branch and investigator 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

- Uba Backonja, R.N., *National Institute of Nursing Research GPP Predoctoral Fellow*
- Katherine Sapra, M.Phil., M.P.H., *Predoctoral IRTA Fellow*
- Melissa Smarr, Ph.D., *Postdoctoral IRTA Fellow*

2014 Professional Awards

Uba Backonja, Ph.D., R.N.
Recipient of the Barbara L. Tate Scholarship Fund Award

Katherine Sapra, M.Phil., M.P.H.
Selection for the Society for Epidemiologic Research's Dissertation Workshop
Student Prize Paper Award, American College of Epidemiology
Prize Paper, American Society for Reproductive Medicine

Germaine Buck Louis, Ph.D., M.S.
President's Award (inaugural), Society for Pediatric and Perinatal Research

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 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 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 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 perfluorochemicals (PFCs). Urine samples were used to quantify short-lived chemicals such as bisphenol A (BPA), benzophenone-type UV filter chemicals, phthalates, 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 notable discoveries in 2014, investigators published the first papers suggesting that two classes of environmental chemicals – benzophenone type-UV filters and phthalates – were associated with diminished couple fecundity resulting in a longer time to pregnancy, but the findings were limited to the concentrations in male not female partners (Buck Louis et al. *American Journal of Epidemiology* and *Fertility and Sterility* 2014). These findings underscore the importance of assessing both partners of the couple to avoid missing potential signals for future investigation. With regard to semen quality, investigators did not find it to be associated with the time couples required to become pregnant after adjusting for couples' ages and body mass indices (Buck Louis et al. *Fertility and Sterility* 2014). However, overweight and obese males had a higher prevalence of low ejaculate volume, sperm concentration and total sperm count in comparison to normal weight men even when accounting for physical activity

(Eisenberg et al. *Human Reproduction* 2014). Similarly, males' serum lipids concentrations were adversely associated with semen quality (Schisterman et al. *Andrology* 2014) and also with a longer time to pregnancy (Schisterman et al. *Journal of Clinical Endocrinology and Metabolism* 2014). With regard to infertility, investigators published the first data focusing on preconception stress, as measured by salivary alpha amylase concentrations, and risk of infertility. A significant twofold increase risk of infertility was observed for women with the highest relative to lowest concentrations (Lynch et al. *Human Reproduction* 2014). This paper was selected as the 2015 Human Reproduction's Keynote paper at the forth coming annual meeting of the *European Society of Human Reproduction and Embryology* to be held in Lisbon, Portugal. Other notable discoveries from the LIFE Study focusing on gravid diseases and pregnancy loss include the first report that the perfluorinated chemical PFOS is associated with a higher odds of gestational diabetes (Zhang et al. *Fertility and Sterility* 2014), and that women experiencing pregnancy losses take longer to conceive when trying for subsequent pregnancies (Sapra et al. *Human Reproduction* 2014).

Investigators are continuing to assess environmental chemicals and lifestyle in relation to other outcomes such as pregnancy loss and infant birth size. Of note is the role of our fellows who are researching the symptomology of pregnancy loss and parental chemical exposures and length of gestation, birth size and the secondary sex ratio (Ji Suk Bae, Katherine Sapra and Melissa Smarr).

Principal Investigator

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

Collaborators

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

2014 LIFE Study Publications

1. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney A, Lynch CD, Kim S, Maisog JM, Gore-Langton R, Chen Z. Semen quality and time-to-pregnancy, the LIFE Study. *Fertility and Sterility* 2014; 101(2):453-62.

2. Eisenberg ML, Kim S, Sundaram R, Schisterman EF, Buck Louis GM. The relationship between male body mass index, adiposity, and activity level on semen quality, LIFE Study. *Human Reproduction* 2014; 29(2):193-200.

3. Buck Louis GM. Persistent environmental pollutants and couple fecundity: an overview. *Reproduction* 2014;147(4):R97-R104.

4. Buck Louis GM, Sundaram R, Sweeney AM, Schisterman EF, Maisog J, Kannan K. Urinary bisphenol A, phthalates and couple fecundity, The LIFE Study. *Fertility and Sterility* 2014;101(5):1359-1366.

5. Schisterman EF, Mumford SL, Chen Z, Browne RW, Barr DB, Sundaram R, Kim S, Buck Louis GM. Lipid concentrations and semen quality: The LIFE Study. *Andrology* 2014;2(3):408-415.

6. Lynch CD, Sundaram R, Maisog J, Sweeney AM, Buck Louis GM. Preconception stress increases the risk of infertility: results from a couple-based prospective cohort study, The LIFE Study. *Human Reproduction* 2014; 29(5):1067-1075.

7. Schisterman EF, Mumford SL, Browne RW, Boyd Barr D, Chen Z, Buck Louis GM. Serum lipid levels and couple fecundity: The LIFE Study. *Journal of Clinical Endocrinology and Metabolism* 2014;99(8):2786-2794.

8. Mumford SL, Sundaram R, Schisterman EF, Sweeney AM, Barr DB, Rybak ME, Maisog JM, Parker DL, Pfeiffer CM, Buck Louis GM. Female, not male, urinary lignan concentrations associated with shorter time to pregnancy. *Journal of Nutrition* 2014;144(3):352-358.

9. Sapra KJ, McLain AC, Maisog JM, Sundaram R, Buck Louis GM. Successive time-to-pregnancy among women experiencing hCG pregnancy loss. *Human Reproduction* 2014;29(11):2553-2559.

10. Buck Louis GM, Kannan K, Sapra KJ, Maisog J, Sundaram R. Urinary concentrations of benzophenone-type UV filters and couple fecundity. *American Journal of Epidemiology* 2014;180(12):1168-1175.

11. Mumford SL, Kim S, Chen Z, Gore-Langton R, Barr DB, Buck Louis GM. Persistent organic pollutants and semen quality: The LIFE Study. *Chemosphere* 2014; Nov.28. Pii:S0045-6536(14)1278-8.

12. Guo Y, Weck J, Sundaram R, Goldstone A, Buck Louis GM, Kannan K. Urinary concentrations of phthalates in couples planning pregnancy and its association with 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative stress. *Environmental Science and Technology* 2014;48(16):9804-9811.

13. 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.

14. 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.

15. 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.

16. 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.

17. Bae J, Kim S, Kannan K, Buck Louis GM. Couples' urinary bisphenol A and phthalate metabolite concentrations and the secondary sex ratio. *Reproductive Toxicology* (In Press).

Endometriosis: Natural History, Diagnosis and Outcomes (ENDO) Study ENDO

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 isk of reproductive site cancers and autoimmune disorders than unaffected women, underscoring the interrelatedness between gynecologic disorders and later onset disease. 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. The operative cohort underwent laparoscopy/laparotomy examination while 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), perfluorchemicals (PFCs), phthalates, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), trace elements, and UV-filters. Other biologic specimens were collected from women undergoing surgery and included endometrium (norm and ectopic, omentum fat, and peritoneal fluid).

In 2014, we leveraged the ENDO Study to consider chemicals and gynecologic pathology beyond endometriosis. Specifically, we focused on fibroids given how prevalent they are for reproductive aged women. Important 2014 discoveries included findings that serum p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) concentrations were associated with a postoperative diagnosis of fibroids, as were several PCB congeners as quantified in omental fat (Trabert et al. *Journal of Exposure Science and Environmental Epidemiology* 2014). In addition, higher concentrations of blood metals (i.e., cadmium, cobalt, lead) were associated with fibroids as well (Johnstone et al. *Reproductive Toxicology* 2014). Collectively, these are among the first human data suggesting a role for environmental agents and fibroid formation.

We also collaborated with omics investigators in Dr. Susan Fisher's laboratory at the University of California, San Francisco to assess whether endometriosis was associated with changes in the protein composition of peritoneal fluid, urine and/or omental fat. A protein of unknown function (FAM49B) along with two proteinases (metalloproteinase-9 and neutrophil elastase) were down regulated in the omental fat of women with in comparison to women without endometriosis (Williams et al. *Journal of Proteomics* 2015). When we considered protein expression in relation to the environmental chemicals, FAM49B and neutrophil elastase levels were associated with higher levels of a subset of environmental chemicals. Thus, this work is generating hypotheses for consideration in future studies

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.
- Uba Backjona, Ph.D. (departed in 2014)

2014 ENDO Study Publications

1. Trabert B, Chen Z, Kannan K, Peterson CM, Pollack A, Sun L, Buck Louis GM. Persistent environmental chemicals and fibroids. *Journal of Exposure Science and Environmental Epidemiology* 2014 May 7. doi: 10.1038/jes.2014.31.

2. Johnstone EB, Buck Louis GM, Parsons PJ, Steuerwald AJ, Palmer CD, Chen Z, Hammoud AO, Dorais J, Peterson CM. Increased whole blood concentrations of cadmium and mercury in women with uterine leiomyomata: Findings from the ENDO Study. *Reproductive Toxicology* 2014 Jun 30;49C:27-32. doi: 10.1016/j.reprotox.2014.06.007.

3. Williams KE, Miroshnychenko O, Johansen EB, Niles RK, Sundaram R, Kannan K, Albertolle M, Drake P, Giudice LC, Hall SC, Witkowska HE, Buck Louis GM, Fisher SJ. Urine, peritoneal fluid and omental fat proteomes of reproductive age women: endometriosis-related changes and associations with endocrine disrupting chemicals. *Journal of Proteomics* 2014; 113:194-205.

Environmental Chemicals and Fetal Growth

This project leverages the NICHD Fetal Growth Studies (*c.f.* Epidemiology Branch) 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).

A final component of the environment and fetal growth study currently underway is to assess thermal indices obtained from serial ultrasounds and prenatal medications use relative to pregnancy outcomes. 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.
- Sungduk Kim, Ph.D.
- Melissa Smarr, Ph.D.
- Jennifer Weck, Ph.D.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

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 & 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.

2014 Other Division Publications

1. Andersen NJ, Mondal TK, Freed BM, Stockinger S, Preissler MT, Bell E, Druschel C, Buck Louis GM, Lawrence DA. Detection of immunoglobulin isotypes from dried blood spots. *Journal of Immunological Methods* 2014;404:24-32.

2. Brite J, Shiroma E, Bowers K, Yeung E, Laughon SK, Grewal J, Zhang C. Height and risk of gestational diabetes: Does maternal race make a difference? *Diabetic Medicine* 2014;31(3):332-340.

3. Buck Louis GM, Hediger ML, Bell EM, Kus CA, Sundaram R, McLain A, Hills EA, Thoma ME, Druschell CM. Methodology for establishing a population-based birth cohort focusing on couple fertility and children's health, the Upstate KIDS Study. *Paediatric and Perinatal Epidemiology* 2014;28(3):191-202.

4. Kissell KA, Danaher MR, Schisterman EF, Wactawski-Wende J, Ahrens KA, Schliep K, Perkins NJ, Sjaarda L, Weck J, Mumford SL. Biological variability in serum anti-Müllerian hormone throughout the menstrual cycle in ovulatory and sporadic anovulatory cycles in eumenorrheic women. *Human Reproduction* 2014 Aug;29(8):1764-72.

5. Laughon SK, McClain A, Sundaram R, Catov JM, Buck Louis GM. Maternal lipid change in relation to length of gestation: a prospective cohort study with preconception enrollment of women. *Gynecologic and Obstetric Investigation* 2014;77(1):6-13.

6. Ma W-L, Gao C, Bell EM, Druschel CM, Caggana M, Aldous KM, Buck Louis GM, Kannan K. Analysis of polychlorinated biphenyls (PCBs) and organochlorine pesticides in archived dried blood spots and its application to track temporal trends in environmental chemicals in newborns. *Environmental Research* 2014;133:204-210.

7. McLain AC, Sundaram R, Thoma ME, Buck Louis GM. Semi-parametric modeling of grouped current duration data with preferential reporting. *Statistics in Medicine* 2014;33(23):3961-72.

8. 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(2):339-357.

9. Prasad A, Mumford SL, Buck Louis GM, Ahrens KA, Sjaarda LA, Schliep KC, Perkins NJ, Kissell KA, Wactawski-Wende J, Schisterman EF. Sexual activity and its effect on endogenous reproductive hormones and ovulation. *Hormones and Behavior* 2014; 66(2):330-338.

10. Sjaarda LA, Mumford SL, Kissell K, Schliep KC, Hammoud AO, Perkins NJ, Weck J, Wactawski-Wende J, Schisterman EF. Increased androgen, anti-Müllerian hormone, and sporadic anovulation in healthy, eumenorrheic women: a mild PCOS-like phenotype. *Clinical Endocrinology and Metabolism* 2014 Jun;99(6):2208-16.

11. Tobias DK, Gaskins AJ, Missmer SA, Hu FB, Manson JE**,** Buck Louis GM, Zhang C, Chavarro JE. History of infertility and risk of type 2 diabetes mellitus: a prospective cohort study. *Diabetologia* (In Press).

12. Vitonis AF, Vincent K, Rahioglu N, Fassbender A, Buck Louis GM, Hummelshoj L, Giudice LC, Stratton P, Adamson GD, Becker CM, Zondervan KT, Missmer SA. WERF endometriosis phenome and biobanking harmonization project (EPHect): II. Clinical and covariate phenotype data collection in endometriosis research. *Fertility and Sterility* 2014;S0015-0282(14)01885-8.

Biostatistics & 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.

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 2014 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 developed new statistical methods for analyzing biomarker data. For example, in 2014 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. We have also developed new statistical methodology for the identification of multiple change points in mean biomarker levels across time in longitudinal biomarker data. In 2014, 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 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 2014, BBB investigators have developed new statistical methodology for association analysis of quantitative and qualitative traits using functional data analytical techniques at the gene level, along with new methods for detecting gene-gene and gene-environmental interactions of complex diseases.

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.

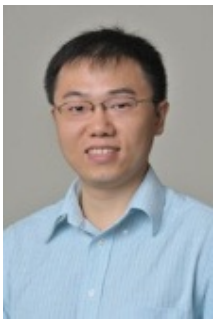
Staff

- 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

- Olive Buhule, Ph.D., *Postdoctoral Fellow*
- Ashok Chaurasia, Ph.D., *Postdoctoral Fellow*
- Jared Foster, Ph.D., *Postdoctoral Fellow*
- Yifan Wang, Ph.D., *Postdoctoral Fellow* (departed in 2014)
- Beom Seuk Hwang, Ph.D., *Postdoctoral Fellow*
- Kirsten J. Lum, M.S., *Predoctoral Fellow* (departed in 2014)
- Rachel Hill, B.S. *Postbaccalaureate Fellow*
- Alicia Johns, B.S., *Postbaccalaureate Fellow* (departed in 2014)

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.

Liu and Albert (2014) proposed new methods for combining longitudinal imaging biomarkers to predict poor pregnancy outcomes. Fulton and colleagues (*Annals of Applied Statistics* 2014) developed a new regression model for dealing with zero-inflation in clustered binary data, which was developed to study factors associated with dating violence in the NEXT study.

2014 Longitudinal and Correlated Data Publications

1. Albert PS, Shih JH. Modeling batched Gaussian longitudinal data subject to informative dropout. *Statistical Methods in Medical Research* 23: 203-217, 2014.

2. Cheon K, Thoma M, Kong X, and Albert PS. A mixture of Markov models for Heterogeneous longitudinal ordinal data: with applications to analyzing longitudinal bacterial vaginosis data. *Statistics in Medicine* 33: 3204-3213, 2014.

3. Fulton KA, Liu D, Albert PS, and Haynie DL. 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*, in press.

4. Fan R, Chen, V, Xie, Y, Yin, L, Kim, SD, Albert, PS, and Simons-Morton, B. Functional data analysis approach to analyze circadian rhythm patterns in activity counts for teenage girls. *Journal of Circadian Rhythms*, in press.

5. Hunsberger SA, Albert PS, Thoma, M. Approaches for retrospective sampling for longitudinal transition models. *Statistics and its interface* 7: 75-85, 2014.

6. 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*, in press.

7. Jackson, JC, Albert PS, Zhang Z. A two-state mixed hidden Markov model for risky teenage driving behavior. *Annals of Applied Statistics,* in press.

8. Lai Y and Albert PS. Identifying multiple change-points in a linear mixed model. *Statistics in Medicine* 33: 1015-1028, 2014.

9. Liu D and Albert PS. Combination of longitudinal biomarkers in predicting binary events. *Biostatistics* 15:706-718, 2014.

10. McLain AC and Albert PS. Modeling longitudinal data with a random change point and no time-zero: applications to inference and prediction of the labor curve. *Biometric*s 70: 1052-1060, 2014.

11. 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,* in press.

12. 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*, in press.

13. 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*, in press.

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.

2014 Time-to-Event Publications

1. McLain AC, Sundaram R, Thoma M, Buck Louis GM. Semiparametric modeling of grouped current duration data with preferential reporting. *Statistics in Medicine* doi:10.1002/sim.6216, 2014.

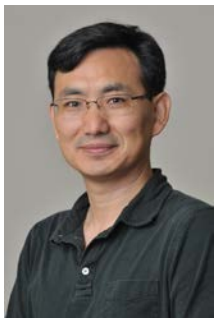
2. Lum K, Sundaram R, Louis T. Accounting for length-bias and selection effects in estimating the effects of menstrual cycle length. *Biostatistics* 16:113-128, 2015.

3. 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-Series C* doi: 10.1111/rssc.12075.

4. Katki HA, Cheung LC, Fetterman B, Castle PE, 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, in press.

Analysis of Biomarker Data

Aiyi Liu, Ph.D.



Zhen Chen, Ph.D.

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 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.

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.

2014 Analysis of Biomarkers Publications

1. Albert PS, Liu A, Nansel T. Estimation and design for logistic regression under an imperfect population identifier. *Biometrics* 70:175-184, 2014.

2. Chen Z and Xie Y. Marginal analysis of measurement agreement among multiple raters with non-ignorable missing ratings. *Statistics and Its Interface* 7:113-120, 2014.

3. Foster JC, Taylor JM, Kaciroti, N, and Nan B. Simple subgroup approximations to optimal treatment regimens from randomized clinical trial data. *Biostatistics,* in press.

4. Li ZB, Liu A, Li ZH, Li QZ. Rank-based tests for comparison of multiple endpoints among several populations. *Statistics and Its Interface* 7:9-18, 2014.

5. Liu CL, Liu A, Hu J, Yuan V, Halabi S. Adjusting for misclassification in stratified biomarker clinical trials. *Statistics in Medicine* 33:3100-3113, 2014.

6. Malinovsky, Y, Albert, PS, and Roy, A. A note on the evaluation of group testing algorithms in the presence of misclassification. *Biometrics*, in press.

7. Malinovsky, Y and Albert PS. A note on the minimax solution for the two-stage group testing problem. *The American Statistician*, in press.

8. Taylor JMG, Cheng, W, and Foster JC. Reader Reaction to "A robust method for estimating optimal treatment regimes. *Biometrics*, in press.

9. Zhang Z, Nie L, Soon G, Liu A. The use of covariates and random effects in evaluating predictive biomarkers under a potential outcome framework. *Annals of Applied Statistics*, 8:2336–2355, 2014.

10. Zhang Z, Liu C, Kim S, Liu A. Prevalence Estimation Subject to Misclassification: the Misspecification Bias and Some Remedies. *Statistics in Medicine*, 33:4482-4500, 2014.

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 and qualitative traits when the outcomes are longitudinal, and in developing statistical methods for detecting gene-gene and gene-environmental interactions of complex diseases. In 2014, 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, stochastic dynamic models and Chebyshev splines, gene-gene and gene-environment interactions of complex diseases, and pleiotropy analysis of multiple quantitative traits. To facilitate translation of our methods, four sets of R-codes are publically available: http://www.nichd.nih.gov/about/org/diphr/bbb/software/fan/Pages/default.aspx

2014 Analysis of Genetic Data Publications

1. Fan RZ, Wang YF, Mills JL, Carter TC, Lobach I, Wilson AF, Bailey-Wilson JE, Weeks DE, and Xiong MM. Generalized functional linear models for case-control association studies. *Genetic Epidemiology* 38:622-637, 2014.

2. Fan RZ, Zhu B, and Wang Y. Stochastic dynamic models and Chebyshev splines. The *Canadian Journal of Statistics* 42:610-634, 2014.

3. Lobach I, Fan RZ, and Manga P. Genotype-Based association models of complex diseases to detect gene-gene and gene-environment interactions. *Statistics and Its Interface* 7:51-60, 2014.

4. Li QZ, Xiong WJ, Chen J, Zheng G, Li ZH, Mills JM, Liu A. A robust test for quantitative traits in genetic association studies. *Statistics and Its Interface* 7:61-68, 2014.

5. Wang YF, Liu AY, Mills JL, Wilson AF, Bailey-Wilson JE, Xiong MM, Wu CO, and Fan RZ. Pleiotropy analysis of quantitative traits at gene level by multivariate functional linear models. *Genetic Epidemiology*, in press.

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.

2014 Collaborative Publications

1. Albert PS and Grantz KL. Fetal growth and ethnic variation. *Lancet Diabetes and Endocrinology* 2: 773, 2014.

2. Bao W, Tobias DK, Bowers K, Chavarro J, Vaag A, Grunnet LG, Strøm M, Mills J, Liu A, Kiely M, Zhang C. Physical activity and sedentary behaviors associated with risk of progression from gestational diabetes mellitus to type 2 diabetes mellitus: a prospective cohort study. *JAMA Internal Medicine*, 174:1047-1055, 2014.

3. Bloom MS, Louis GMB, Sundaram R, Maisog JM, Steuerwald AJ, Parsons PJ. Birth outcomes and background exposures to select elements, the longitudinal investigation for Fertility and Environment (LIFE). *Environmental Research*, in press.

4. Boghossian NS, Yeung EH, Albert, PS, Mendola P, Laughon SK, Hinkle SN, Zhang C. Changes in diabetes status between pregnancies and impact on subsequent newborn outcomes*. American College of Obstetrics* 431: e1-e14, 2014.

5. Boghossian, NS, Albert PS, Mendola, P, Hinkle, SN, Laughon, SK, Zhang, C, and Yeung, EH. Predictive factors differ between recurrent and incident preeclampsia. *Annals of Epidemiology*, in press.

6. Buck Louis GM, Sundaram R, Schisterman E, Sweeney A, Lynch C, Kim S, Maisog J, Gore-Langton R, Eisenberg M and Chen Z. Semen quality and time-to-pregnancy, the LIFE Study. *Fertility and Sterility* 101(2):453-462, 2014.

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

8. Buck Louis GM, Hediger ML, Bell EM, Kus CA, Sundaram R, McLain AC, Yeung E, Hills EA, Thoma ME, Druschel CM. Methodology for establishing a population-based birth cohort focusing on couple fertility and children's development, the Upstate KIDS study. *Paediatric and Perinatal Epidemiology*, 28(3):191-202, 2014.

9. Buck Louis GM, Kannan K, Sapra KJ, Maisog J, Sundaram R. Urinary concentrations of benzophene-type uv filters and couple fecundity. *American Journal of Epidemiology*, 180(12): 1168-1175, 2014.

10. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney A, Lynch CD, Kim SD, Maisog JM, Gore-Langton R, Eisenberg ML, Chen Z. Urinary bisphenol A, phthalates, and couple fecundity: the longitudinal investigation of fertility and sterility. *Fertility and Sterility*, 101(5):1359-1366, 2014.

11. Chen G, Li J, Ying Q, Sherman S, Perkins N, Sundaram R, Mendola P. Evaluation of observation-fused regional air quality model results for air pollution exposure estimation. *Science of the Total Environment* 485:563-574, 2014.

12. Deac O, Mills JL, Shane B, Midttun O, Ueland PM, Brosnan JT, Brosnan ME, Laird E, Gibney ER, Fan RZ, Wang YF, Brody LC, Molloy AM. Evaluation of the influence of lifestyle factors and vitamin B6 status on tryptophan metabolism in a young healthy population. *The Journal of Nutrition*, in press.

13. Downes, KL, Hinkle, SN, Sjaarda, LA, Albert PS, and Grantz, KL. Prior prelabor or intrapartum cesarean delivery and risk of placenta previa. *The American Journal of Obstetrics and Gynecology*, in press.

14. Ehsani J, Simons-Morton B, Xie Y, Klauer, SG, and Albert PS. The association between kinematic risky driving among parents and their teenage children: moderation by shared personality characteristics. *Accident Analysis and Prevention* 67C, 1-6, 2014.

15. Eisenberg ML, Kim SD, Chen Z, Sundaram R, Schisterman EF, Buck Louis GM. The relationship between male body mass index, adiposity, and activity level on semen quality: data from the LIFE Study. *Human Reproduction*, 29:193-200, 2014.

16. Gee BT, Nansel TN, 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*, in press.

17. Ghosh, G, Laughon, SK, Mendola, P, Mannisto, T, Chen, Z, Xie, Y, and Grewal, J. Racial/ethnic differences in pregnancy-related hypertensive disease in nulliparous women. *Ethnicity and Disease*, 24:283-289, 2014.

18. 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.

19. Goodman M, Lakind JS, Fagliano JA, Lash TL, Wiemels JL, Winn DM, Patel C, Van Eenwyk, J Kohler BA, Schisterman EF, Albert PS, Mattison DR. Cancer cluster investigations: review of the past and proposals for the future. *International Journal of Environmental Research and Public Health* 11:1479-1499, 2014.

20. 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*, in press.

21. Guo Y-, Weck J, Sundaram R, Goldstone AE, Buck Louis GM, Kannan K. Urinary concentrations of phthalates in couples planning pregnancy and its association with 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative stress: the longitudinal investigation of fertility and the environment (LIFE) study. *Environmental Science and Technology*, 48:9804-9811, 2014.

22. Hinkle SN, Albert PS, Mendola P, Sjaarda, LA, Yeung, E, Boghossian NS, Laughon SK. The association between parity and birthweight in a longitudinal consecutive pregnancy cohort. *Paediatric and Perinatal Epidemiology* 28:106-115, 2014.

23. Hinkle SN, Albert PS, Boghossian NS, Mendola P, Sjaarda L, Yeung E, Laughon K. Differences in risk factors for incidence and recurrent small-for-gestational-age birthweight: a hospital-based cohort study. *British Journal of Obstetrics and Gynecology* 121: 1080-1088, 2014.

24. Johnstone EB, Louis GM, Parsons PJ, Steuerwald AJ, Palmer CD, Chen Z, Sun L, Hammoud AO, Dorais J and Peterson CM. Increased urinary cobalt and whole blood concentrations of cadmium and lead in women with uterine leiomyomata: Findings from the ENDO Study. *Reproductive Toxicology* 49:27-32, 2014.

25. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD consecutive pregnancies study: recurrent preterm delivery by subtype. *American Journal of Obstetrics and Gynecology* 210: e1-e11, 2014.

26. Laughon SK, Berghella V, Reddy U, Sundaram R, Lu Z, Hoffman M. Neonatal and maternal outcomes with prolongs second stage of delivery. *Obstetrics and Gynecology*, 124(1):57-67, 2014.

27. Laughon SK, McLain AC, Sundaram R, Catov J, Buck Louis GM. Maternal lipid change in relation to length of gestation: a prospective cohort study with preconception enrollment of women. *Gynecologic and Obstetric Investigation*, 77:6-13, 2014.

28. Levin SW, Baker EH, Zein WM, Zhongjian Zhang Z, Quezado ZMH, Miao N, Gropman A, KJ, Bianconi S, Chandra G, Khan OI, Caruso RC, Liu, A, Mukherjee AB. A bench-to-bedside clinical trial using a combination of cystagon and mucomyst for patients with INCL. *Lancet Neurology*, 13:777-787, 2014.

29. Luque-Fernandez, MA, ananth, CV, Jadoe, V., Gaillard, R, Albert PS, Schomaker, M, McElduff, P, Enquobahrie, DA, Gelaye B, and Williams, MA. Is the fetoplacental ratio a differential maker of fetal growth restriction in small for gestational age infants? *European Journal of Epidemiology*, in press.

30. Lynch C, Sundaram R, Maisog J, Sweeney A, Buck Louis GM. Increased levels of physiologic stress are associated with decreased fecundability: results from a couple-based prospective study, the LIFE study. *Human Reproduction*, 29(5):1067-1075, 2014.

31. Männistö T, Mendola P, Liu D, Leishear K, Ying Q, 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*, doi:10.1007/s11869-014-0268-5, 2014.

32. Mendola, P, Männistö, T, Leishear, K, Reddy, U, Chen, Z and Laughon, K. Neonatal health of infants born to mothers with asthma. *Journal of Allergy and Clinical Immunology* 133(1):85-90, 2014.

33. Mills JL, Fan R, Brody LC, Liu, A, Ueland PM, Wang Y, Kirke PN, Shane B, Anne Molloy AM. Maternal choline concentrations during pregnancy and choline-related genetic variants as risk factors for neural tube defects. *The American Journal of Clinical Nutrition* 100:1069-1074, 2014.

34. Molloy AM, Einri CN, Jain D, Laird E, Fan RZ, Wang YF, Scott J, Shane B, Brody LC, Kirke PN, Mills JL. Is low iron status a risk factor for neural tube defects? Birth Defects Research Part A: *Clinical and Molecular Teratology* 100:100–106, 2014.

35. Mumford S, Sundaram R, Schisterman E, Maisog J, Chen Z, Kim S, Sweeney A, Buck Louis GM. Higher urinary lignan concentrations in women but not men are positively associates with shorter time-to-pregnancy. *The Journal of Nutrition* 144(3):352-358, 2014.

36. Nansel T, Lipsky LM, Liu A, Laffel L, Mehta S. Contextual factors are associated with diet quality in youth with type 1 diabetes. *Journal of the Academy of Nutrition and Dietetics* 114:1223-1229, 2014.

37. 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* 137C:101-7, 2014.

38. Prikh, L, Reddy, U, Männistö, T, Mendola, P, Sjaarda, L, Hinkle, S, Lu, Z, Chen, Z, Laughon, K. Neonatal outcomes in early term birth. *American Journal of Obstetrics and Gynecology* 211(3):265.e1-e11, 2014.

39. Rigler SL, Kay DM, Sicko RJ, Fan R, Liu A, Caggana M, Browne ML, Druschel CM, Romitti PA, Brody LC, Mills JL. Novel Copy Number Variants in a Population-Based Investigation of Classic Heterotaxy. *Genetics in Medicine,* in press

40. Robledo CA, Mendola P, Yeung E, Männistö T, Sundaram R, Liu D, Ying Q, Sherman S, Lipsky L, Laughon SK. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. *Environmental Research*, 137: 316-322, 2015.

41. Sadeghi, N, Nayak, A, Walker, L, Irfanoghula, MO, Albert, PS, Pierpaoli, C, and the Brain Development Cooperative 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. *Neuroimage*, in press.

42. Sapra K, Mclain AC, Maisog JM, Sundaram R, Buck Louis GM. Successive time to pregnancies among women experiencing hCG pregnancy loss. *Human Reproduction*, 29 (11): 2553-2559, 2014.

43. Schisterman, EF, Mumford, SL, Chen, Z, Browne, RW, Barr, DB, Kim, S and Buck Louis, GM. Lipid concentrations and semen quality: the LIFE Study. *Andrology* 2(3):408-15, 2014.

44. Schisterman, EF, Mumford, SL, Browne, RW, Barr, DB, Chen, Z and Buck Louis, GM. Lipid concentrations and couple fecundity: the LIFE Study. *Journal of Clinical Endocrinology and Metabolism* 99(8):2786-94, 2014.

45. Sjaarda LA, Albert PS, Mumford SL, Hinkle SN, Mendola P, Laughon SK. Customized large-for-gestational-age birthweight at term and the association with adverse perinatal outcomes. *American Journal of Obstetrics and Gynecology* 210: e1-e11,2014.

46. Trabert, B, Chen, Z, Kannan, K, Peterson, CM, Pollack, A, Sun, LP and Buck Louis, GM. Persistent organic pollutants (POPs) and fibroids: results from the ENDO Study. *Journal of Exposure Science and Environmental Epidemiology*, doi:10.1038/jes.2014.31, 2014.

47. Williams KE, Miroshnychenko O, Johansen ER, Niles RK, Sundaram R, Kurunthachalam K, Albertolle M, Drake P, Giudice LC, Hall SC, Witkowska HE, Buck Louis GM, Fisher SJ. Urine, peritoneal fluid and omental fat proteomes of reproductive aged women: endometriosis related changes and associations with endocrine disrupting chemicals. *Journal of Proteomics*, 113(15):194-205, 2015.

48. Winer, KK, Fulton, K, Peterson, D, Nixon-Jones, Albert PS, and Cutler, GB. Effectiveness of parathyroid hormone I-34 replacement therapy via pump versus twice daily injections: a randomized crossover study in children with severe congenital hypoparathyroidism. *Journal of Pediatrics* 165, 556-563, 2014.

49. Wylie A, Sundaram R, Kus C, Ghassabian A, Yeung EH. Maternal pre-pregnancy obesity and achievement of infant motor development milestones in the Upstate KIDS Study. *Obesity*, in press.

50. Yeung EH, Liu, A, James Mills J, Zhang C, Männistö T, Lu Z, Tsai MY, Pauline Mendola P. Increased levels of copeptin before clinical diagnosis of preeclampsia. *Hypertension*. 64:1362-1367, 2014.

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

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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*
- Michele Kiely, Dr.P.H., *Staff Scientist* (departed in 2014)
- Katherine Laughon Grantz, M.D., M.S., *Investigator*
- 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

- Katherine A. Ahrens, Ph.D., M.P.H., *Postdoctoral Fellow (departed in 2014)*
- Uba Backonja, M.S., R.N., *Predoctoral Fellow (departed in 2014)*
- Ji Suk Bae, M.D., *Visiting Fellow*
- Wei Bao, M.D., Ph.D., *Postdoctoral Fellow*
- Nansi S. Boghossian, Ph.D., M.P.H., *Postdoctoral Fellow (departed in 2014)*
- Nikhita Chahal, B.S., *Postbaccalaureate Fellow*
- Sharon Dar, M.P.H., *Special Volunteer*
- Katheryne Downes, M.P.H., *Special Volunteer Predoctoral Fellow*
- Angela Dimopoulos, M.D., *Postdoctoral Fellow*
- Nikira Epps, B.A., *Postbaccalaureate Fellow*
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- Shanshan Li, Ph.D., *Postdoctoral Fellow*
- Rebecca Matyas, B.A., *Postbaccalaureate Fellow (departed in 2014)*
- Kara Michels, Ph.D., *Postdoctoral Fellow*
- Emily M. Mitchell, Ph.D., *Postdoctoral Fellow*
- Torie Plowden, M.D., *Clinical Fellow*
- Rose Radin, Ph.D., M.P.H., *Postdoctoral Fellow*
- Candace Robledo, Ph.D., M.P.H., *Postdoctoral Fellow (departed in 2014)*
- Karen C. Schliep, Ph.D., M.S.P.H., *Postdoctoral Fellow*
- Melissa Smarr, Ph.D., *Postdoctoral Fellow*
- Maeve Wallace, Ph.D., *Postdoctoral Fellow*
- Shvetha Zarek, M.D., *Clinical Fellow*
- Yeyi Zhu, Ph.D., *Postdoctoral Fellow*

2014 Awards

- Katherine A. Ahrens, Ph.D., *Postdoctoral Fellow* (Mentor: Enrique F. Schisterman, Ph.D.), Fellows Award for Research Excellence, National Institutes of Health, Bethesda, MD.

- Katherine A. Ahrens, Ph.D., *Postdoctoral Fellow* (Mentor: Enrique F. Schisterman, Ph.D.), Society for Epidemiologic Research, Student-Postdoc Travel Award, Boston, MA.

- Nansi S. Boghossian, Ph.D., M.P.H, *Postdoctoral Fellow* (Mentor: Edwina H. Yeung, Ph.D. Sc. M.), Teratology Society, Fellow Travel Award, Seattle, WA.

- Emily M. Mitchell, Ph.D., *Postdoctoral Fellow* (Mentor: Enrique F. Schisterman, Ph.D.), Fellows Award for Research Excellence, National Institutes of Health, Bethesda, MD.

- Sunni L. Mumford, Ph.D., *Earl Stadtman Investigator*, Society for Pediatric and Perinatal Epidemiologic Research, Rising Star Award, Seattle, WA.

- Sunni L. Mumford, Ph.D., *Earl Stadtman Investigator,* Fertility and Sterility Star Reviewer Award, Honolulu, HI.

- Karen Schliep, Ph.D., *Postdoctoral Fellow* (Mentor: Sunni L. Mumford, Ph.D.), Society for Epidemiologic Research, Student-Postdoc Travel Scholarship, Seattle, WA.

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

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- Shvetha Zarek, M.D.

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, 59 papers have been published. We have shown that metabolic markers such as markers of oxidative stress, lipoprotein cholesterol, inflammatory markers, glucose metabolism markers, and uric acid vary significantly across the menstrual cycle among healthy, regularly cycling women (Schisterman et al. *Epidemiology Reviews* 2014). While absolute changes were generally modest, we observed that women passed between clinically relevant risk categories depending on which phase of the menstrual cycle biomarkers were measured (e.g., nearly twice as many women had elevated cholesterol levels warranting therapy (≥200 mg/dL) during the follicular phase compared with the luteal phase (14.3% vs. 7.9%). Overall, only 3% of women had consistently high levels during all phases of the cycle. These findings have implications for clinical practice (i.e., certain doctor visits should be timed to menstrual cycle phase) and for study designs including women of reproductive age.

The BioCycle Study has also contributed substantially to the field of nutritional epidemiology, offering valuable insights into the benefits of a healthy diet for young premenopausal women. In particular, sweetened soda was associated with elevated alanine aminotransferase, a surrogate marker of liver fat content (Shimony et al. *European Journal of Nutrition* 2014). 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 delineating the impact of a healthy diet on hormonal function and ovulation and later onset chronic diseases.

Using banked serum samples, we found women with higher testosterone concentrations also had relatively elevated anti-mullerian hormone (AMH) concentrations and more frequent sporadic anovulation. These data suggested that the combination of elevated androgens and AMH may identify an intermediate phenotype or subclassification of polycystic ovary syndrome in otherwise healthy young women (Sjaarda et al. *The Journal of Clinical Endocrinology & Metabolism* 2014). We also found significant associations between time-varying leptin levels and reproductive hormones with an indication of leptin triggering ovulation, suggesting that leptin is associated with enhanced fertility and preparing the body for the increased energy demands of pregnancy (Ahrens et al. *American Journal of Obstetrics and Gynecology* 2014).

Collectively, the BioCycle Team has made important discoveries regarding normal hormonal variations during menstrual cycle phases, and also variations indicative of underlying pathology or potential risk factors for abnormal menstrual cycle function. The team will continue analyzing data resulting from this study to answer important public health questions for women of reproductive age regarding lifestyle and dietary influences on reproductive function.

2014 BioCycle Study Publications

1. Ahrens K, Mumford SL, Schliep KC, Kissell KA, Perkins NJ, Wactawski-Wende J, Schisterman EF. Serum leptin levels and reproductive function during the menstrual cycle. *American Journal of Obstetrics and Gynecology* 2014; 210(3):248.e1-9.

2. Ahrens KA, Vladutiu CJ, Mumford SL, Schliep KC, Perkins NJ, Wactawski-Wende J, Schisterman EF. The effect of physical activity across the menstrual cycle on reproductive function. *Annals of Epidemiology* 2014; 24(2):127-34.

3. Danaher M, Roy A, Chen Z, Mumford SL, Schisterman EF. Minkowski-Weyl priors for models with parameter constraints: an analysis of the BioCycle Study. *Journal of the American Statistical Association* 2014; In press.

4. Kissell KA, Danaher MR, Schisterman EF, Wactawski-Wende J, Ahrens KA, Schliep KC, Perkins NJ, Sjaarda L, Mumford SL. Biological variability in serum anti-mullerian hormone throughout the menstrual cycle in ovulatory and sporadic anovulatory cycles in eumenorrheric women. *Human Reproduction* 2014; 29(8):1764-1772.

5. Lynch KE, Mumford SL, Schliep KC, Whitcomb BW, Zarek SM, Pollack AZ, Bertone-Johnson ER, Danaher M, Wactawski-Wende J, Gaskins AJ, Schisterman EF. Assessment of anovulation in eumenorrheic women: comparison of ovulation detection algorithms. *Fertility and Sterility* 2014; 102(2):511-518.e2.

6. Pollack AZ, Mumford SL, Mendola P, Perkins NJ, Rotman Y, Wactawski-Wende J, Schisterman EF. Blood lead, mercury and cadmium in relation to kidney and liver biomarkers in premenopausal women. *Journal of Toxicology and Environmental Health Part A: Current Issue*s 2014; 78(2): 119-131.

7. Pollack AZ, Sjaarda LA, Ahrens KA, Mumford SL, Browne RW, Wactawski-Wende J, Schisterman EF. Association of cadmium, lead and mercury with paraoxonase 1 activity in women. *PLOS One* 2014; 9(3):e92152.

8. Prasad A, Mumford SL, Buck Louis GM, Ahrens KA, Sjaarda LA, Schliep KC, Perkins NJ, Kissell KA, Wactawski-Wende J, Schisterman EF Sexual activity, endogenous reproductive hormones and ovulation in premenopausal women. *Hormones and Behavior* 2014; 66(2):330-338.

9. Prasad A, Mumford SL, Schliep KC, Ahrens KA, Sjaarda LA, Perkins NJ, Matyas R, Wactawski-Wende J, Schisterman EF. Depressive symptoms and their relationship with endogenous reproductive hormones and sporadic anovulation in premenopausal women. *Annals of Epidemiology* 2014; 24(12):920-924.

10. Schisterman EF, Mumford SL, Sjaarda LA. Failure to consider the menstrual cycle phase may cause misinterpretation of clinical and research findings of cardiometabolic biomarkers in premenopausal women. *Epidemiology Reviews* 2014; 36(1):71-82.

11. Schliep KC, Mumford SL, Hammoud AO, Stanford JB, Kissell KA, Sjaarda LA, Perkins NJ, Ahrens KA, Wactawski-Wende J, Mendola P, Schisterman E. Luteal phase deficiency in regularly menstruating women: Prevalence and overlap in identification based on clinical and biochemical diagnostic criteria. *The Journal of Clinical Endocrinology & Metabolism* 2014; 99:e1007-14.

12. Schliep KC, Mumford SL, Vladutiu CJ, Ahrens KA, Perkins NJ, Sjaarda LA, Kissell KA, Prasad A, Wactawski-Wende J, Schisterman EF. Perceived stress, reproductive hormones, and ovulatory function: a prospective cohort study. *Epidemiology* 2014; In Press.

13. Shimony MK, Schliep KC, Schisterman EF, Ahrens K, Sjaarda LA, Rotman Y, Perkins NJ, Pollack AZ, Wactawski-Wende J, Mumford SL. The relationship between added sugar consumption and liver enzymes among healthy premenopausal women: a prospective cohort study. *European Journal of Nutrition* 2014; *In Press.*

14. Sjaarda LA, Mumford SL, Kissell K, Schliep KC, Hammoud AO, Perkins NJ, Weck J, Wactawski-Wende J, Schisterman EF. Increased androgen, anti-mullerian hormone and sporadic anovulation in healthy, eumenorrheic women: a mild PCOS-like phenotype? *The Journal of Clinical Endocrinology & Metabolism* 2014; 99(6):2208-2216.

15. Whitcomb BW, Mumford SL, Perkins NJ, Wactawski-Wende J, Bertone-Johnson ER, Lynch KE, Schisterman EF. Urinary cytokine and chemokine profiles across the menstrual cycle in healthy reproductive-aged women. *Fertility and Sterility* 2014; 101(5):1383-1391.e2.

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

Principal Investigators

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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 key findings from this study were published in 2014 (Schisterman et al. *Lancet* 2014). Overall, we observed that preconception low-dose aspirin use was not associated with live birth or pregnancy loss among women with one or two prior pregnancy losses (Schisterman et al. *Lancet* 2014). However, we did find that among the original stratum of women (or those with only one prior loss at <20 weeks' gestation in the previous year) there was a higher live birth rate in the low-dose aspirin group (Schisterman et al. *Lancet* 2014), along with a shorter time to pregnancy (Schisterman et al. *The Journal of Clinical Endocrinology & Metabolism* 2014).

Interestingly, women who took low-dose aspirin were more likely to have a positive pregnancy test and an ultrasound-confirmed pregnancy than the placebo arm. The fact that low-dose aspirin had a significant effect on positive pregnancy tests for both strata combined is suggestive that low-dose aspirin could have favorable effects on fecundity. In addition, low-dose aspirin was not significantly associated with the overall rate of preterm birth, though there was a trend towards lower rates of preterm birth in women treated with low-dose aspirin, particularly among women with a single recent early pregnancy loss (Silver et al. *Obstetrics and Gynecology* 2014). It is important to note that major adverse events were infrequent and similar in the low-dose aspirin and placebo groups. Women who took low-dose aspirin were more likely to report vaginal bleeding, but these women were no more likely to experience a pregnancy loss. The remaining secondary outcomes are in progress and multiple secondary analyses are ongoing.

2014 EAGeR Study Publications

1. 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, Schisterman EF. Recruitment for Longitudinal, Randomized Pregnancy Trials Initiated Preconception: Lessons from the EAGeR Trial. *Paediatric and Perinatal Epidemiology* 2014; In Press.

2. 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, Silver RM. Preconception Low Dose Aspirin and Time to Pregnancy: Findings from the EAGeR (Effects of Aspirin in Gestation and Reproduction) Randomized Trial. *The Journal of Clinical Endocrinology & Metabolism* 2014*;* Accepted.

3. Schisterman EF, Silver RM, Lesher LL, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Perkins NJ, Mumford SL, Galai N. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet* 2014; 384:29-36.

4. Silver RM, Ahrens K, Wong LF, Perkins NJ, Galai N, Lesher LL, Faraggi D, Wactawski-Wende J, Townsend JM, Lynch AM, Mumford SL, Sjaarda LA, Schisterman EF. Low Dose Aspirin and Preterm Birth: A Randomized Controlled Trial. *Obstetrics and Gynecology* 2014; In Press.

5. Wong LF, Schliep KC, Silver RM, Mumford SL, Perkins NJ, Ye A, Galai N, Wactawski-Wende J, Lynch AM, Townsend JM, Faraggi D, Schisterman EF. The effect of a very short interpregnancy interval and pregnancy outcomes following a previous pregnancy loss. *American Journal of Obstetrics and Gynecology* 2014; In Press.

Folic Acid and Zinc Supplementation Trial (FAZST)

Principal Investigators

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Infertility affects 15% 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 folate 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.)

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

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.

Consortium on Safe Labor

Principal Investigators

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

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- Katrina Flores, M.P.H.
- Stefanie Hinkle, Ph.D.
- Sung Soo Kim, Ph.D.
- Danping Liu, Ph.D.
- Pauline Mendola, Ph.D., M.S.
- Lindsey A. Sjaarda, Ph.D., M.S.
- Maeve Wallace, Ph.D.
- Candace Robledo, Ph.D.
- Raji Sundaram, Ph.D.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

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. A number of key findings were published in 2014, including an evaluation of prolonged second stage of labor, which is the time from 10 cm cervical dilation to delivery of a baby. Specifically, a prolonged second stage of labor was defined in this study using conventional cut-offs (1-3 hours) dependent on whether a

woman had delivered a baby before and whether or not epidural anesthesia was used. Women were found to achieve high rates of vaginal delivery with a prolonged second stage. However, there were small increases in morbidity for both mothers and their neonates (Laughon et al. *Obstetrics and Gynecology* 2014). For first time mothers, a prolonged second stage of labor was associated with a one-day longer hospital stay, an increased risk of chorioamnionitis, and an increased risk of maternal perineal tears. In first-time mothers with an epidural, a prolonged second stage of labor was associated with greater neonatal sepsis and a slight increased risk of asphyxia. Collectively, these data suggest that the benefits of achieving a vaginal delivery, over cesarean delivery, should be weighed against potential small increases in maternal and neonatal risks that were found to be associated with a prolonged second stage of labor.

Other recent findings focusing on infant outcomes reflected greater neonatal morbidity as measured by neonatal intensive care unit (NICU) admission; respiratory morbidity; sepsis or evaluation to rule out sepsis; hypoxic ischemic encephalopathy, asphyxia, or seizures; and birth trauma for early term (37 - 38 weeks of gestation) birth compared to full term birth (Parikh et al. *American Journal of Obstetrics and Gynecology* 2014). Neonatal morbidity was lowest at or beyond 39 weeks gestational age and was significantly lower compared to 37 weeks' gestation; the differences between 38 and 39 weeks were less clear. Importantly, in planned cesarean deliveries for healthy pregnancies with no complications, neonatal respiratory morbidity was lowest at 39 weeks of gestation. Other areas of ongoing research include determining the optimal time for 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 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. Initial reports show pollutant exposures are associated with increased maternal blood pressure at the time of admission to labor/delivery (Männistö et al. *American Journal of Hypertension* 2014), and also that combustion-related pollutant exposure early in pregnancy increases the risk for gestational diabetes (Robledo et al. *Environmental Research* 2014).

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

2014 Consortium on Safe Labor Publications

1. Brite J, Laughon SK, Troendle J, Mills J. Maternal obesity and risk of congenital heart defects in offspring. *International Journal of Obesity* 2014; 38(6):878-82.

2. Brite J, Shiroma E, Bowers K, Yeung E, Laughon SK, Grewal U, Zhang C. Height and risk of gestational diabetes: Does maternal race make a difference? *Diabetic Medicine* 2014; 31(3):332-40.

3. Chen G, Li J, Ying Q, Sherman S, Perkins N, Sundaram R, Mendola P. Evaluation of observation-fused regional air quality model results for air pollution exposure estimation. *Science of the Total Environment* 2014; 485-486:563-574.

4. Ghosh G, Mendola P, Chen Z, Mannisto T, Xie Y, Grewal J, Laughon SK. Racial/ethnic differences in pregnancy related hypertensive disease among nulliparous women. *Ethnicity & Disease* 2014; 24(3):283-9.

5. Laughon SK, Berghella V, Sundaram R, Reddy UM, Lu Z, Hoffman MK. Neonatal and maternal outcomes with prolonged second stage of labor. *Obstetrics and Gynecology* 2014; 124(1):57-67.

6. Männistö T, Mendola P, Liu D, Leishear K, Sherman S, Laughon SK. Acute air pollution exposure and blood pressure at delivery among women with and without hypertension. *American Journal of Hypertension* 2014; In press.

7. Männistö T, Mendola P, Liu D, Leishear K, Ying Q, 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* 2014; In press.

8. Mendola P, Männistö T, Leishear K, Reddy UM, Chen Z, Laughon SK. Neonatal health of infants born to mothers with asthma. *Journal of Allergy and Clinical Immunology* 2014; 133(1):85-90.e4.

9. Mendola P, Mumford SL, Männistö TI, Holston A, Reddy UM, Laughon SK. Estimating the direct effect of preeclampsia on neonatal outcomes independent of preterm delivery using marginal structural models. *Epidemiology* 2014; In press.

10. Parikh LI, Männistö T, Mendola P, Sjaarda LA, Hinkle SN, Lu Z, Chen Z, Reddy UM, Laughon SK. Neonatal outcomes in early term birth. *American Journal of Obstetrics and Gynecology* 2014; 211:265.e1-11.

11. Robledo C, Mendola P, Yeung E, Sundaram, R, Liu D, Ying Q, Sherman S, Grantz KL. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. *Environmental Research* 2014; In press.

12. Sjaarda LA, Albert PS, Mumford SL, Hinkle SN, Mendola P, Laughon SK. Customized large-for-gestational-age birthweight at term and the association with adverse perinatal outcomes. *American Journal of Obstetrics and Gynecology* 2014; 210(1):63.e1-63.e11.

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 2014 include: a prior history of diabetes even without recurrent diabetes was a risk factor for delivering large-for-gestational-age (Boghossian et al. *American Journal of Obstetrics and Gynecology* 2014), prepregnancy BMI impacts incident preeclampsia more than recurrent cases (Boghossian et al. *Annals of Epidemiology* 2014), and delivery blood pressure levels in a previous pregnancy can be a strong indicator of having a hypertensive disorder in the subsequent pregnancy. We also found that prior medically-indicated preterm birth was strongly associated with subsequent indicated preterm birth as well as increasing risk for subsequent spontaneous preterm births (Laughon et al. *American Journal of Obstetrics and Gynecology* 2014). Although prior history remains an important predictor for repeated outcomes, intriguingly some factors are important for prediction of incident outcomes in a second pregnancy, such as young maternal age and hypertensive disorders, which increased risk for small-for-gestational age birth after a normal first pregnancy (Hinkle et al. *British Journal of Obstetrics and Gynaecology* 2014).

2014 Consecutive Pregnancies Study Publications

1. Boghossian N, Yeung E, Albert PS, Mendola P, Laughon SK, Hinkle SN, Zhang C. Changes in diabetes status between pregnancies and newborn outcomes. *American Journal of Obstetrics and Gynecology* 2014; 210(5):431.e1-14.

2. Boghossian NS, Yeung E, Mendola P, Hinkle SN, Laughon K, Zhang C, Albert PS. Risk factors differ between recurrent and incident preeclampsia: a hospital-based cohort study. *Annals of Epidemiology* 2014; 24(12):871-877.

3. Boghossian NS, Albert PS, Mendola P, Grantz K, Yeung E. Delivery blood pressure and other first pregnancy risk factors in relation to hypertensive disorders in second pregnancies. *American Journal of Hypertension* 2014; In press.

4. Hinkle SN, Albert P, Sjaarda LA, Mendola P, Boghossian N, Yeung E, Laughon SK. The association between parity and birthweight in a longitudinal consecutive pregnancy cohort. *Paediatric and Perinatal Epidemiology* 2014; 28(2):106-15.

5. Hinkle SN, Albert PS, Mendola P, Sjaarda LA, Boghossian NS, Yeung E, Laughon SK. Differences in risk factors for incident and recurrent small-for-gestational-age birthweight: a hospital based cohort study. *British Journal of Obstetrics and Gynaecology* 2014; In press.

6. Laughon SK, Albert P, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: Recurrent preterm delivery by subtype. *American Journal of Obstetrics and Gynecology* 2014; 210(2):131.e1-8.

7. Shih JH, Albert PS, Mendola P, Grantz KL. Modeling the type and timing of consecutive events: application to predicting preterm birth in repeated pregnancies. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 2014; In press.

Diabetes & Women's Health (DWH) Study

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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 healthful dietary patterns, recreational physical activity (Bao et al. *Journal of the American Medical Association Internal Medicine* 2014), and maintaining a healthy weight (Bao et al. *Diabetologia*; In press) were strongly and independently related to a lower risk of progression from GDM to T2DM, which is a hopeful message for women who develop diabetes in pregnancy.

2014 Diabetes & Women's Health Publications

1. Bao W, Bowers K, Tobias D, Vaag A, Chavarro JE, Liu A, Strom M, Zhang C. Physical activity and sedentary behaviors associated with risk of progression from gestational diabetes mellitus to type 2 diabetes mellitus: a prospective cohort study. *Journal of the American Medical Association Internal Medicine* 2014; 174:1047-55.

2. Bao W, Chavarro JE, Liu A, Vaag A, 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*; In press.

3. Tobias DK, Gaskins AJ, Missmer SA, Manson JA, Buck Louis GM, Zhang C, Chavarro JE History of infertility and risk of type 2 diabetes mellitus: a prospective cohort study. *Diabetologia*; In press.

4. Zhang C, Hu F, Olsen SF, Vaag A, Gore-Langton R, Chavarro JE, Bao W, Yeung E, Bowers K, Grunnet LG, Sherman S, Kiely M, Strøm M, Hansen S, Liu A, Mills J, Fan R; DWH study team. Rationale, design, and method of the Diabetes & Women's Health study - a study of long-term health implications of glucose intolerance in pregnancy and their determinants. *Acta Obstetricia et Gynecologica Scandinavica* 2014; 93:1123-30.

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:

- 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.

- 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.

- 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 a couple of potentially modifiable factors before pregnancy that are significantly related to GDM risk, such as a high animal fat, low carbohydrate diet (Bao et al. *American Journal of Clinical Nutrition* 2014) and fried food consumptions (Bao et al. *Diabetalogia* 2014). We demonstrated that women could prevent more than 40% of GDM events if they maintained or adopted a healthy diet, lifestyle, and body weight before pregnancy (Zhang et al. *British Medical Journal* 2014). This is true even among overweight or obese women (Zhang et al. *British Medical Journal* 2014). In addition, our work 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* 2014). Taken together, findings from our research highlight the importance of exposures in pre-gravid time window in the development of GDM.

2014 Gestational Diabetes Mellitus Publications

1. Bao W, Baecker A, Song Y, Liu S, Zhang C Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: a systematic review. *Metabolism* 2014; In press.

2. Bao W, Bowers K, Tobias DK, Olsen S, Zhang C. Low-carbohydrate diets and risk of gestational diabetes: a prospective cohort study. *American Journal of Clinical Nutrition* 2014; 99:1378-1384.

3. Bao W, Tobias DK, Olsen S, Zhang C. Pre-pregnancy fried food consumption and risk of gestational diabetes. *Diabetalogia* 2014; 57:2485-91.

4. Brite J, Shiroma E, Bowers K, Yeung E, Laughon SK, Grewal U, Zhang C. Height and risk of gestational diabetes: Does maternal race make a difference? *Diabetic Medicine* 2014; 31(3):332-40.

5. Zhang C, Sundaram R, Maisog J, Calafat A, Barr DB, Buck Louis GM. Pre-gravid serum concentrations of perfluorooctanoic acid and the risk of hyperglycemia in pregnancy: A prospective study in the LIFE Study. *Fertility and Sterility* 2014; In press

6. Zhang C, Tobias D, Bao W, Kay S, Hu F. Adherence to healthy lifestyle and the risk of gestational diabetes: a prospective cohort study. *British Medical Journal* 2014; 349:g5450.

NICHD Fetal Growth Studies: Singletons and Twins

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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 2,504 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. The overarching goal of the study is to determine the optimal fetal growth for four race/ethnic groups of women, and to develop methods for the clinical estimation of birth size, with the eventual goal of predicting the optimal timing of delivery. The goal for twin pregnancies is to establish contemporary growth trajectories, and for the obese cohort, is to have a better understanding how fetuses grow and the implications for gravid diseases and fetal health. Data analysis is underway.

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

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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 plan to recruit women in early pregnancy (400 women with asthma and 150 non-asthmatic women). Recruitment for women with asthma will target 200 with good asthma control and 200 women with poorly controlled asthma prior to pregnancy. Non-asthmatic women will have no history of asthma or clinical visits or medication for asthma in the year prior to pregnancy. Three study visits during pregnancy and one post-partum visit are planned as well as daily measures of lung function and symptoms. Enrollment is anticipated to begin in early 2015.

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

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The Birth Defects Research Group is an interdisciplinary team led by NICHD to investigate the causes of birth defects. A primary focus is the effect of dietary factors on birth defect risks. 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, and the Department of Biochemistry, Trinity College, Dublin.

Because this group has performed genome wide association genotyping and extensive biochemical testing of over 40 metabolites on 2500 students (Trinity Student Study), it has been possible to collaborate with a number of institutions wishing to search for genetic factors affecting metabolites of interest. In 2014, one such collaboration resulted in a publication reflecting genetic factors' influence on plasminogen levels (Ma et al. *Blood* 2014). The International League Against Epilepsy Consortium on Complex Epilepsies also collaborated with our group in its investigation of genetic factors in epilepsy. This study identified a new locus implicated in epilepsy and showed that some genetic risk factors are involved in multiple types of epilepsy, while others are associated with only one epilepsy sub-type (Anney et al. *Lancet Neurology* 2014).

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. Most recently we conducted a study to evaluate whether genes that were seen in a study of neural tube defect candidate genes, but were not significant after strict correction for multiple tests, were truly risk genes. Despite having a fairly large population for this confirmatory study, none of the genes were significantly associated after correction for multiple testing. Nonetheless, this study provides good targets for future analysis (Pangilinan et al. *BMC Medical Genetics* 2014).

In the past year we expanded our investigation of nutrients to determine whether poor iron status, a risk factor for neural tube defects in animals, was a risk factor in humans. We found that iron status was not related to neural tube defects (Molloy et al. *Birth Defects Research Part A: Clinical and Molecular Teratology* 2014).

Poor maternal choline status has been reported to be a risk factor for neural tube defects; however, the findings have been inconsistent. We measured choline and betaine in samples collected during affected and control pregnancies and found no association. These results have some public health implications, as women are advised to take folic acid prior to conception to prevent neural tube defects. If women were advised to take choline as well, it does not appear that it would provide additional protection (Mills et al. *American Journal of Clinical Nutrition* 2014).

Ongoing research involves examining quantitative traits in The Trinity Student Study, the genome wide association study. 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. As noted above, this has been done successfully with hematologists in the past year.

2014 Birth Defects Research Group Publications

1. Fan R, Wang Y, Mills JL, Carter TC, Lobach I, Wilson AF, Bailey-Wilson JE, Weeks DE, Xiong M. Generalized functional linear models for gene-based case-control association studies. *Genetic Epidemiology* 2014; 38:622-37.

2. Li Q, Xiong W, Chen J, Zheng G, Li Z, Mills, JL, Liu A. A robust test for quantitative trait analysis with model uncertainty in genetic association studies. *Statistics and its Interface* 2014; 7:61-68.

3. Ma Q, Ozel AB, Ramdas S, McGee B, Khoriaty R, Siemieniak D, Li HD, Guan Y, Brody LC, Mills JL, Molloy AM, Ginsburg D, Li JZ, Desch KC. Genetic variants in PLG, LPA and SIGLEC 14 as well as smoking contribute to plasma plasminogen levels. *Blood* 2014; 124:3155-64.

4. Mills JL, Fan R, Brody LC, Liu A, Ueland PM, Wang Y, Kirke PN, Shane B, Molloy AM. Maternal choline concentrations during pregnancy and choline-related genetic variants as risk factors for neural tube defects. *American Journal of Clinical Nutrition* 2014; 100:1069-74.

5. Molloy AM, Einri CN, Jain D, Laird E, Fan R, Wang Y, Scott JM, Shane B, Brody LC, Kirke PN, Mills J. Is low iron status a risk factor for neural tube defects? *Birth Defects Research Part A: Clinical and Molecular Teratology* 2014; 100:100-6.

6. Pangilinan F, Molloy AM, Mills JL, Troendle JF, Parle-McDermott A, Kay DM, Browne ML, McGrath EC, Abaan H, Sutton M, Kirke PN, Caggana M, Shane B, Scott JM, Brody LC. Replication and exploratory analysis of 24 candidate risk polymorphisms for neural tube defects. *BMC Medical Genetics* 2014; 15:102.

7. Anney RJL, Avbersek A, Balding D, Baum L, Becker F, Berkovic SF, Bradfield JP, Brody LC, Buono RJ, Catarino CB, Cavalleri GL, Cherny SS, Chinthapalli K, Coffey AJ, Compston A, Cossette P, de Haan G, De Jonghe P, de Kovel CGF, Delanty N, Depondt C, Dlugos DJ, Doherty CP, Elger CE, Ferraro TN, Feucht M, Franke A, French J, Gaus V, Goldstein DB, Gui H, Guo Y, Hakonarson H, Hallmann K, Erin L Heinzen EL, Ingo Helbig I, Helle Hjalgrim H, Margaret Jackson M, Jennifer Jamnadas-Khoda J, Dieter Janz D, Johnson MR, Kälviäinen R, Kantanen A, Kasperavičiūte D, Kasteleijn-Nolst D, Trenite DK, Koeleman BPC, Kunz WS, Kwan P, Lau YL, Lehesjoki A, Lerche H, Leu C, Lieb W, Lindhout D, Lo W, Lowenstein DH, Malovini A, Marson AG, McCormack M, Mills JL, Moerzinger M, Møller RS, Molloy AM, Muhle H, Newton M, Ng P, Nöthen MM, Nürnberg P, O'Brien TJ, Oliver KL, Palotie A, Pangilinan F, Pernhorst K, Petrovski S, Privitera M, Radtke R, Reif PS, Rosenow F, Ruppert A, Sander T, Scattergood T, Schachter S, Schankin C, Scheffer IE, Schmitz B, Schoch S, Sham PC, Sisodiya S, Smith DF, Smith PE, Speed D, Sperling MR, Steffens M, Stephani U, Striano P, Stroink H, Surges R, Tan KM, The KORA study group, Thomas GN, Todaro M, Tostevin A, Tozzi R, Trucks H, Visscher F, von Spiczak S, Walley NM, Weber YG, Wei Z, Whelan C, Yang W, Zara F, Zimprich F, International League Against Epilepsy Consortium on Complex Epilepsies. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. *Lancet Neurology* 2014; 13:893-903.

Genetic Factors in Birth Defects Study

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- 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 now 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 entering collaborations 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.

The first results of the copy number variant effort identified 20 rare copy number variants in heterotaxy cases. Heterotaxy is a serious malformation in which the body organs are often on the wrong side, e.g. the heart is on the right, and have structural defects. The most noteworthy copy number variants we discovered were: a deletion in BMP2, a known cause of heterotaxy in mice never before documented in humans, a large, terminal deletion of 10q, and a microdeletion at 1q23.1 involving the MNDA gene. Both are rare variants that were suspected to be associated with heterotaxy. These findings will enhance our understanding of the causes of heterotaxy and may provide clues for preventing the condition.

A collaboration has been initiated with the Pediatric Endocrinology Branch to conduct whole exome sequencing of DNA from subjects who have rare pediatric conditions of the endocrine system.

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 more such studies. The group is also interested in exploring collaborations with investigators conducting such studies.

2014 Genetic Factors in Birth Defects Study Publications

1. Rigler SL, Kay DM, Sicko RJ, Fan R, Liu A, Caggana M, Browne ML, Druschel CM, Romitti PA, Brody LC, Mills JL. Novel copy-number variants in a population-based investigation of classic heterotaxy. *Genetic Medicine* 2014; In press.

Upstate KIDS Study

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


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

Division Collaborators

- Nansi S. Boghossian, Ph.D., M.P.H.
- Nikhita Chahal, B.S.
- Akhgar Ghassabian, M.D., Ph.D.
- Germaine M. Buck Louis, Ph.D., M.S.
- Kara Ann Michels, Ph.D.
- 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.

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 & 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 approximately 600 children, targeting 300 who screened positive for developmental delay and 300 who did not, were conducted at three specialized developmental centers across the state. The study ended data collection in June 2014. The study design paper (Buck Louis et al. *Pediatric and Perinatal Epidemiology* 2014) and papers focusing on the feasibility and utility of using newborn blood spots for targeted research questions have been published (Andersen et al. *Journal of Immunological Methods* 2014; Ma et al. *Environmental Research* 2014). Analyses are underway for the primary papers of the study focusing on birth outcomes, infant growth, and development.

2014 Upstate KIDS Study Publications

1. Andersen NJ, Mondal TK, Freed BM, Stockinger S, Preissler MT, Bell E, Druschel C, Buck Louis GM, Lawrence DA. Detection of immunoglobulin isotypes from dried blood spots. *Journal of Immunological Methods* 2014; 404:24-32.

2. Buck Louis GM, Hediger ML, Bell EM, Kus CA, Sundaram R, McLain AC, Yeung E, Hills EA, Thoma ME, Druschel CM. Methodology for establishing a population-based birth cohort focusing on couple fertility and children's development, the Upstate KIDS Study. *Paediatric and Perinatal Epidemiology* 2014; 28(3):191-202.

3. Ma W-L, Gao C, Bell EM, Druschel CM, Caggana M, Aldous KM**,** Buck Louis GM**,** Kannan K. Analysis of polychlorinated biphenyls (PCBs) and organochlorine pesticides in archived dried blood spots and its application to track temporal trends in environmental chemicals in newborns. *Environmental Research* 2014; 133:204-210.

4. Wylie A, Sundaram R, Kus C, Ghassabian A. Yeung EH. Maternal pre-pregnancy obesity and achievement of infant motor developmental milestones in the Upstate KIDS Study. *Obesity* 2014; In press.

Upstate KIDS CVD Follow-Up Study

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


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

Division Collaborators

- Paul S. Albert, Ph.D.
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- Akhgar Ghassabian, M.D., Ph.D.
- Pauline Mendola, Ph.D., M.S.
- Kara Ann Michels, Ph.D.
- 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 is anticipated to begin in 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. 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.

Methods that compare biomarker diagnostic effectiveness and novel study designs that reduce cost and leverage statistical efficiency are also a major focus of Division researchers (Mitchell et al. *Biometrics* 2014; Mitchell et al. *American Journal of Epidemiology* 2014; In Press; Mitchell et al. *Statistics in Medicine* 2014). These methods, originally created for receiver operating characteristic (ROC) curves, have been adapted and found to have equally useful application to 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.

2014 Biomarker Analytical Development Publications

1. Danaher MR, Roy A, Chen Z, Mumford SL, Schisterman EF. Minkowski-Weyl priors for models with parameter constraints: an analysis of the BioCycle Study. *Journal of the American Statistical Association* 2014; In press.

2. Goodman M, LaKind JS, Fagliano JA, Lash TL, Wiemels JL, Winn DM, Patel C, Van Eenwyk J, Kohler BA, Schisterman EF, Albert P, Mattison DR. Cancer cluster investigations: review of the past and proposals for the future. *International Journal of Environmental Research and Public Health* 2014; 11(2):1479-99.

3. Lynch KE, Mumford SL, Schliep KC, Whitcomb BW, Zarek SM, Pollack AZ, Bertone-Johnson ER, Danaher M, Wactawski-Wende J, Gaskins AJ, Schisterman EF. Assessment of anovulation in eumenorrheic women: comparison of ovulation detection algorithms. *Fertility and Sterility* 2014; 102(2):511-518.e2.

4. Mitchell EM, Lyles RH, Danaher M, Perkins NJ, , Manatunga AK, Schisterman EF. Regression for skewed biomarker outcomes subject to pooling. *Biometrics* 2014; 70(1):202-11.

5. Mitchell EM, Lyles RH, Manatunga AK, Schisterman EF. Semi-parametric regression models for a right-skewed outcome subject to pooling. *American Journal of Epidemiology* 2014; In Press.

6. Mitchell EM, Lyles RH, Perkins NJ, Manatunga AK, Schisterman EF. A highly efficient design strategy for regression with outcome pooling. *Statistics in Medicine* 2014; 33(28):5028-5040.

7. Schisterman EF, Mumford SL, Sjaarda LA. Failure to consider the menstrual cycle phase may cause misinterpretation of clinical and research findings of cardiometabolic biomarkers in premenopausal women. *Epidemiology Reviews* 2014; 36(1):71-82.

Causal Inference in Reproductive Epidemiology

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

Division Collaborators

- Katherine Ahrens, Ph.D., M.P.H.
- Emily M. Mitchell, Ph.D.
- Sunni L. Mumford, Ph.D., M.S.
- Neil J. Perkins, Ph.D., M.S.

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

Causal inference and the usefulness of directed acyclic graphs (DAGs) as a tool for evaluating causal relations and addressing questions of model specification are well established in

epidemiology. Division researchers have the goal of extending the methodological framework for causal inference to reproductive and perinatal epidemiology. The objective of this research is to develop methods using causal inference tools, specifically as they improve researchers' understanding of confounding and colliders, and as applied to the birth weight paradox and the role of birth weight in analysis of perinatal data. In addition, our objective is to apply the same tools to better understand the role of history of prior outcomes in appropriate modeling. 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* 2014). 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).

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* 2014). 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.

2014 Causal Inference in Reproductive Epidemiology Publications

1. Ahrens KA, Cole SR, Westreich D, Platt RW, Schisterman EF. A cautionary note about estimating effect of secondary exposures in cohort studies. *American Journal of Epidemiology* 2014; In Press.

2. Hernán MA, Schisterman EF, Hernández-Díaz S. Composite outcomes as an attempt to escape from selection bias and related paradoxes. *American Journal of Epidemiology* 2014; 179(3):368-70.

3. López T, Pumarega JA, Pollack AZ, Lee DH, Richiardi L, Jacobs DR Jr, Schisterman EF, Porta M. Adjusting serum concentrations of organochlorine compounds by lipids and symptoms: a causal framework for the association with K-ras mutations in pancreatic cancer. *Chemosphere* 2014; 114: 219-25.

4. Mumford SL, Schisterman EF, Cole SR, Westreich D, Platt RW. Time at risk and intention to treat analyses: parallels and implications for inference. *Epidemiology* 2014; In Press.

Health Behavior Branch

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

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

The mission of the Health Behavior Branch is to: 1) conduct research on child and adolescent health and health 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 behavior and tests the effectiveness of behavioral and environmental strategies to improve or protect child, adolescent and maternal health. The research is conducted within a developmental framework and emphasizes family context, characteristics of the individual, and the social and physical environment. Our studies are guided by social cognitive and social norms theories and draw on concepts of adolescent development and authoritative parenting. The Branch's research is organized according to three themes: 1) young drivers; 2) adolescent health, and 3) behavioral interventions in health care.

Our program of research on young drivers, headed by Dr. Bruce Simons-Morton, includes studies employing naturalistic, observational, and experimental study designs. This research has examined the prevalence and patterns of risky driving, the effects of corrective feedback and, separately, teenage passengers on risky driving, and the effects of distraction on crash outcomes.

Our research on adolescent health behavior, directed by Drs. Bruce Simons-Morton and Denise Haynie, focuses on longitudinal trajectories and determinants of substance use, diet, obesity, physical activity, risky driving, and other behaviors through adolescence and into the transition to early adulthood.

Our research on behavioral interventions in health care, headed by Dr. Tonja Nansel, utilizes our understanding of the determinants of health behaviors and health behavioral change to develop and test theory-based interventions for sustained health behavior change among patients in clinical care. One focus in this area is youth with type 1 diabetes and their families, including diabetes management and dietary intake. New research was implemented examining dietary intake and food responsivity among overweight/obese pregnant women.

Staff

- Bruce G. Simons-Morton, Ed.D., M.P.H., *Senior Investigator and Chief*
- Tonja Nansel, Ph.D., *Senior Investigator*
- Denise Haynie, Ph.D., M.P.H., *Staff Scientist*
- Leah Lipsky, Ph.D., *Staff Scientist*

Fellows

- Kaigang Li, Ph.D., Research Fellow
- Johnathan Ehsani, Ph.D., Postdoctoral Fellow
- Fearghal O'Brien, Ph.D., Postdoctoral Fellow
- Miriam Eisenberg, Ph.D., Postdoctoral Fellow
- Jessamyn Perlus, B.A. Postbaccalaureate Fellow (departed in 2014)
- Dexter Thomas, B.A., Undergraduate Scholars Program (departed in 2014)
- Benjamin Gee, B.A., Postbaccalaureate Fellow
- Cheyenne Fox Tree-McGrath, B.A., Postbaccalaureate Fellow
- Hira Palla, B.S., Postbaccalaureate Fellow
- Virginia Quick, Ph.D., R.D., Postdoctoral Fellow (departed in 2014)
- Wynette Williams, B.A., Postbaccalaureate Fellow

Research on Young Drivers

Principal Investigator

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

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

Division Collaborators

- Paul S. Albert, Ph.D., Senior Investigator
- Danping Liu, Ph.D., Senior Investigator
- Zen Chen, Ph.D., Investigator
- Kim Sunduk, Ph.D., Staff Scientist
- Kaigang Li, Ph.D., Research Fellow
- Johnathan Ehsani, Ph.D., Postdoctoral Fellow
- Fearghal O'Brien, Ph.D., Postdoctoral Fellow
- Jessamyn Perlus, B.S., Postbaccalaureate Fellow
- Cheyenne Fox Tree-McGrath, B.A., Postbaccalaureate Fellow

Crash risk is highest early in licensure, declining rapidly for a period of months thereafter, and then slowly decreases over a period of years, reaching adult levels when young adults are in their mid-twenties. Compared with older drivers, teenage and young adults are more likely to drive late at night, carry multiple passengers, and possibly drink alcohol before driving, characteristics that contribute to their relatively higher crash rates. Additionally, the presence of teenage passengers has been shown to increase crash risk. However, little is known about how teenage driving behavior varies over time.

Our program of research on young drivers is varied, with studies covering several 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. Currently we are conducting a unique series of experimental studies using driving simulation to evaluate the effects of teenage passengers on teenage driving performance. We have integrated assessments of fMRI and executive functioning 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 study 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.

The study is already a landmark among driving studies. We have published papers on methods, driving exposure, crash risk, and dangerous driving. Notably, we found that distraction due to secondary task engagement increased crash risk among novice drivers (Klauer, et al., 2014) and longer glances away from the forward roadway increased crash risk more than shorter glances (Simons-Morton, et al., 2014). Cortisol responsivity was associated with crash risk and risky driving (Ouimet, 2014). However, the association between kinematic risky driving among parents and their teenage children was modest and moderated by shared personality characteristics (Ehsani, 2014).

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 the 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 supervise practice driving prior to licensure. Only one previous naturalistic study of supervised practice driving has been conducted although no exposure data were collected nor did the authors address the effects of supervised practice driving on independent driving. In collaboration with the Virginia Transportation Technology Institute (VTTI), we recruited a sample (n=90) of adolescents soon after they obtained their learner's permit, 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) and data reduction and coding is proceeding so that data will be available for analysis by March 2015. One unique aspect of the study is the evaluation of audio recordings of teen-parent verbal communications during instructional drives. Analyses of the practice driving period are underway and preliminary analyses were presented at the Transportation Research Board Annual meeting in January 2015. Papers are in preparation.

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. Notably, Ouimet and colleagues (2010) reported that male teenage passengers increased fatal crash risk among teenage and young adult drivers, particularly male drivers. In previous research we observed vehicles exiting high school parking lots and found that teenage drivers with male teenage passengers drove faster and closer to the lead vehicle than other drivers (Simons-Morton, Lerner, Singer, 2005). However, in the NTDS we found that teen passengers (including males and females) provided a slightly protective effect on crash/near crash and kinematic risky driving compared to the no passenger condition. A series of simulation studies is being conducted to learn more about the nature of teen passenger influences in collaboration with the University of Michigan Transportation Research Institute (UMTRI; Ray Bingham, PI). One study will be completed each year over a 4-5 year period, incorporating what is learned from each study into the next study.

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. We used a randomized block design with 2 conditions (passenger: risk-accepting vs. risk-averse) X 2 drive orders (driving alone first vs. driving with the passenger first). Analyses 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 ($p=0.04$) 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; moreover, passenger presence reduced eye scan (Pradhan et al., 2014).

Neuroimaging of sensitivity to social exclusion was measured in TSP1 using a cyber-ball task in which participants passed (using a mouse) a cyber-ball ostensibly with peers (the game is actually computerized) while being imaged. Gradually, the participant was excluded and the imaging indicated the teenager's reaction to exclusion. Theoretically, when a person is affected by social exclusion 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 (Falk, 2014). In another paper based on neuroimaging data, we reported that participants with greater response inhibition based on their responses to a standard "Go No Go" evaluation of impulsivity were less susceptible to teen passengers' influences on risky simulated driving (Cascio, 2014).

The TPS2 tested the effect of male teenage peer pressure on male teenage risky driving performance. The study design is 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. The main study results are 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. No effect of pre-drive passenger mood on driving performance was observed. The paper is currently under review.

The Uniform Naturalistic Teenage Driving Study (UNTDS)

One of the limitations of naturalistic research to date has been small sample size. Larger samples are needed for analyses of risk by driving conditions and among subgroups. Toward this end, the HBB will obtain data from the SHRP2 Naturalistic Driving Study, which used similar instrumentation as the Naturalistic Teenage Driving Study and Supervised Practice Driving Study to create a large unified database. 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 to provide a large data that would allow 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) What is the effect on driving outcomes of the type of passengers and driving context? 4) What is the relationship between 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? The SHRP2 data will be available in April 2015.

NEXT Naturalistic Driving Study (NEXT NDS)

Little is known about how driving behavior varies over time, particularly among young drivers. Naturalistic driving methods lend themselves to longitudinal assessment, but to date most studies have included few study participants and have been of short duration. This study assesses the driving performance of a sample of 100 young drivers starting in the 12th grade (ages 17-18) and ending when the participants are 21-22 years of age. Assessment is done using the DriveCam driving assessment device. The study sample is drawn from the NEXT Study and will: 1) examine the variability within the sample and over time in driving performance (elevated g-force events and crash/near crash); and 2) identify individual and driving condition factors associated with risky driving and crashes/near crashes. Data collection is currently ongoing. Study participants will be followed for a period of 4 years, concluding in 2016.

2014 Publications: Research on Young Drivers

1. Cascio, C.N., Carp, J., O'Donnell, M.B., Tinney, F.J. Jr, Bingham, C.R., Shope, J.T., Ouimet, M.C., Pradhan, A.K., Simons-Morton, B.G., Falk, E.B. (2014). Buffering Social Influence: Neural Correlates of Response Inhibition Predict Driving Safety in the Presence of a Peer. *Journal of Cognitive Neuroscience*, 6:1-13. DOI:10.1162/jocn_a_00693; PMID: 25100217

2. Ehsani, J.P., Simons-Morton, B., Xie, Y., Klauer, S.G., Albert, P.S. (2014). The association between kinematic risky driving among parents and their teenage children: Moderation by shared personality characteristics. *Accident Analysis & Prevention*. DOI: 10.1016/j.aap.2014.01.010; PMID: 24561886.

3. Falk, E.B., Cascio, C.N., Carp, J., Tinney, F. O'Donnell, M.B., Bingham, R., Shope, J., Pradhan, A.K., Simons-Morton, B.G. (2014). Neural responses to exclusion predict susceptibility to social influence. *Journal of Adolescent Health*. 54(5S), S22-S31. DOI: 10.1016/jadohealth.2013.12.035; PMID: 24759437

4. Lambert, A. E., Simons-Morton, B. G., Cain, S. A., Weisz, S., Cox, D. J. (2014). Considerations of a dual-systems model of cognitive development and risky driving. *Journal of Research on Adolescence,* 24(3), 541-550. DOI:10.1111/jora.12126.

5. Liu, D., Tran, V., Pradhan, A.K., Li, K., Bingham, C.R., Simons-Morton, B.G., Albert, P.S. (in press). Assessing Risk-Taking in a Driving Simulator Study: Modeling Longitudinal Semi-Continuous Driving Data Using a Two-Part Regression Model with Correlated Random Effects Analytic Methods in Accident Research. *Analytic Methods in Accident Research*.

6. Ouimet, M.C., Brooks-Russell, A., Ehsani, J.P., Pradhan, A.K., Li, K., Simons-Morton, B.G. (in press). The effect of teenage passengers on teenage driving outcomes: a systematic review. *Journal of Adolescent Health*. PMID: 15106200

7. Ouimet, M.C., Brown, T.G., Guo, F, Klauer, S.G., Simons-Morton, B.G., Fang, Y., Lee, S.E., Gianoulakis, C., Dingus, T.A. (2014). Higher crash and near-crash rates in teenage drivers with lower cortisol reactivity: an 18-month longitudinal, naturalistic study. *JAMA Pediatrics*. 168(6), 517-522. Doi:10.1001/jamapediatrics.2013.5387; PMID: 24710522

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Adolescent Health Behavior

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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 influence of the social (peers and parents) and physical environment (e.g., place of residence, local programs, policies, and resources) 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 2770 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 (substance use), diet, physical activity, sleep, and driving. At the end of the recently completed Wave 5 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 540 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 83%.

In the past year, we reported significant associations between driving while intoxicated (DWI) and riding with an intoxicated driver (RWI) (Li, 2014). Furthermore, we found that parenting practice were associated with DWI prevalence (Li, 2014). Regarding alcohol use, we found longitudinal relationships between drinking with peers, norms about alcohol, and participant self-reported alcohol use in the 11th grade (Brooks-Russell, 2014). We also reported the positive effects of motivation, planning and social support on increased physical activity among adolescents (Li, 2014). Analyses are ongoing to identify determinants of diet patterns, physical activity, and substance use among study participants the first year following high school.

2014 Adolescent Health Publications

1. Bendtsen, P., Damsgaard, M.T., Huckle, T., Casswell, S., Kuntsche, E., Arnold, P., de Looze, M., Hofmann, F., Hublet, A., Simons-Morton, B., Ter Bogt, T.F., Holstein, B.E. (2014). Adolescent alcohol use: a reflection of national drinking patterns and policy? *Addiction*, July 8, Epub ahead of print. DOI:10.1111/add.12681; PMID: 25041190

2. Brooks-Russell, A., Farhat, T., Haynie, D., Simons-Morton, B.G. Trends in adolescent substance use among 6-10th grade students from 1998 to 2010: findings from a national probability study. *Journal of Early Adolescence*, in press.

3. Brooks-Russell A, Simons-Morton B, Ehsani J. (2014). Parents are the key to improving teen driving safety. *Journal of Adolescent Health*. 55(5):600-601. Doi: 10.1016/j.jadohealth.2014.08.008; PMID: 25344032.

4. Brooks-Russell, A., Simons-Morton, B., Haynie, D., Farhat, T., Wang, J. (2014). Longitudinal relationship between drinking with peers, descriptive norms, and adolescent alcohol use. *Prevention Science,* April 15, 497-505. Doi: 10.1007/s11121-013-0391-9; PMID 23564529

5. Finigan, N., Haynie, D., Chen, T., Gielen, A., Simons-Morton, BG. (2014). Using the Theory of Planned Behavior to Predict Aggression and Weapons Carrying Behavior in Urban African American Early Adolescent Youth. *Health Education and Behavior*. Published online September 16, 2014. DOI: 0:1177/1090198711458479; PMID: 25228369.

6. Fulton, K., Liu, D., Albert, P., & Haynie, D. Zero-inflation in clustered binary response data: mixed model and estimating equation approaches. *Annals of Applied Statistics,* in press.

7. Li, K., Iannotti, R .J. Haynie, D. L., Perlus, J. G., Simons-Morton, B. G. (2014). The Effect of motivation, planning, and social support on physical activity among U.S. adolescents. *International Journal of Behavioral Nutrition and Physical Activity*. 11(1), 42. DOI: 10.1186/1479-5868-11-42; PMID: 24639277.

8. Li, K.-G., Simons-Morton, B.G., Brooks-Russell, A., Ehsani, J., Hingson, R. (2014). Drinking and parenting practices as predictors of impaired driving behaviors among US adolescents. *Journal of Studies on Alcohol and Drugs*. 75(1), 5-15. PMID: 24411792.

9. Li, K., Simons-Morton, B.G., Vaca, F.E., Hingson, R. (2014). Association between riding with an impaired driver and driving while impaired. *Pediatrics*, 144(4), 620-626. DOI:10.154/peds.2013-2786; PMID: 24639277.

10. Li, K., Simons-Morton, B. G., Vaca, F. E., & Hingson, R. Reciprocal associations between parental monitoring knowledge and impaired driving in adolescent novice drivers. *Traffic Injury Prevention,* in press.

Behavioral Intervention in Health Care

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Tonja Nansel, Ph.D., M.A.,

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

Management of type 1 diabetes is complex and involves a series of intensive tasks, including 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. Careful management of type 1 diabetes is important to prevent short- and long-term complications. 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 adaptation to 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 health 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. A multi-component behavioral intervention that integrates behavioral principles into medical management of diabetes is likely to enhance family management of diabetes during early adolescence 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 promote improved 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. Previous findings from the Family Management of Diabetes Multisite Trial demonstrated an intervention effect on glycemic control at two-year follow-up. Analyses of secondary outcomes demonstrated 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, in press). 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 in *post hoc* analyses, we determined that the intervention was similarly effective in improving glycemic control across family income groups (Nansel, under review). 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. Observational analyses further informed an understanding of the association of income with adherence and glycemic control in this population, demonstrating that lower family income may negatively impact the quality of parent-child relationships, with adverse effects on diabetes management (Thomas, under review).

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. Concurrently, children with type 1 diabetes are consuming diets low in fruits, vegetables, and whole grains, and high in saturated fat. Poor diet quality is particularly concerning due to the increased risk of dyslipidemia and cardiovascular disease and the high prevalence of cardiovascular risk factors recently observed in youth with diabetes. A growing body of evidence suggests that dietary intake, particularly carbohydrate quality, may affect blood sugar control, insulin demand, and weight management. To date, little research has examined individual and family determinants of dietary intake in youth with type 1 diabetes or tested approaches to improve dietary quality among this population. Research within the general population indicates a complex interplay of socio-environmental and personal factors impacting children's dietary intake. 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.

A cross-sectional study enrolled 291 families (parent-youth dyads) to examine psychosocial factors related to eating behaviors in families with youth with type 1 diabetes. Data were obtained using medical record abstraction, parent-youth interview, youth self-report surveys, parent self-report surveys, and youth's 3-day diet records. Key findings include the poor dietary quality of youth with type 1 diabetes, the inverse association of food neophobia and pickiness with dietary variety and quality (Quick, 2014), inverse associations of fiber intake with glycemic control (Katz, 2014), significant associations of meal contextual factors with dietary intake (Nansel, 2014), and associations of the family environment with disordered eating behaviors (Caccavale, in press). We developed a self-report measure of diabetes management adherence reflecting contemporary diabetes care regimens (Mehta, in press). We have also developed an extensive food cost database, providing estimated costs of all foods reported by study subjects in the 3-day diet records. Our examination of the association of food cost with diet quality indicates very modest relations, and suggests that cost need not be a barrier to healthful eating (Nansel, 2014).

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, providing for cyclical learning and behavior change. 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 3-day diet records, parental 3-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 include glycemic control and dietary intake. The findings indicate that the intervention was successful in improving diet quality of youth receiving the behavioral intervention (Nansel, under review). Youth in the intervention group demonstrated greater intake of whole plant foods and a higher Healthy Eating Index 2005 score. However, there was no intervention effect on glycemic control. These findings are currently under review, with other papers in preparation including those focusing on the psychosocial determinants of dietary intake, the longitudinal associations of diet quality with diet cost, and influences of diet on various health indicators.

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. At least half of women of reproductive age now enter pregnancy at a high body mass index, and the majority experience pregnancy-associated weight gains in excess of Institute of Medicine (IOM) guidelines, leading to increased perinatal and chronic health risks for both mother and child. Limited intervention research has indicated 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. This observational study, currently in development, will address 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. 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 maternal diet and weight change, leading to improved maternal and child health trajectories.

PEAS is an observational cohort study examining the role of food reward responsivity and food reward value in weight change and dietary intake during pregnancy and postpartum. The study will further examine the importance of food reward in the context of behavioral control and other related 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 will be enrolled early in pregnancy (before 12 weeks postpartum) and followed until 1 year postpartum. Assessments will occur at baseline (<12 weeks postpartum), during pregnancy at 13-18 weeks gestation, 16-22 weeks, and 28-32 weeks, and postpartum at 4-6 weeks, 6 months, 9 months and 12 months. Measures

include assessments of food reward and related constructs, dietary intake, other health behaviors, and anthropometrics. Clinical data and biological specimens will be obtained. Infant anthropometrics and feeding practices will also be assessed. Primary exposures include aspects of food reward and behavioral control, which will be 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.

2014 Behavioral Intervention in Health Care Publications

1. Albert, P., Liu, A., Nansel, T. (2014). Efficient logistic regression designs under an imperfect population identifier. *Biometrics,* 70(1), 175-184. DOI: 10.1111/biom.12106; PMID: 24261471.

2. Caccavale, L.J., Nansel, T.R., Quick, V., Lipsky, L., Laffel, L., Mehta, S. Relationships of disordered eating behaviors, family environment, and quality of life among adolescents with type 1 diabetes and their parents. *Journal of Developmental and Behavioral Pediatrics*, in press.

3. Gee, B.T., Nansel, T.R., 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*, in press.

4. Katz, M., Mehta, S., Nansel, T.R., Lipsky, L., Quinn, H., Laffel, L. (2014). Associations of nutrient intake with glycemic control in youth with type 1 diabetes: difference by insulin regimen. *Diabetes Technology and Therapeutics*, 16(8), 512-518. DOI: 10.1089/dia.2013.0389; PMID: 24766666.

5. Nansel, T.R., Lipsky, L., Liu, A., Laffel, L., Mehta, S. (2014). Contextual factors are associated with diet quality in youth with type 1 diabetes. *Journal of the Academy of Nutrition and Dietetics*, 114(8), 1223-1229. DOI: 10.1016/j.jand.2014.01.012; PMID: 24651028.

6. Nansel, T.R., Haynie, D., Lipsky, L., Mehta, S., Laffel, L. (2014). 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,* Published online September 26, 2014. pii: S2212-2672(14)01218-0. DOI: 10.1016/j.jand.2014.07.035.

7. Mehta, S.N., Nansel, T.R., Volkening, L.K., Butler, D.A., Haynie, D.L., Laffel, L.M.B. Validation of a contemporary adherence measure for youth with type 1 diabetes: the Diabetes Management Questionnaire. *Diabetic Medicine*, in press.

8. Quick, V., Lipsky, L., Nansel, T.R., Quinn, H., Laffel, L., Mehta, S. (2014). Relationships among neophobia, pickiness, dietary variety and dietary quality in youth with type 1 diabetes. *European Journal of Clinical Nutrition*, 68(1), 131-136. DOI: 10.1038/ejcn.2013.239; PMID: 24253761.

9. Quick, V., Nansel, T.R., Liu, D., Lipsky, L., Due, P., Iannotti, R. (2014). Body image and weight control in youth: 9-year international trends from 24 countries. *International Journal of Obesity*, 38, 988-994. DOI:10.1038/ijo.2014.62; PMID: 24722544.