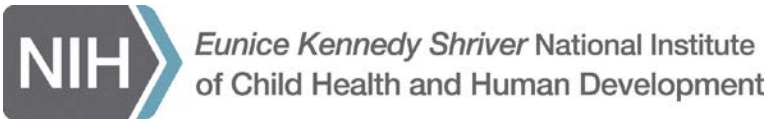
Division of Intramural Population Health Research

2013 Annual Report



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

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

In 2013, the Division successfully completed its 2-year strategic planning process to ensure its alignment with the Institute's new vision and underscoring its commitment to population health. On September 6, 2013, the Division was officially reorganized as the Office of the Director and three intramural research branches: 1) Biostatistics and Bioinformatics Branch, 2) Epidemiology Branch and 3) Health Behavior Branch. Building upon our legacy that commenced in 1967, only five years following the establishment of the Institute, we are now the Division of Intramural Population Health Research. Our new name is intended to reflect both our mission for promoting and improving population health, while clarifying our role as intramural researchers.

In addition to designing etiologic, intervention and prevention research, the Division remains committed to ensuring its research focuses on health and not just disease outcomes. This commitment includes the health of vulnerable population subgroups, such as pregnant women, fetuses, children, and young adults. Our research also considers health and disease across sensitive windows of human development and, to the extent possible, the life course. Notable research accomplishments in 2013 include the successful completion of two intervention trials: Effects of Aspirin for Gestation and Reproduction (EAGeR Study) and Cultivating Healthy Eating in Families with Youth with Type 1 Diabetes (CHEF Study). In addition, two prospective cohort studies aimed at improving the well-being of pregnant women—B-WELL-Moms' Study and Diet, Weight, Change and Obesity During Pregnancy—will soon be implemented. Also, we are actively investigating how best to model the mixtures of biomarkers and environmental exposures that so typically characterize human health and disease. We remain steadfast in our efforts for developing methods relevant for human health research, and in the translation of all our findings.

Currently, the Division comprises 31 researchers, 25 Intramural Research Fellows, 8 Visiting Fellows, 2 Clinical Fellows, along with an annual compliment of approximately 10 to 12 summer interns. We also host (under)graduate students who are in varying stages of training and completing academic research requirements. We are particularly proud that our fellows represent 32 different academic and clinical institutions. This diversity helps promote the formulation of better research questions and study designs, while building a geographical infrastructure required for improving population health. Division investigators continue mentoring fellows as they transition to early stage careers and, in turn, we tap them for continued governmental service over the course of their professions. We are pleased that our fellows are selected for competitive appointments in various settings including academe, government and the private sector. We also welcome and benefit from our many Special Volunteers who so generously give of their time and effort in helping to promote our mission.

I am especially appreciative and proud of the considerable service Division scientists provide to the Institute, the National Institutes of Health (NIH) and other governmental agencies, and also

for numerous other research and advisory entities and professional societies. Examples include providing service for the Centers for Disease Control and Prevention, U.S. Environmental Protection Agency, Transportation Research Board, The National Academies, and many other private and public organizations. Of added note is the editorial service provided by our scientists and their roles as elected officers for professional societies. I am appreciative of the generosity of so many.

In closing, I would like to highlight a few of the Division's key discoveries selected from 131 independent peer-reviewed papers published in 2013. I encourage you to read about other discoveries as further described in individual Branch sections.

Key Discoveries

Office of the Director

- Persistent environmental chemicals (e.g., polychlorinated biphenyls [PCBs] and organochlorine pesticides [OCPs]) measured in the serum of men and women trying to become pregnant were associated with a 20% reduction in couple fecundity, as measured by a longer time required to become pregnant (Buck Louis et al., 2013).

- Both persistent (e.g., OCPs, PCBs, perfluorinated chemicals [PFCs]) and short-lived (e.g., benzophenones, phthalates) environmental chemicals were associated with a higher odds of being diagnosed with endometriosis in comparison to women with lower serum and urinary concentrations of these chemicals, but findings varied by choice of study cohort (Buck Louis et al., 2013).

Biostatistics and Bioinformatics Branch

- A new statistical tool was developed for characterizing the sources of variation in kinematic (g-force) behavior among teenage drivers and is useful in predicting crashes from previous kinematic events (Kim et al., 2013).

- A new functional data analytic approach was developed for gene-level association analyses of quantitative traits (Fan et al., 2013).

- A new design was found for studying associations and for prediction when study populations are identified with error (Albert et al., 2014).

- Developed new statistical methods for assessing the diagnostic accuracy of a continuous biomarker when the disease status is only available on a fraction of individuals (Liu, D and Zhou, 2013).

Epidemiology Branch

- Pre-pregnancy obesity, weight gain, and gestational diabetes were jointly associated with sevenfold increased odds of excessive fetal growth, with the strongest relation observed for non-Hispanic White women relative to Asian women. These findings signal the need for targeting high-risk groups of pregnant women for intervention (Bowers et al., 2013).

- Greater consumption of red meat before pregnancy was associated with a higher odds of developing gestational diabetes, whereas higher intakes of vegetable protein, especially nuts, were associated with lower odds (Bao et al., 2013).

Health Behavior Branch

- Among U.S. adolescents age 11-16 years, 26% were found to have unhealthy, 27% healthy, and 47% typical dietary and physical activity habits, reflecting the need for continued interventions for motivating adolescents to improve their diets and get moving (Iannotti et al., 2013).

- The key role of parents in influencing children's and teenagers' dietary intakes was highlighted in research among youth with type 1 diabetes, supporting the relevance of family-based interventions (Nansel et al., 2013).

- Increased insulin administered for improving glycemic control may increase Body Mass Index (BMI) in youth with type 1 diabetes, underscoring the need to identify ways to minimize weight gain while optimizing glycemic control (Nansel et al., 2013).

In closing, we remain committed to improving the health and well-being of populations. We meet our mission by the successful design and completion of novel research and the translation of our discoveries, while being good stewards of the resources offered by the NIH intramural community. We are appreciative of the support we receive from our Institute's Director, Dr. Alan E. Guttmacher, and also that from the Institute's Scientific Director, Dr. Constantine A. Stratakis. I welcome your input (louisg@mail.nih.gov) about all matters pertaining to the Division's mission, and encourage everyone to think of us when looking for training and collaboration opportunities.

Appreciatively,

/s/

Germaine M. Buck Louis, Ph.D., M.S.
Director & 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 and three intramural research Branches: Biostatistics and Bioinformatics Branch, Epidemiology Branch, and Health Behavior Branch. The Office of the Director provides administrative, laboratory, and programming support for all population scientists, trainees, and visitors. Dr. Buck Louis serves as Director of the Division, while maintaining an active research program focusing on the environmental influences on human reproduction and development. She is the Principal Investigator for the Longitudinal Investigation of Fertility and the Environment (LIFE) Study, Endometriosis: Natural History, Diagnosis and Outcomes (ENDO) Study, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies, and the Exposome.

Una Grewal, Ph.D.,

The Division has greatly benefited from the recent appointment of Dr. Jagteshwar (Una) Grewal as its Assistant Director for Research Programs and Operations in April 2013. As the Assistant Director, Dr. Grewal provides oversight for orientation, mentoring and policy related activities for the Division. In addition, Dr. Grewal continues to pursue 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 section.

Jennifer Weck, Ph.D.

Following her appointment in November 2012 as the Division's first Laboratory Health Specialist, Dr. Jennifer Weck provides guidance and support for the Division. Dr. Weck's background in the basic science of female reproductive genes has allowed her to guide the Division's research projects to ensure accurate and cost-effective laboratory analysis of biomarkers. In addition, Dr. Weck administers the Division's Biospecimen Repository Access and Data Sharing (BRADS) program, which provides access to the Division's archived data and biospecimens to qualified researchers. She also is active in the Institute's on-going efforts to promote data sharing and administers the NICHD 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 Branch investigators is provided in their individual sections.

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., *Assistant Director for Research Programs and Operations*
- Adrienne Lonaberger, *Program Analyst*
- Jennifer Weck, Ph.D., *Laboratory Health Specialist*

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 have an early origin (preconception through 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. 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 are shedding insight on the role of environmental chemicals and human reproduction as described below.

Longitudinal Investigation of Fertility and the Environment (LIFE Study)

The goal of the LIFE Study is to determine whether ubiquitous persistent 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 developed a cohort comprising 501 couples who completed daily journals while trying to become pregnant and during pregnancy. Blood samples were taken to quantify persistent chemicals such as metals, OCPs, polybrominated diphenyl ethers (PBDEs), PCBs, and PFCs. Urine samples were used to quantify short-lived chemicals such as bisphenol A (BPA), benzophenone-like chemicals (UV filters) and phthalates. 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.

The LIFE Study's design and methods paper was published in 2011, followed by papers focusing on individual classes of chemicals and couple fecundity, as measured by time required to become pregnant. We found approximately a 20% reduction in couple fecundity for PCB congeners #118, 167, 209, and perfluorooctane sulfonamide when measured in women. Even stronger reductions in couple fecundity were for found for males' chemical concentrations, particularly *p,p'*-DDE and select PCB congeners (#138, 156, 157, 167, 170, and 172) (Buck Louis et al., 2013). These reductions in couple fecundity meant that couples with higher chemical concentrations took longer to become pregnant relative to couples with lower concentrations.

Two recent papers focused on semen quality of male partners. We found that semen quality was associated with time-to-pregnancy (TTP), but not after adjusting for couples' ages and body mass indices underscoring the importance of age and weight for optimizing fertility (Buck Louis et al., 2013). Also, overweight and obese males had a higher prevalence of low ejaculate volume, sperm concentration and total sperm count in comparison to normal weight men (Eisenberg et al., 2013). Physical activity did not change the relation between body mass index and semen quality.

Principal Investigator

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

Division Collaborators

- Zhen Chen, Ph.D.
- Sungduk Kim, Ph.D.
- Sunni Mumford, Ph.D., M.S.
- Enrique SchistermanPh.D., M.A.
- Rajeshwari Sundaram, Ph.D.
- Iris Bae, M.D., Korean Visiting Fellow
- Katherine Sapra, M.P.H., M.Phil., Predoctoral Intramural Research Training Award (IRTA) Fellow

2013 LIFE Study Publications

1. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Maisog J, Kim S, Chen Z, Barr DB. Persistent environmental pollutants and couple fecundity, The LIFE Study. *Environmental Health Perspectives* 2013; 121(2):231-236.

2. 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* 2013, Nov 14. [DOI: 10.1016/ j.fertnstert. 2013.10.022]

3. 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* 2013, Nov 14 [Epub ahead of print].

4. Buck Louis GM. Persistent environmental pollutants and couple fecundity: An overview. *Reproduction* 2013, Dec 5 [Epub ahead of print].

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

Endometriosis is a gynecologic disorder affecting menstruating women resulting in the implantation of endometrial glands and stroma outside the uterine cavity. The etiology of endometriosis is unknown, but increasing evidence suggests that environmental chemicals may play an important role. Moreover, recent findings suggest that women with endometriosis may be at increased risk of reproductive site cancers and autoimmune disorders than unaffected women, underscoring the interrelatedness between gynecologic disorders and later onset disease. The goal of the ENDO Study is 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 utilized a matched cohort design comprising two study cohorts: an operative and population cohort. The operative cohort underwent laparoscopy/laparotomy

examination while the population underwent pelvic magnetic resonance imaging (MRI) for the diagnosis of endometriosis. Blood and urine samples were collected for the quantification of BPA, metals, OCPs, phthalates, PBDEs, PCBs, and PFCs.

Several key research findings followed the publication of the ENDO Study's design and methods paper in 2011. While a number of persistent lipophilic chemicals were reported in previous years to be associated with endometriosis, we observed no significant associations with urinary or blood trace elements among women in the population cohort; however, blood cadmium was associated with a reduced adjusted odds of diagnosis (OR=0.55; 95% CI: 0.31, 0.98) and urinary chromium and copper with an increased adjusted odds (OR=1.97; 95% CI: 1.21, 3.19; aOR=2.66; 95% CI: 1.26, 5.64, respectively) in the operative cohort (Pollack et al., 2013).

With regard to short-lived chemicals, six phthaltes (mBP, mECPP, mCMHP, mEHHP, mEOHP, and mEHP) were significantly associated with approximately a twofold increase in the odds of MRI diagnosed endometriosis diagnosis among women in the population cohort. Two phthalates were found associated with endometriosis. mOP was associated with surgically visualized and histologically confirmed endometriosis (OR=1.38; 95% CI: 1.10, 1.72) and mEHP with surgically visualized endometriosis when restricting the comparison women to those with a postoperative diagnosis of a normal pelvis (OR=1.35; 95% CI: 1.03, 1.78) (Buck Louis et al., 2013).

Other findings from the ENDO Study include the inability to identify consistent risk factors for endometriosis across our two cohorts (operative and population), with the exception of infertility. A self-reported history of infertility upon enrollment was associated with more than a twofold increased adjusted odds of endometriosis (OR=2.43; 95% CI: 1.57, 3.76) in the operative cohort, and approximately an eightfold increased odds in the population cohort (AOR=7.91; 95% CI: 1.69, 37.2) (Peterson et al., 2013).

Principal Investigator

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

Division Collaborators

- Zhen Chen, Ph.D.
- Sunni Mumford, Ph.D., M.S.
- Karen Schliep, Ph.D., M.S.P.H.
- Rajeshwari Sundaram, Ph.D.
- Uba Backjona, M.S., R.N. NIH Graduates Partnership Program (GPP) Predoctoral Fellow

2013 ENDO Study Publications

1. Peterson CM, Boiman Johnstone E, Hammoud AO, Stanford JB, Varner MW, Kennedy A, Chen Z, Buck Louis GM. Risk factors associated with endometriosis: Importance of study

population for characterizing disease – the ENDO Study. *American Journal of Obstetrics and Gynecology* 2013; 451:e1-11.

2. Steuerwald AJ, Parsons PJ, Arnason JG, Chen Z, Peterson CM, Buck Louis GM. Trace element analysis of human urine collected after administration of Gd-based MRI contrast agents: Characterizing spectral interferences using inorganic mass spectrometry. *Journal of Analytical Atomic Spectrometry* (In Press). DOI:10.1039/C3JA30331D.

3. Buck Louis GM, Peterson CM, Chen Z, Croughan M, Sundaram R, Stanford J, Varner J, Kennedy A, Giudice L, Fujimoto V, Sun L, Wang L, Guo Y, Kannan K. Bisphenol A and phthalates and endometriosis, The LIFE Study. *Fertility and Sterility* 2013; 100(1):162-169.

4. Pollack AZ, Buck Louis GM, Chen Z, Peterson CM, Sundaram R, Croughan MS, Sun L, Hediger ML, Stanford JB, Varner MW, Palmer CD, Steuerwald AJ, Parsons PJ. Trace element and endometriosis: The ENDO Study. *Reproductive Toxicology* 2013; 42:41-48.

NICHD Fetal Growth Studies

These studies are described in the Epidemiology Branch section of this report.

Exposome

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 repositories, we designed this proof-of-concept study as our initial foray into the exposome research. This work has two research aims: 1) characterize and quantify the "normal" pregnancy exposome using an existing pregnancy cohort study (Trial of Calcium for Preeclampsia Prevention); and 2) determine its utility and feasibility for design and implementation on a larger scale. Laboratory analyses are underway in which a mixture of persistent (i.e., metals and trace elements, OCPs, OPPs, PBBs, PBDEs, PCBs, PFCs) and non-persistent chemicals (e.g., pesticides, parabens, phenols, phthalates) are being quantified in blood and urine, respectively, during each trimester of pregnancy. Both nontargeted proteomic and metabolomics analyses and targeted analysis of other biomarkers (e.g., angiogenesis, glucose homeostasis, hormones, inflammation, oxidative stress) are underway. Analysis is planned for the summer of 2014.

Principal Investigator

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

Division Collaborators

- Paul Albert, Ph.D.
- S. Katherine Laughon, M.D., M.S.
- Rajeshwari Sundaram, Ph.D.
- Edwina Yeung, Ph.D., Sc.M.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

2013 Exposome Publications

1. Buck Louis GM, Yeung E, Sundaram R, Laughon SK, Zhang C. The exposome: Exciting opportunities for discoveries in reproductive and perinatal epidemiology. *Paediatric and Perinatal Epidemiology* 2013; 27(3):229-36.

Other 2013 Division Publications

1. Brenner RA, Taneja GS, Schroeder TJ, Trumble AC, Moyer PM, Buck Louis GM. Injury rates among youth with and without developmental disabilities*. International Journal of Injury Control and Safety Promotion* 2013; 20(3):259-65.

2. Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, Buck Louis GM. The prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. *Fertility and Sterility* 2013; 99(5):1324-1331.

3. Hediger ML, Bell EA, Druschel CM, Buck Louis GM. Assisted reproductive technologies and children's neurodevelopmental status. *Fertility Sterility* 2013; 99(2):311-17.

4. Tobias DK, Chavarro J, Williams MA, Buck Louis GM, Hu FB, Rich-Edwards J, Missmer S, Zhang C. History of infertility and risk of gestational diabetes mellitus: A prospective analysis of 40,773 pregnancies. *American Journal of Epidemiology* 2013; 178(8):1219-1225.

5. Louis JF, Thoma ME, Sorensen DN, McLain AC, King RB, Sundaram R, Keiding N, Buck Louis GM. The prevalence of couple infertility in the United States from a male

perspective: Evidence from a nationally-representative sample. *Andrology* 2013, 1(5):741-748.

6. Ma WL, Yun S, Bell EM, Druschel CM, Caggana M, Aldous KM, Buck Louis GM, Kannan K. Temporal trends of polybrominated diphenyl ethers (PBDEs) in the blood of newborns from New York State during 1997-2011: Analysis of dried blood spots from the Newborn Screening Program. *Environmental Science and Technology* 2013; 47(14):8015-8021.

7. McLain AC, Sundaram R, Buck Louis GM. Modeling fecundity in the presence of a sterile fraction using a semi-parametric transformation model for grouped survival data. *Statistics and Medicine* 2013; 31(22):2569-2575.

8. 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* December 2013 [DOI:10.1159/000355100].

9. 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* 2013; Dec. 13 [DOI: 10.1016/j.jim.2013.12.001].

10. Männistö T, Mendola P, Grewal J, Xie Y, Chen Z, Laughon SK. Thyroid diseases and adverse pregnancy outcomes in a contemporary observational cohort from the United States. *Journal of Clinical Endocrinology and Metabolism* 2013; 98(7):2725-2733.

11. Peruzzi G, Femnou L, Gil-Krzewska A, Borrego F, Weck J, Krzewski K, Coligan JE. Membrane-type 6 matrix metalloproteinase regulates the activation-induced downmodulation of CD16 in human primary NK cells. *Journal of Immunology* 2013; 191(4):1883-1894.

12. Law NC,* Weck J,* Kyriss B, Nilson JH, Hunzicker-Dunn M. Lhcgr expression in granulosa cells: Roles for PKA-phosphorylated β-catenin, TCF3, and FOXO1. *Molecular Endocrinology* 2013; 27(8):1295-1310. (*Denotes shared first authorship).

Biostatistics & Bioinformatics Branch (BBB)

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

Paul Albert, Ph.D.

The mission of the BBB is to: 1) conduct both collaborative and methodological research that is important to the mission of the Division and Institute; 2) provide statistical 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, the Institute, the 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 for 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 2013 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 2013 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 receiver operating characteristic (ROC) curves with clustered data. In 2013, BBB investigators have collaborated with Health Behavior Branch scientists in developed 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 for which no "gold standard" test is available.

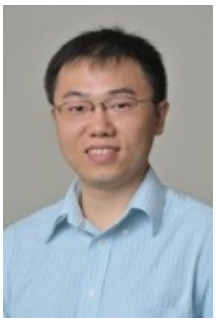
During 2013, BBB investigators have developed new statistical methodology for association analysis of quantitative trails using functional data analytical techniques at the gene level, along with new methods for detecting gene-gene and gene-environmental interactions of complex diseases.

BBB investigators are involved in all aspects of the study from its earliest concept, including study design, implementation and data quality, 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 Institutional Review Board (IRB), the NIH Biometry and Epidemiology Tenure Committee, and numerous NIH Data Safety and Monitoring Boards (DSMBs).

Staff

- Paul S. Albert, Ph.D., *Senior Investigator and Chief*
- Aiyi Liu, Ph.D., *Senior Investigator*
- Zhen Chen, Ph.D., *Investigator*
- Ruzong Fan, Ph.D., *Investigator*
- Danping Liu, Ph.D., *Investigator*
- Rajeshwari Sundaram, Ph.D., *Investigator*
- SungDuk Kim, Ph.D., *Staff Scientist*
- Ashok Chaurasia, Ph.D., *Postdoctoral Fellow*
- Jared Foster, Ph.D., *Postdoctoral Fellow*
- Yifan Wang, Ph.D., *Postdoctoral Fellow*
- Kirsten J. Lum, M.S., *Predoctoral Fellow*
- Kara Fulton, B.S., *Postbaccalaureate Fellow (departed 2013)*
- Alicia Johns, B.S., *Postbaccalaureate Fellow*

Longitudinal and Correlated Data Analysis



Danping Liu, Ph.D.

SungDuk 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 LIFE Study as well as to the NICHD Fetal Growth Studies); 2) characterizing longitudinal menstrual cycle and circadian rhythm patterns in longitudinal data with applications to the BioCycle Study and the NEXT Study; and 3) development of new modeling approaches for predicting crashes from longitudinal kinematic (g-force) events.

Kim et al., (2013) proposed new Bayesian methodology for analyzing intensively collected longitudinal count data that was encountered in collaborations with the HBB on studying naturalistic driving in teenagers. Liu et al. (submitted for publication) has proposed new methods for combining multiple outcomes in longitudinal studies with applications to teenage simulation driving studies.

2013 Longitudinal and Correlated Data Publications

1. Albert PS, Shih JH. Modeling batched Gaussian longitudinal data subject to informative dropout. *Statistical Methods in Medical Research* (In press).

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* (In press).

3. Jackson J, Albert PS, Zhang Z, Simons-Morton B. Ordinal latent variable models and their application in the study of newly licensed teenage drivers. *Journal of the Royal Statistical Society* 2013; Series C 62: 435-450.

4. Hunsberger SA, Albert PS, Thoma, M. Approaches for retrospective sampling for longitudinal transition models. *Statistics and Its Interface* (In press).

5. Kang L, Liu A, Tian L. Linear combination methods to improve diagnostic/prognostic accuracy on future observations. *Statistical Methods in Medical Research* (In press).

6. Kim S, Chen, MH, Ibrahim, JH, Shah, AK, Lin J. Bayesian inference for multivariate meta-analysis box-cox transformation models for individual patient data with applications to evaluation of cholesterol lowering drugs. *Statistics in Medicine* 2013; 32:3972-3990.

7. Kim S, Chen Z, Zhang Z, Simons-Morton B, and Albert PS. Bayesian hierarchical Poisson regression models: an application to a driving study with kinematics events. *Journal of the American Statistical Association* 2013; 108:494-503.

8. Lai Y and Albert PS. Identifying multiple change-points in a linear mixed model. *Statistics in Medicine* (In press).

9. Li QZ, Li ZB, Liu A, Li ZH. Rank-based tests for comparison of multiple endpoints among several populations. *Statistics and Its Interface* (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 is 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 preterm birth due to preeclampsia) and modeling the gap times between pregnancies.

2013 Time-to-Event Publications

1. McLain AC, Sundaram R, Louis GMB. Modeling time to pregnancy in presence of sterile fraction using transformation survival model. *Statistical Methods in Medical Research* (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 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 for which 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 ENDO Study, which is focused on comparing and evaluating different measures for diagnosing endometriosis in the absence of a gold standard.

2013 Analysis of Biomarkers Publications

1. Albert PS, Liu A, Nansel T. Estimation and design for logistic regression under an imperfect population identifier. *Biometrics* (In press).

2. Chen Z and Xie Y. Marginal analysis of measurement agreement among multiple raters with non-ignorable missing ratings. *Statistics and Its Interface* (In press).

3. Jin M, Liu A, Chen Z, Li ZH. Group sequential design in inter-rater reliability study. *Statistica Sinica* 2013; 23:1743-1759.

4. Kang L, Liu A, Tian L. Linear combination methods to improve diagnostic/prognostic accuracy on future observations. *Statistical Methods in Medical Research* (In press).

5. Liu D, Zhou XH. Covariate adjustment in estimating the area under an ROC curve with partially missing gold standard. *Biometrics* 2013; 69:91-100.

6. Liu D, Zhou XH. ROC analysis in biomarker combination with covariate adjustment. *Academic Radiology* 2013; 20:874-882.

7. Tang L, Kang L, Schisterman EF, Liu A. An additive selection of markers to improve diagnostic accuracy based on a discriminatory measure. *Academic Radiology* 2013; 20:854-862.

8. Tang L, Liu A, Chen Z, Schisterman EF, Zhang B, Miao Z. Nonparametric ROC summary statistics for clustered diagnostic marker data. *Statistics in Medicine* 2013; 32:2209-2220.

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, especially when dealing with data related to birth defects. For example, Division studies often have genetic information on a particular child as well as on both parents (triads), resulting in difficult analytic and design issues. BBB investigators address these issues by developing new methodologies for analyzing quantitative and qualitative traits when the outcomes are longitudinal, and in developing entropy-based methods for detecting gene-gene and gene-environmental interactions of complex diseases. BBB investigators have also developed methodologies for estimating gene-environment interactions in the presence of measurement error with regard to environmental factors.

2013 Analysis of Genetic Data Publications

1. Fan R, Lee A, Lu Z, Liu A, Troendle, JF, Mills JL. Association analysis of complex disease using triads, parent-child dyads and singleton monads. *BMC Genetics* 2013; 14:78.

2. Fan RZ, Wang YF, Mills JL, Wilson, AF, Bailey-Wilson JE, Xiong, MM. Functional linear models for association analysis of quantitative traits. *Genetic Epidemiology* 2013; 37:726-742.

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* (In press).

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* (In press).

Collaborative Research

BBB investigators are essential members of the research team on all major projects in the Epidemiology Branch and Health Behavior Branch, 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, the goal of which 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.

2013 Collaborative Research Publications

1. Boghossian NS, Yeung EH, Lipsky LM, Poon AK, Albert PS. Dietary indices in association with postpartum weight retention. *American Journal of Clinical Nutrition* (In press).

2. 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 Journal of Obstetrics and Gynecology* (In press).

3. Bowers K, Laughon SK, Kiely M, Brite J, Chen Z, and Zhang C. Gestational diabetes, pre-pregnancy obesity, and pregnancy weight gain in relation to excess fetal growth: variations by race/ethnicity. *Diabetologia* 2013; 55(6):1263-71.

4. Buck Louis GM, Peterson M, Chen Z, Croughan M, Sundaram S, Stanford J, Varner M, Kennedy A, Giudice L, Fujimoto VY, Sun L, Wang L, Guo Y, and Kannan K. Bisphenol A and phthalates and endometriosis, The ENDO Study. *Fertility & Sterility* 2013; 100(1):162-9.

5. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Maisog J, Kim S, Chen Z, Barr DB. Persistent environmental pollutants and couple fecundity, The LIFE Study. *Environmental Health Perspectives* 2013; 121:231-236.

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 & Sterility* 2013 (online).

7. Buck Louis GM, Yeung, E, Sundaram R, Laughon SK, Zhang C. The exposome: Exciting opportunities for discoveries in reproductive and perinatal epidemiology. *Paediatric and Perinatal Epidemiology* 2013; 27:229-236.

8. Carter TC, Kay DM, Browne ML, Liu A, Romitti PA, Kuehn D, Conley MR, Caggana M, Druschel CM, Brody LC, Mills JM. Anorectal atresia and variants at predicted regulatory sites in candidate genes. *Journal of Human Genetics* 2013; 77:31-46.

9. Ehsani J, Simons-Morton B, Albert PS, Klauer SG. The association between kinematic risky driving among parents and their teenage children. *Journal of Adolescent Health* (In press).

10. Eisenberg M, Kim S, Chen Z, Sundaram R, Schisterman E, and Buck Louis G. The relationship between male body mass index and adiposity on semen quality: Data from the LIFE Study. *Human Reproduction* 2013; 29:193-200.

11. Goodman M, Lakind JS, Fagliano JA, Lash TL, Wiemels JL, Winn DM, Patel C, Van Eenwyk, 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* (In press).

12. Feenstra B, Geller F, Carstensen L, Romitti PA, Korberg IB, Bedell B, Krogh C, Fan RZ, Svenningsson A, Caggana M, Nordenskold A, Mills JL, Murray JC, Melbye M. Plasma lipids, chromosome 11q23.3, and the risk of infantile hypertrophic pyloric stenosis. *Journal of American Medical Association* 2013; 310(7):714-721.

13. 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* (In press).

14. 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* (In press).

15. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD consecutive pregnancies study: recurrent preterm delivery by subtype. *American Journal of Obstetrics and Gynecology* (In press).

16. Laughon SK, McLain AC, Sundaram R, Catov J, Louis GMB. Maternal lipid change in relation to length of gestation: A prospective cohort study with preconception enrollment of women. *Gynecologic and Obstetric Investigation* 2013 (online).

17. Louis JF, Thoma ME, Sorensen DN, McLain AC, King RB, Sundaram R, Keiding N, Louis GMB. The prevalence of couple infertility in the United States from a male perspective: evidence from a nationally representative sample. *Journal of Andrology* 2013; 1(5) 741-748.

18. Männistö TI, Mendola P, Grewal J, Xie Y, Chen Z, and Laughon S. Thyroid diseases and adverse pregnancy outcomes in a contemporary observational cohort from the United States. *Journal of Clinical Endocrinology & Metabolism* 2013; 98(7):2725-33.

19. Mao S, Goodrich RJ, Hauser R, Schrader SM, Chen Z, and Krawetz S. Evaluation of the effectiveness of semen storage and sperm purification methods for spermatozoa transcript profiling. *Systems Biology in Reproductive Medicine* 2013; 59(5):287-95.

20. Mendola P, Laughon SK, Männistö TI, Leishear K, Reddy UM, Chen Z, Zhang J. Obstetric complications among US women with asthma. *American Journal of Obstetrics & Gynecology* 2013; 208(2):127.e1-8.

21. 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* (In Press).

22. Mumford SL, Steiner AZ, Pollack AZ, Perkins NJ, Filiberto AC, Albert PS, Mattison DR, Wactawski-Wende J, Schisterman EF*. The hormonal profile and its effect on menstrual cycle length. Journal of Clinical Endocrinology & Metabolism* (In press).

23. 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 Academy of Nutrition and Dietetics* (In press).

24. Peterson CM, Johnstone EM, Hammoud AO, Stanfford JB, Varner MW, Kennedy A, Chen Z, Sun L, Fujimoto VY, Hediger ML, Buck Louis GM, on behalf of the ENDO Study Working Group. Risk factors associated with endometriosis: Importance of study population for characterizing disease in the ENDO Study. *Obstetrics & Gynecology* 2013, 208(6):451.e1-e11.

25. Pollack AZ, Louis GMB, Chen Z, Peterson CM, Sundaram S, Croughan MS, Sun LP, Hediger ML, Stanford JB, Varner MW, Palmer CD, Steuerwald A, and Parsons P. Trace elements and endometriosis: The ENDO Study. *Reproductive Toxicology* 2013; 42:41-48.

26. Sarkar C, Chandra G, Peng S, Zhang Z, Liu A, Mukherjee A. A Thioesterase-mimetic arrests neurophathology and extends lifespan in a mouse model of a neurodegenerative lysosomal storage disease. *Nature Neuroscience* 2013l 16:1608-1617.

27. Simons-Morton BG, Cheon K, Guo F, Albert PS. Trajectories of kinematic risky driving among novice teenagers. *Accident Analysis & Prevention* 2013; 51:27-32.

28. Sjaarda LA, Albert PS, Mumford SL, Hinkle SN, Mendola P, Laughon0 SK. Customized large-for-gestational-age birthweight at term and the association with adverse perinatal outcomes. *American Journal of Obstetrics and Gynecology* 2014; 210: e1-e11.

29. Steuerwald A, Parsons P, Amason J, Chen Z, Peterson M, and Buck Louis G. Trace element analysis of human urine collected after administration of Gd-based MRI contrast agents: Characterizing spectral interferences using inorganic mass spectrometry. *Journal of Analytical Atomic Spectrometry* 2013; 28(6):821-30.

30. Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, Buck Louis GM. The prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. *Fertility & Sterility* 2013; 99:1324-1331.

31. Waldmain TA, Colon KC, Steward, DM, Worthy, TA, Janik, JE, Fleisher TA, Albert PS, Fig WD, Morris, JC. Phase I clinical trial of blockade of IL-15 transpresentation using humanized MIK-Beta-1 monoclonal antibody directed toward IL-2/IL-15R beta in patients with T-cell large granular lymphocytic leukemia. *Blood* 2013; 121:476-484.

32. Wolff EF, Hediger ML, Sundaram R, Peterson CM, Chen Z, Buck Louis GM. In utero exposures and endometriosis, the ENDO Study. *Fertility & Sterility* 2013; 99:790-795.

33. Wolff EF, Sun L, Hediger ML, Sundaram R, Peterson CM, Chen Z, and Buck Louis GM. In utero exposures and endometriosis: The Endometriosis, Natural History, Disease, Outcome (ENDO) Study. *Fertility & Sterility* 2013; 99(3):790-5.

34. Yeung EH, Zhang C, Albert PS, Ye A, Mumford SL, Perkins NJ, Hediger ML, Wactawski-Wende J, Schisterman EF. The influence of adiposity on menstrual cycle patterns of sex hormones: the BioCycle Study. *International Journal of Obesity* 2013; 37, 237-243.

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, NICHD, 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 and trainees at various stages of their professional careers to provide them with 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, Epidemiology Branch initiatives are furthering our understanding of the etiology and determinants of gestational diabetes, as well as genetic and lifestyle determinants of birth defects through important international collaborations. Moreover, the Epidemiology Branch is focused on clinical trials of low-cost widely-available interventions to improve reproductive health, with substantial potential public health impact. The Branch is committed to providing evidence to improve clinical management for the parturient woman, particularly in light of the secular changes in the obstetrical population. The Branch also focuses on abnormal fetal growth in relation to pregnancy complications. The effects of nutrition and the environment on reproduction and pregnancy are also of great importance, as we seek to understand the lifestyle determinants that impact reproduction to design effective interventions.

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, and pediatric epidemiology. The research the Branch conducts has the potential to change public health practice in important ways.

Staff

- Enrique F. Schisterman, Ph.D., M.A., *Senior Investigator and Chief*
- Jagteshwar (Una) Grewal, Ph.D., M.P.H., *Staff Scientist (departed in 2013)*
- Mary L. Hediger, Ph.D., *Deputy Director and Staff Scientist (departed in 2013)*
- Michele Kiely, Dr.P.H., *Staff Scientist*
- S. Katherine Laughon, M.D., M.S., *Investigator*
- Sunni L. Mumford, Ph.D., M.S., *Investigator*
- Pauline Mendola, Ph.D., M.S., *Investigator*
- James L. Mills, M.D., M.S., *Senior Investigator*
- Neil J. Perkins, Ph.D., M.S., *Staff Scientist*
- Edwina H. Yeung, Ph.D., Sc.M., *Investigator*
- Cuilin Zhang, M.D., Ph.D., M.P.H., *Investigator*

Fellows

- Katherine A. Ahrens, Ph.D., M.P.H., *Postdoctoral Fellow*
- Uba Backonja, M.S., R.N., *Predoctoral Fellow*
- 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*
- Michelle Danaher, Ph.D., M.S.**,** *Postdoctoral Fellow (departed in 2013)*
- Katrina Flores, B.A., M.P.H., *Postbaccalaureate Fellow*
- Stefanie Hinkle, Ph.D., *Postdoctoral Fellow*
- Kerri Kissell, M.D., *Clinical Fellow*
- Tuija Männistö, M.D., Ph.D., *Postdoctoral Fellow (departed in 2013)*
- Rebecca Matyas, B.A., Postbaccalaureate Fellow
- Emily M. Mitchell, Ph.D., *Postdoctoral Fellow*
- Anna Z. Pollack, Ph.D., M.P.H., *Postdoctoral Fellow (departed in 2013)*
- Ankita Prasad, B.A., *Postbaccalaureate Fellow (departed in 2013)*
- Candace Robledo, Ph.D., M.P.H., *Postdoctoral Fellow*
- Katherine J. Sapra, M.P.H., M.Phil., *Predoctoral Fellow*
- Karen C. Schliep, Ph.D., M.S.P.H., *Postdoctoral Fellow*
- Lindsey A. Sjaarda, Ph.D., M.S., *Postdoctoral Fellow*
- Marie Thoma, Ph.D., M.S., *Postdoctoral Fellow (departed in 2013)*
- Maeve Wallace, Ph.D., *Postdoctoral Fellow*
- Shvetha Zarek, M.D., *Clinical Fellow*

2013 Awards and Accomplishments

- Katherine A. Ahrens, Ph.D., *IRTA Postdoctoral Fellow (Mentor Enrique F. Schisterman, Ph.D.),* Fellows Award for Research Excellence (FARE), NIH

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

- Stefanie N. Hinkle, Ph.D., *IRTA Postdoctoral Fellow (Mentor S. Katherine Laughon, M.D., M.S.),* Fellows Award for Research Excellence (FARE), NIH

- Stefanie N. Hinkle, Ph.D., *IRTA Postdoctoral Fellow (Mentor S. Katherine Laughon, M.D., M.S.),* Society for Epidemiologic Research, Student-Postdoc Travel Scholarship. Boston, MA

- Neil J. Perkins, Ph.D., M.S., *Staff Scientist*, NICHD Merit Award, NIH

- Ankita Prasad, B.A., *IRTA Postbaccalaureate Fellow (Mentors Enrique F. Schisterman, Ph.D. and Sunni L. Mumford, Ph.D.)*, Outstanding Poster Award, Postbaccalaurete Poster Day, NIH

Reproductive Epidemiology

The field of reproductive epidemiology focuses on the many various 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. 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 has important reproductive epidemiologic research, particularly the BioCycle Study, Effect 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

Co-Principal Investigators

- Enrique F. Schisterman, Ph.D., M.A.
- Sunni L. Mumford, Ph.D., M.S.

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

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

Division Collaborators

- Katherine Ahrens, Ph.D., M.P.H.
- Paul Albert, Ph.D.
- Michelle Danaher, Ph.D., M.S.
- Kerri Kissell, M.D.
- Rebecca Matyas, B.A.
- Pauline Mendola, Ph.D., M.S.
- Neil J. Perkins, Ph.D., M.S.
- Anna Z. Pollack, Ph.D., M.P.H.
- Ankita Prasad, B.A.
- Karen C. Schliep, Ph.D., M.S.P.H.
- Lindsey A. Sjaarda, Ph.D., M.S.
- Edwina H. Yeung, Ph.D., Sc.M.
- Shvetha Zarek, M.D.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

Detectable oxidative stress in women may be affected by variations in hormone levels that occur as a part of normal menstrual function. Failure to address this underlying biological variability may impair study inference; however, this issue has received little attention. We designed the BioCycle Study with the primary goal to better understand the intricate relation between levels of sex hormones (e.g., estrogen) and oxidative stress during the menstrual cycle. Specifically, we were interested in: 1) the relation between hormone levels and oxidative stress biomarkers during the menstrual cycle in pre-menopausal women; 2) the intra-cycle variation of biomarkers of oxidative stress; and 3) the influence of external factors such as cigarette smoking, alcohol consumption, and exercise on oxidative stress and hormone levels.

The BioCycle Study was a prospective longitudinal cohort study comprising 259 women age 18 to 44 years (98% follow-up rate). Participants were followed for two menstrual cycles. Blood and urine samples were obtained for key days of each menstrual cycle based on hormone levels approximated by fertility monitors. Serum samples were evaluated for levels of the oxidative stress markers F2-isoprostanes and conjugate dienes, as well as fasting glucose and insulin, total cholesterol, and serum antioxidant vitamins. At each of the 16 clinic visits, we prospectively collected data on diet, physical activity, and other behavioral and environmental exposures.

Since completion of the study, much progress has been made in the analysis of the BioCycle Study data. To date, 50 papers have been published using data from the BioCycle Study. 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. 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. These findings have implications for clinical practice (i.e., certain doctor visits should be timed to menstrual cycle phase) and for study designs among 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. Isoflavone intake was found to be not associated with sporadic anovulation and not related to sex hormone concentrations or anovulation, but was associated with minimally increased Sex hormone-binding globulin (SHBG) concentrations. These results suggest potential endocrine effects with no subsequent effects on ovulation, easing concerns regarding their impacts on fertility. In a separate paper evaluating the association of energy-containing beverages, researchers found that even at moderate consumption amounts, sweetened soda is associated with elevated follicular estradiol concentrations among premenopausal women but does not appear to affect ovulatory function. Further research into the mechanism driving the association between energy-containing beverages and reproductive hormones, and its potential implications for women's health, is warranted. Finally, meeting the 5-A-Day-For-Better-Health Program recommendation was associated with lower oxidative stress and improved antioxidant status in analyses of typical diet (via the Food Frequency Questionnaire) and in menstrual cycle phase-specific analyses using 24-hour recalls. These papers have been influential in describing the impact of a healthy diet on hormonal function and ovulation, and in linking previous research regarding the effects of a healthy diet on later chronic disease outcomes among reproductive age women.

Moreover, additional biomarkers were measured in stored serum samples. Specifically, leptin, anti-Müllerian hormone (AMH), inhibin B, testosterone, and folate were measured and are being analyzed in conjunction with the extensive data already collected in the BioCycle Study to assess how these biomarkers vary across the menstrual cycle, and how other dietary and lifestyle factors may affect their profiling.

2013 BioCycle Study Publications

1. Yeung EH, Zhang C, Albert PS, Mumford SL, Ye A, Perkins NJ, Wactawski-Wende J, Schisterman EF. Adiposity and sex hormones across the menstrual cycle: The BioCycle Study. *International Journal of Obesity* 2013; 37(2):237-43.

2. Pollack AZ, Perkins NJ, Mumford SL, Schisterman EF. Correlated biomarker measurement error: An important threat to inference in environmental epidemiology. *American Journal of Epidemiology* 2013; 177(1):84-92.

3. Schliep KC, Schisterman EF, Mumford SL, Perkins NJ, Ye A, Pollack AZ, Zhang C, Porucznik CA, VanDerslice JA, Stanford JB, Wactawski-Wende J. Validation of different instruments for caffeine measurement among premenopausal women in the BioCycle Study. *American Journal of Epidemiology* 2013; 177(7):690-9.

4. Pollack AZ, Mumford SL, Wactawski-Wende J, Yeung E, Mendola P, Mattison D, Schisterman EF. Bone mineral density and blood metals in premenopausal women. *Environmental Research* 2013; 120:76-81.

5. 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* (In press).

6. Blondin S, Yeung EH, Mumford SL, Zhang C, Browne RW, Wactawski-Wende J, Schisterman EF. Serum retinol and carotenoids in association with biomarkers of insulin resistance among premenopausal women. *ISRN Nutrition* 2013; 2013:619516.

7. Boghossian NS, Yeung EH, Mumford SL, Zhang C, Gaskins AJ, Wactawski-Wende J, Schisterman EF. Adherence to the Mediterranean diet and body fat distribution in reproductive aged women. *European Journal of Clinical Nutrition* 2013; 67(3):289-94.

8. Schliep KC, Schisterman EF, Mumford SL, Pollack AZ, Perkins NJ, Ye A, Zhang C, Stanford JB, Porucznik CA, Hammoud AO, Wactawski-Wende J. Energy-containing beverages: Reproductive hormones and ovarian function in the BioCycle Study. *American Journal of Clinical Nutrition* 2013; 97(3):621-630.

9. Rink SM, Mendola P, Mumford SL, Poudrier JK, Browne RW, Wactawski-Wende J, Perkins NJ, Schisterman EF. Self-report of fruit and vegetable intake that meets the 5-A-Day recommendation is associated with reduced levels of oxidative stress biomarkers and increased levels of antioxidant defense in premenopausal women. *Journal of the Academy of Nutrition and Dietetics* 2013; 113(6):776-85.

10. Mumford SL, Dasharathy SS, Pollack AZ, Perkins NJ, Mattison DR, Cole SR, Wactawski-Wende J, Schisterman EF. Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle: Findings from the BioCycle Study. *Human Reproduction* 2013; 28(7):1853-62.

11. Hambridge HL, Mumford SL, Mattison DR, Ye A, Pollack AZ, Bloom MS, Mendola P, Lynch KL, Wactawski-Wende J, Schisterman EF. The influence of sporadic anovulation on hormone levels in ovulatory cycles. *Human Reproduction* 2013; 28(6):1687-94.

12. Filiberto AC, Mumford SL, Pollack AZ, Zhang C, Yeung EH, Perkins NJ, Wactawski-Wende J, Schisterman EF. Habitual dietary isoflavone intake is associated with decreased C-reactive protein concentrations among healthy premenopausal women: The BioCycle Study. *Journal of Nutrition* 2013; 143(6):900-6.

13. 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. *Epidemiologic Reviews* (In Press).

14. Filiberto AC, Mumford SL, Pollack AZ, Zhang C, Yeung EH, Schliep KC, Perkins NJ, Wactawski-Wende J, Schisterman EF. Usual dietary isoflavone intake and reproductive function across the menstrual cycle. *Fertility and Sterility* 2013; 100(6):1727-34.

15. 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* 2013; [Epub ahead of print].

16. 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* 2013; [Epub ahead of print].

17. Whitcomb BW, Mumford SL, Perkins NJ, Chegini N, Wactawski-Wende J, Bertone-Johnson ER, Lynch KE, Schisterman EF. Cytokine and chemokine profiles across the menstrual cycle in healthy reproductive age women. *Fertility and Sterility* (In Press).

Effects of Aspirin in Gestation and Reproduction (EAGeR) Study

Co-Principal Investigators

- Enrique F. Schisterman, Ph.D., M.A.
- Sunni L. Mumford, Ph.D., M.S.

Division Collaborators

- Katherine Ahrens, Ph.D., M.P.H.
- Paul Albert, Ph.D.
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The EAGeR Study is a multi-site, prospective, double-blind trial designed to assess the effects of low-dose aspirin on pregnancy implantation and pregnancy outcome. In this trial, 1,228 regularly menstruating women age 18-40 years with up to two recent miscarriages and who planned to become pregnant again were randomized to either the treatment group (daily aspirin [81mg] plus folic acid [0.4 mg]) or the placebo group with folic acid only. Treatment or placebo administration began prior to conception and continued during pregnancy. Fertility monitors were used to assist with timing of intercourse; home digital pregnancy testing kits were used to indicate pregnancy; and daily urine samples were collected to monitor very early pregnancy and pregnancy loss.

Women were followed by the clinic through regular visits as well as phone interviews. During follow-up, women were in "active follow-up" for two menstrual cycles. In this follow-up phase, women kept daily diaries and visited the clinic four times, where they filled out questionnaires and provided blood samples, in addition to their daily urine samples. They then entered "passive follow-up" for an additional four cycles, visiting the clinic at the end of each cycle. At the end of passive follow-up, if no pregnancy was confirmed, women were considered to have completed the study. However, if a woman became pregnant at any time during this stage, she switched to pregnancy follow-up. Women in pregnancy follow-up were followed actively for 4 weeks post-conception and passively through parturition. Pregnancy loss, pregnancy complications, and perinatal outcomes were monitored throughout pregnancy. The trial completed in September 2012 and the results of the trial are currently in press with *The Lancet*.

2013 EAGeR Study Publications

1. Schisterman EF, Silver RM, Perkins NJ, Mumford SL, Whitcomb BW, Stanford JB, Lesher LL, Faraggi D, Wactawski-Wende J, Browne RW, Townsend JM, White M, Lynch AM, Galai N. A randomised trial to evaluate the Effects of low dose Aspirin in Gestation and Reproduction (EAGeR): Design and baseline characteristics. *Paediatric and Perinatal Epidemiology* 2013; 27(6):598-609.

2. 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: Findings from the EAGeR (Effects of Aspirin in Gestation and Reproduction) randomized trial. *Lancet* (In Press).

Folic Acid and Zinc Supplementation Trial (FAZST)

Co-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, with largely an unknown etiology. 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 (ART) outcomes.

FAZST is a multi-center, double-blind, block-randomized, placebo-controlled trial to assess the effects of folic acid and zinc dietary supplementation on semen quality, and indirectly on conception rates and pregnancy outcomes among 2,400 male partners of couples seeking

assisted reproduction. Male participants will be randomized equally (1:1) either to active study dietary supplements (folic acid and zinc daily), or to a matching placebo. Only the male partners of each couple will be randomized to study dietary supplement or placebo. Treatment will continue for 6 months. Following a screening visit, participants will return at baseline, 2, 4, and 6 months. The trial is ongoing and currently recruiting with expected completion in 2017 (NCT Clinical Trials.gov Number: NCT01857310).

Perinatal Epidemiology

Perinatal epidemiologic research focuses on pregnant women and their pregnancy outcomes within a life course epidemiologic paradigm. As such, pregnancy complications are understood not only in the context of pre- and peri-conceptional factors and also later onset diseases and transgenerational effects. Research in the Branch includes effort to understand common complications of pregnancy such as gestational diabetes, which have both short- and long-term impact on the health of mothers and offspring. 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, we explore the importance of maternal chronic disease in pregnancy given that increasing maternal age and obesity rates among women at reproductive age result in large proportions of women who enter pregnancy in suboptimal health. The Branch's perinatal research includes the following studies: 1) Consortium on Safe Labor (CSL); 2) Diabetes and Women's Health (DWH) Study; 3) Gestational Diabetes Mellitus: Epidemiology, Etiology and Health Consequences; 4) NICHD Fetal Growth Studies; and 5) the B*reathe*-Wellbeing, Environment, Lifestyle and Lung Function (B-WELL-Mom) Study. A brief description of each study follows.

Consortium on Safe Labor (CSL)

Principal Investigators

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

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- Stefanie Hinkle, Ph.D.
- Tuija Männistö, M.D., Ph.D.
- Pauline Mendola, Ph.D., M.S.
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The CSL was a multicenter retrospective observational study of 228,562 deliveries at 12 clinical centers across the United States to determine the course of labor associated with optimal maternal and neonatal outcomes. This past year, we investigated the indications for primary cesarean delivery to identify opportunities to lower the primary cesarean rate in the United States. The most common indications for primary cesarean delivery were failure to progress (35.4%), non-reassuring fetal heart rate tracing (27.3%), and fetal malpresentation (18.5%), although frequencies for each indication varied by parity. Among women with failure to progress, 42.6% of primiparas and 33.5% of multiparas were < 6 cm dilated prior to cesarean delivery. Among women who reached second stage of labor, 17.3% underwent cesarean delivery for arrest of descent before 2 hours. Based on these findings, the team concluded that important strategies to reduce the primary cesarean delivery rate included decreasing the number of cesarean deliveries done for failure to progress by using 6 cm as the cutoff for active labor when assessing failure to progress and conservatively managing the second stage of labor by allowing adequate time and encouraging operative vaginal delivery, when appropriate. These actions may be particularly important in the primipara at term with a singleton fetus in vertex presentation.

The impacts of maternal chronic disease on both obstetric and neonatal health also were explored. Both maternal hypo- and hyperthyroidism increased risk for preeclampsia, preterm birth and other obstetric complications (Männistö et al., 2013) as well as neonatal intensive care admissions (Männistö et al., 2013). Maternal asthma increased risks for nearly all obstetric complications studied including pulmonary embolism (Mendola, et al., 2013) and our detailed assessment of preterm birth risk associated with maternal asthma showed that risks were low early in gestation and significantly increased after 33 weeks among singletons(Mendola, et al., 2013). When we expanded our investigation to look at twins, maternal chronic disease was not as strong a factor for complications of labor and delivery as twinning itself (Werder et al., 2013).

In addition, work to evaluate recently recommended changes to the definition of large-for-gestational-age birthweight was initiated in the past year using the CSL database. Specifically, the first publication in this domain identified that newly proposed methods which customize birthweight were not decisively superior to standard population-based birthweight percentile cutoffs when assessing the application of such cutoffs to identifying maternal delivery complications and neonatal morbidity (Sjaarda L et al., 2013).

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

2013 Consortium 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* 2013; [Epub ahead of print].

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* 2013; [Epub ahead of print].

3. 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* 2013; [Epub ahead of print].

4. 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* 2013; [Epub ahead of print].

5. Timofeev J, Reddy UM, Huang C, Driggers RW, Landy HJ, Laughon SK. Obstetric complications, neonatal morbidity and indications for cesarean delivery by maternal age. *Obstetrics & Gynecology* 2013; 122(6):1184-95.

6. Männistö T, Mendola P, Grewal J, Xie Y, Chen Z, Laughon SK. Thyroid diseases and adverse pregnancy outcomes in a contemporary U.S. cohort. *The Journal of Clinical Endocrinology & Metabolism* 2013; 98(7):2725-33.

7. Boyle A, Reddy UM, Landy HJ, Huang C, Driggers RW, Laughon SK. Primary cesarean delivery in the United States. *Obstetrics & Gynecology* 2013; 122(1):33-40. (Article selected for ABOG Maintenance of Certification.)

8. Bowers K, Laughon SK, Kim SD, Mumford SL, Brite J, Kiely M, Zhang C. The association between a medical history of depression and gestational diabetes in a large multi-ethnic cohort of the United States. *Paediatric and Perinatal Epidemiology* 2013; 27:323–328.

9. Männistö T, Mendola P, Reddy UM, Laughon SK. Neonatal outcomes and birth weight in pregnancies complicated by maternal thyroid disease. *American Journal of Epidemiology* 2013; 178(5):731-40.

10. Bowers K, Laughon SK, Kiely M, Brite J, Zhang C. Gestational diabetes, pre-pregnancy obesity, and pregnancy weight gain in relation to excess fetal growth: Variations by race/ethnicity. *Diabetologia* 2013; 56(6):1263-71.

11. Werder E, Mendola P, Männistö T, O'Loughlin J, Laughon SK. Effect of maternal chronic disease on obstetric complications in twin pregnancies in a U.S. cohort. *Fertility and Sterility* 2013; 100(1):142-149.e2.

12. Mendola P, Laughon SK, Männistö T, Leishear K, Chen Z, Zhang J. Obstetric complications among U.S. women with asthma. *American Journal of Obstetrics & Gynecology* 2013; 208(2):127.e1-8.

Diabetes & Women's Health (DWH) Study: A Study of Long-Term Health Implications of Glucose Intolerance in Pregnancy and Their Determinants

Principal Investigator

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The DWH Study, based on a retrospective cohort design, aims to understand and discover novel pathways and determinants underlying the progression from gestational diabetes (GDM) to type 2 diabetes (T2DM) and 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 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 and of understanding the underlying molecular mechanisms. 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 is built upon two large existing cohorts: The Nurses' Health Study II (NHS-II) and the Danish National Birth Cohort (DNBC). In the present study, we are enrolling approximately 4,000 women with a history of GDM who were members of either the NHS-II or DNBC. After enrollment, participants are followed for additional years to collect

updated information on major clinical and environmental factors including, but not limited to diet, physical activity, and anthropometric information that may predict T2DM risk. Biospecimen collection is to measure genetic and biochemical markers (both pathway specific and non-targeted) believed relevant for 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. Ninety-five percent of the study population has been enrolled to date.

2013 Diabetes and Women's Health Publications

1. Bao W, Hu FB, Rong S, Rong Y, Bowers K, Schisterman EF, Liu L, Zhang C. Predicting risk of type 2 diabetes mellitus with genetic risk models on the basis of established genome-wide association markers: A systematic review. *American Journal of Epidemiology* 2013; 178(8):1197-207.

Gestational Diabetes Mellitus (GDM): Epidemiology, Etiology, and Health Consequences

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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 and impaired glucose metabolism, and adulthood onset diabetes. Along this line of research, we are conducting research 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 University 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 NHS-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 will also be analyzed for the discovery of new pathways and/or biochemical markers related to glucose intolerance and subsequent adverse fetal outcomes. Data collection in the Fetal Growth Studies has been successfully completed. Measurement of longitudinal samples for biomarkers in multiple pathways for GDM is 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 DWH Study and the CSL.

2013 Gestational Diabetes Mellitus Publications

1. Zhang C, Bao W, Rong Y, Yang H, Bowers K, Yeung E, Kiely M. Genetic variants and the risk of gestational diabetes mellitus: A systematic review. *Human Reproduction Update* 2013; 19(4):376-390.

2. Bao W, Bowers K, Tobias DK, Hu FB, Zhang C. Prepregnancy dietary protein intake, major dietary protein sources, and the risk of gestational diabetes mellitus: A prospective cohort study. *Diabetes Care* 2013; 36(7):2001-2008.

3. Bowers K, Laughon SK, Kiely M, Brite J, Zhang C. Gestational diabetes, pre-pregnancy obesity, and pregnancy weight gain in relation to excess fetal growth: Variations by race/ethnicity. *Diabetologia* 2013; 56(6):1263-71.

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* 2013; [Epub ahead of print].

5. Boghossian N, Yeung E, Albert PS, Mendola P, Laughon SK, Hinkle SN, Zhang C. Changes in diabetes status between pregnancies and impact on subsequent newborn outcomes. *American Journal of Obstetrics and Gynecology* (In press).

6. Bowers K, Laughon SK, Kim S, Mumford SL, Brite J, Kiely M, Zhang C. The association between a medical history of depression and gestational diabetes in a large multi-ethnic cohort of the United States. *Paediatric and Perinatal Epidemiology* 2013; 27(4):323-8.

7. Tobias DK, Chavarro JE, Williams MA, Buck Louis GM, Hu FB, Rich-Edwards J, Missmer SA, Zhang C. History of infertility and risk of gestational diabetes mellitus: a prospective

analysis of 40,773 pregnancies. *American Journal of Epidemiology.* 2013, [Epub ahead of print].

NICHD Fetal Growth Studies

Principal Investigator

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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 disorders and heart disease later in life. Thus, delineating optimal fetal growth has implications for clinical care and population health. The NICHD Fetal Growth Studies are an ambitious observational epidemiologic study that recruited 2,504 low risk pregnant women from 12 clinical sites in the United States. 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 twin pregnancies (n=171) also were 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 racial/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; for the obese cohort, the goal is to have a better understanding how fetuses grow and the implications for gravid diseases and fetal health. Follow-up of women was completed in August 2013. Data analysis is underway.

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

Principal Investigator

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- Candace Robledo, Ph.D.
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- Maeve Wallace, Ph.D.
- Jennifer Weck, Ph.D.

The B-WELL-Mom Study aims to increase understanding of factors that predict poor asthma control during pregnancy as well as add to our knowledge of the basic immunology of pregnancy. Asthma is a common chronic disease, and some women experience exacerbation and worsening of their asthma during pregnancy while others improve. The maternal immune response to pregnancy suggests that humoral immune responses are preserved and that 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 postpartum visit are planned as well as daily measures of lung function and symptoms. Enrollment is anticipated to begin in the fall of 2014.

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 particularly fund pediatric research including birth defects and intellectual disabilities. To continue this mission, the pediatric epidemiology research conducted by the Epidemiology Branch is exploring a range of factors of 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 has three research projects, 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

Principal Investigator

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- Yifan Wang, Ph.D.
- Aiyi Liu, Ph.D.

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

The Birth Defects Research Group is a multicenter multidisciplinary group 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, National Human Genome Research Institute, The Health Research Board of Ireland, and the Department of Biochemistry, Trinity College, Dublin.

Research continues to explore genetic factors related to folate and vitamin B12 status to identify additional risk genes for 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.

Recent work, submitted for publication, has continued the search for nutritional factors related to neural tube defect risk. The first study tested the association reported in the literature between maternal choline status and neural tube defect risk. Our actual measurement of maternal choline levels during pregnancy demonstrated that choline status was not related to neural tube defect risk. The second study tested a finding in mice that poor iron and ferritin

status increased the risk of having offspring with neural tube defects. We found no association between iron or ferritin concentrations in mothers and neural tube defects.

Ongoing research involves examining quantitative traits in a genome wide association study given that the genetic analysis is complete. Collected samples have been stored for further analysis of genetic factors.

A study of genetic factors associated with von Willebrand factor has been published. This study identified a previously unknown genetic factor associated with von Willebrand disease using samples and genetic data generated by our quantitative traits genome wide association study. Additional analyses of micronutrients in the quantitative traits genome wide association study are ongoing.

2013 Birth Defects Publications

1. Desch KC, Ozel AB, Siemieniak D, Kalish Y, Shavit JA, Thornburg CD, Sharathkumar AA, McHugh CP, Laurie CC, Crenshaw A, Mirel DB, Kim Y, Cropp CD, Molloy AM, Kirke PN, Bailey-Wilson JE, Wilson AF, Mills JL, Scott JM, Brody LC, Li JZ, Ginsburg D. Linkage analysis identifies a locus for plasma von Willebrand factor undetected by genome-wide association. *Proceedings of the National Academy of Science USA* 2013; 110(2):588-93.

Genetic Factors in Birth Defects Study

Principal Investigator

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- Yifan Wang, Ph.D.
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The Genetic Factors in Birth Defects Study is a multicenter multidisciplinary study led by NICHD to identify genetic risk factors for a wide range of major birth defects. The collaborating institutions are the NICHD, National Human Genome Research Institute, and the New York State Department of Health. The New York State Congenital Malformations Registry has identified approximately 13,000 children who have major birth defects and suitable unaffected controls from 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.

A variety of defects has been selected and analyzed using a candidate gene approach including omphalocele, Hirschsprung's disease, limb defects, and ano-rectal atresia. We also have expanded our work in several directions. Dr. Ruzong Fan, a statistician with a special interest in statistical genetics, has developed new methods for analyzing large-scale genetic data in collaboration with Dr. Mills. By using techniques of functional data analysis, both fixed and mixed effect functional linear models are built to test the association between quantitative traits and genetic variants adjusting for covariates. After extensive simulation analysis, it is shown that the F-distributed tests of the proposed fixed effect functional linear models have higher power than that of sequence kernel association test (SKAT) and its optimal unified test (SKAT-O) for three scenarios in most cases. The methods are applied to analyze three biochemical traits in data from the Trinity Students Study.

We have recently published data on one of the most important genetic variants in the nutritional area, the folate enzyme gene variant MTHFR C677T. There has been considerable controversy regarding the role of this variant as a risk factor for congenital heart disease. We combined our large New York State population with other populations to demonstrate that, in fact, this variant is not a risk factor. Previous findings suggesting an association may be the result of publication bias.

Perhaps the most novel of our investigations explored plasma lipids, genetic variants near the apolipoprotein A-I (APOA1) gene, and the risk of infantile hypertrophic pyloric stenosis (IHPS), a serious condition in which hypertrophy of the pyloric sphincter muscle layer leads to gastric outlet obstruction. IHPS shows strong familial aggregation and heritability, but knowledge about specific genetic risk variants is limited.

We examined the genome comprehensively for genetic associations with IHPS and validated the findings in three independent sample sets.

We found a new genome-wide significant locus for IHPS at chromosome 11q23.3. The single-nucleotide polymorphism (SNP) with the lowest P value at the locus, rs12721025 (OR=1.59; 95% CI: 1.38-1.83; P=1.9 × 10(-10)), is located 301 bases downstream of the APOA1 gene and is correlated (r^2 between 0.46 and 0.80) with SNPs previously found to be associated with levels of circulating cholesterol. For these SNPs, the cholesterol-lowering allele consistently was associated with increased risk of IHPS.

This study identified a new genome-wide significant locus for IHPS. Characteristics of this locus suggest the possibility of an inverse relationship between levels of circulating cholesterol in neonates and IHPS risk, which warrants further investigation.

This study is one of a number conducted by us as part of large birth defects consortiums. Previous studies have searched for genetic associations with oral facial clefts and

craniosynostosis. We anticipate conducting more such studies in the future. The group is interested in exploring collaborations with investigators conducting such studies.

2013 Genetic Factors and Birth Defects Publications

1. Feenstra B, Geller F, Carstensen L, Romitti PA, Körberg IB, Bedell B, Krogh C, Fan R, Svenningsson A, Caggana M, Nordenskjöld A, Mills JL, Murray JC, Melbye M. Plasma lipids, genetic variants near APOA1, and the risk of infantile hypertrophic pyloric stenosis. *Journal of the American Medical Association* 2013; 310:714-21.

2. Mamasoula C, Prentice RR, Pierscionek T, Pangilinan F, Mills JL, Druschel C, Pass K, Russell MW, Hall D, Töpf A, Brown DL, Zelenika D, Bentham J, Cosgrove C, Bhattacharya S, Riveron JG, Setchfield K, Brook JD, Bu'Lock FA, Thornborough C, Rahman TJ, Doza JP, Tan HL, O'Sullivan J, Stuart AG, Blue G, Winlaw D, Postma AV, Mulder BJ, Zwinderman AH, van Engelen K, Moorman AF, Rauch A, Gewillig M, Breckpot J, Devriendt K, Lathrop GM, Farrall M, Goodship JA, Cordell HJ, Brody LC, Keavney BD. Association between C677T polymorphism of methylene tetrahydrofolate reductase and congenital heart disease: meta-analysis of 7697 cases and 13,125 controls. *Circulation: Cardiovascular Genetics* 2013; 6(4):347-53.

3. Fan R, Wang Y, Mills JL, Wilson AF, Bailey-Wilson JE, Xiong M. Functional linear models for association analysis of quantitative traits. *Genetic Epidemiology* 2013; 37:726-42.

4. Fan R, Lee A, Lu Z, Liu A, Troendle JF, Mills JL. Association analysis of complex diseases using triads, parent-child dyads and singleton monads. *BMC Genetics* 2013; 14:78.

Upstate KIDS Study

Principal Investigator

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

Division Collaborators

- Germaine M. Buck Louis, Ph.D., M.S.
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The Upstate KIDS Study was designed in response to growing albeit equivocal evidence suggesting that pregnancies conceived with ART were at increased risk for pregnancy

complications, perinatal and infant mortality, and decrements in gestation and birth size in both singletons and twins. This provocative body of evidence underscores the early origin of human development, including during sensitive windows or early childhood. However, much of the available evidence stems from cross-sectional data, serving as the impetus for the prospective Upstate KIDS Study with longitudinal data collection.

The Upstate KIDS's Study overarching goal is to determine if fecundity and various infertility treatments adversely affect the growth, motor, and social development of children from birth through age 3 years. A matched-exposure cohort design was used to establish a primary cohort of infants conceived with and without infertility treatment who resided in the 57 counties comprising Upstate New York State (exclusive of New York City) using the "infertility check box" on the birth certificate for cohort selection. Parents and their infants were recruited at approximately 4 months to 8 months of age. The primary matched cohort designed 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 a secondary cohort and were 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. The 36-month follow-up of the cohort is nearly completed. 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 are being completed. The 24-, 30- and 36-month follow-ups of the cohort are in progress. 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 had to be designed before analyses could proceed. Diagnostic visits with approximately 600 children, including 300 who screened positive for developmental delay and 300 who did not, are being conducted at three specialized developmental centers across the state. All data collection will be completed June 2014. Analyses are underway using the baseline and biomarker data.

2013 Upstate KIDS Publications

1. Ma WL, Yun S, Bell EM, Druschel CM, Caggana M, Aldous KM, Buck Louis GM, Kannan K. Temporal trends of polybrominated diphenyl ethers (PBDEs) in the blood of newborns from New York State during 1997-2011: Analysis of dried blood spots from the Newborn Screening Program. *Environmental Science and Technology* 2013; 47(14):8015-8021.

2. Hediger ML, Bell EM, Druschel CM, Buck Louis GM. Assisted reproductive technologies and children's neurodevelopmental outcomes. *Fertility and Sterility* 2013; 99(2):311-7.

3. Yeung EH. Druschel C. Cardiometabolic health of children conceived by assisted reproductive technologies. *Fertility and Sterility* 2013; 99(2):318-26.

4. Andersen NJ, Mondal TP, 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* (In press).

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 are described below.

Methodologic Considerations for Menstrual Cycle Data

Co-Principal Investigators

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

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- Karen Schliep, Ph.D., M.P.H.
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The menstrual cycle is a complex process involving multiple hormones, which are regulated by intricate feedback mechanisms. Hormones such as luteinizing hormone, follicle stimulating hormone, estrogen, and progesterone follow a cyclical pattern, which is coordinated by the hypothalamic-pituitary-ovarian axis. Considerable cycle variability exists within and across women. Hormone levels and cycle characteristics have been associated with various reproductive outcomes, such as fertility and spontaneous abortion, and later onset disease. To better describe factors associated with menstrual cycle function and inform women's health research, appropriate study designs, statistical models and specimen timing considerations are needed which appropriately account for the intricacies of the menstrual cycle biology. Our methodologic research is aimed at developing various approaches for properly considering menstrual cycle data to answer critical data gaps such as:

- What is the "typical" menstrual cycle pattern in a population of women?
- What is the effect of a subject-specific covariate on a typical menstrual cycle?
- How does the variation in menstrual cycle function differ between women and across consecutive cycles for the same woman?
- What is the interrelationship between multiple hormones across the menstrual cycle?
- What are the key hormone-relative time points for sampling?
- What is the proper approach to account for selective sampling and sampling error?

There have been several developments over the last year, in both methodology and application. In particular we have evaluated the combined impact of correlated exposure measurement error, unmeasured confounding, interaction, and limits of detection (LODs) on inference for multiple biomarkers as the use of multiple biomarkers is increasingly common in epidemiology. As we know, examining biomarkers measured in the same medium, prepared with the same process, or analyzed using the same method are issues that all investigators should take into account when measuring biomarker data. We conducted data-driven simulations evaluating bias from correlated measurement error and developed closed-form solutions which provide useful tools for estimating the bias in logistic regression. We have also applied harmonic models to model menstrual cycle function, as well as the use of joint-models to account for the four primary reproductive hormones simultaneously, as well as a host of other biomarkers, which is an exciting way to evaluate multiple parameters relating to the hormonal profile. In addition, marginal structural models have been used in multiple settings to evaluate associations between endogenous hormones and other biomarkers of interest, while properly adjusting for time dependent confounding. For example, these techniques have been applied to better understand fluctuations in leptin and uric acid samples across the cycle, while accounting for the feedback mechanisms at play during the normal menstrual cycle. These are unique applications of causal inference methodology to reproductive epidemiology to answer important etiological questions.

2013 Menstrual Cycle Data Methods Publications

1. Pollack AZ, Perkins NJ, Mumford SL, Schisterman EF. Correlated Biomarker Measurement Error: An Important Threat to Inference in Environmental Epidemiology. *American Journal of Epidemiology* 2013; 177(1):84-92.

2. Schliep KC, Schisterman EF, Mumford SL, Perkins NJ, Ye A, Pollack AZ, Zhang C, Porucznik CA, VanDerslice JA, Stanford JB, Wactawski-Wende J. Validation of Different Instruments for Caffeine Measurement Among Premenopausal Women in the BioCycle Study. *American Journal of Epidemiology* 2013; 177(7):690-9.

3. 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. *Epidemiologic Reviews* (In press).

4. 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* 2013; [Epub ahead of print].

5. Mumford SL, Dasharathy SS, Pollack AZ, Perkins NJ, Mattison DR, Cole SR, Wactawski-Wende J, Schisterman EF. Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle: findings from the BioCycle Study. *Human Reproduction* 2013; 28(7):1853-62.

Biomarkers and Diagnostics

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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 integral 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 affects almost all biomarker measurement. Despite measurement error, biomarkers are extremely useful tools. 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. These methods, originally created for ROC curves, have been adapted and found to be 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 ignored in epidemiological research. These issues have served as the motivation for numerous papers, as well as a collaborative effort funded by the American Chemistry Council, with the goal of providing the methodological tools necessary to assess and address issues related to biomarker measurement and assessment.

2013 Biomarkers and Diagnostic Publications

1. Tang LL, Kang L, Liu C, Schisterman EF, Liu A. An additive selection of markers to improve diagnostic accuracy based on a discriminatory measure. *Academic Radiology* 2013; 20(7):854-62.

2. Perkins NJ, Schisterman EF, Vexler A. Multivariate normally distributed biomarkers subject to limits of detection and receiver operating characteristic curve inference. *Academic Radiology* 2013; 20(7):838-46.

3. Hamasaki-Katagiri N, Salari R, Wu A, Qi Y, Schiller T, Filiberto AC, Schisterman EF, Komar AA, Przytycka TM, Kimchi-Sarfaty C. A gene-specific method for predicting hemophilia-causing point mutations. *Journal of Molecular Biology* 2013; S0022-2836(13)00485-3.

4. Pollack AZ, Perkins NJ, Mumford SL, Schisterman EF. Correlated biomarker measurement error is an important threat to inference in environmental epidemiology. *American Journal of Epidemiology* 2013; 177(1):84-92.

Causal Inference

Principal Investigator

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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. Our team of researchers has made significant contributions to this literature in a variety of areas.

Using causal diagrams, analytical proofs, and an empirical example estimating the total effect of maternal smoking on neonatal mortality, Division researchers illustrated and clarified the definition of overadjustment bias, distinguished overadjustment bias from unwarranted adjustment, and quantified the amount of bias and loss of precision associated with overadjustment and unwarranted adjustment.

Division researchers also made important contributions regarding the role of prior outcomes. Pregnancy outcomes, such as spontaneous abortion and preterm birth, are often predictive of future pregnancy outcomes. As a result, many researchers adjust for reproductive history. Research in this area using DAGs illustrates that this may not always be the correct approach. In fact, there is no single answer as to whether reproductive history should be included in the model; the decision depends on the research question and the underlying DAG.

Selection bias is also a common problem in pediatric and perinatal epidemiology, and truncation can be thought of as missing person time that can result in selection bias. Left truncation, also known as late or staggered entry, may induce selection bias and/or adversely affect precision. We showed that there are two kinds of left truncation: fixed left truncation where the start of follow-up is initiated at a set time, and variable left truncation where follow-up begins at a stochastically varying time-point. We found that fixed or variable, non-differential left truncation results in a loss of precision. The extent and direction of this bias is a function of the size and direction of the association between exposure and outcome, and

occurs in common scenarios and under a wide range of conditions. In general, when present in epidemiologic studies, especially time-to-pregnancy studies, proper accounting for left truncation is just as important as proper accounting for right censoring.

2013 Causal Inference Publications

1. Schisterman EF, Cole SR, Ye A, Platt RW. Accuracy loss due to selection bias in cohort studies with left truncation. *Paediatric and Perinatal Epidemiology* 2013; 27(5):491-502.

2. Ahrens KA, Schisterman EF. A time and place for causal inference methods. *Paediatric and Perinatal Epidemiology* 2013; 27(3):258-62.

3. Hernán MA, Schisterman EF, Hernández-Díaz S. Composite outcomes as an attempt to escape from selection bias and related paradoxes. *American Journal of Epidemiology* (In press).

4. Platt RW, Brookhart AM, Cole SR, Westreich D, Schisterman EF. An information criterion for marginal structural models. *Statistics in Medicine* 2013; 32(8):1383-93.

5. Mumford SL, Dasharathy SS, Pollack AZ, Perkins NJ, Mattison DR, Cole SR, Wactawski-Wende J, Schisterman EF. Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle: Findings from the BioCycle Study. *Human Reproduction* 2013; 28(7):1853-62.

6. Schliep KC, Schisterman EF, Mumford SL, Pollack AZ, Perkins NJ, Ye A, Zhang C, Stanford JB, Porucznik CA, Hammoud AO, Wactawski-Wende J. Energy-containing beverages: Reproductive hormones and ovarian function in the BioCycle Study. *American Journal Clinical Nutrition* 2013; 97(3);621-630.

7. 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* 2013; S0002-9378(13)02008-5.

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 (formerly the Prevention Research Branch) is to: 1) conduct research on child and adolescent health and health behavior; 2) provide service to the Division, Institute, and the scientific community through consultation, collaboration, and assistance to advance the goals of science and public health; and 3) 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 and adolescent 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. Social influence is a common theme across the areas of research. 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, and risky driving through the transition from high school to young 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. The current focus is on youth with type 1 diabetes and their families including diabetes management and dietary intake.

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*
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- Leah Lipsky, Ph.D., *Staff Scientist*

Fellows

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- Johnathan Ehsani, Ph.D., *Postdoctoral Fellow*
- Anuj Pradhan, Ph.D., *Postdoctoral Fellow (departed 2013)*
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Research on Young Drivers

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Crash risk is highly elevated early in licensure, declines rapidly for a period of months and then slowly over a period of years, reaching adult levels in the mid-twenties. Compared with older drivers, teenage and young adult drivers drive more often late at night, with multiple passengers, and possibly after drinking alcohol, which 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. We have studied aspects of driving risk and prevention. Our research has included surveys, observation, naturalistic driving, test track, and simulation. Notably, we conducted one 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 functional MRI (fMRI) and executive functioning into this research.

Thus, we employ the best methodology available to answer key research questions about teenage driving.

Naturalistic Teenage Driving Study (NTDS): The Effect of Driving Experience on the Driving Performance of Newly Licensed Teens

The NTDS was first study to assess driving risk objectively among teenage drivers. The purpose was to assess the prevalence and determinants of crash/near crash (CNC) and risky driving rates. The sample included 42 newly licensed teenage drivers and their parents recruited. The teen's primary vehicle was instrumented with a data acquisition system that included an accelerometer, Global Positioning System (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 on a central processing unit (CPU) in the vehicles' trunks with removable hard drives. Data were successfully collected over 18 months from 41 of 42 study participants.

The study is already a landmark among driving studies. We have published papers on methods, driving exposure, crash risk, and risky driving. Distraction due to secondary task engagement increased crash risk among novice drivers (Klauer, Guo, Simons-Morton, et al., in press). Three trajectory classes of crash risk emerged, a very high risk group, a low-risk group, and a group that started at high risk but declined over time (Guo, Simons-Morton, et al., 2013). Cortisol responsivity was associated with crash risk and risky driving (Ouimet,in press). Elevated g-force event rates predict the likelihood of a CNC in the following month (Simons-Morton et al., 2012). This is important because it established elevated g-force rates as an objective measure of risky driving. With investigators in the Biostatics and Bioinformatics Branch, we published several papers evaluating methods for analyzing the unique data structure of this study, with large numbers of counts (kinematic and CNC events) and data on few subjects (Zhang, Albert, Simons-Morton, 2012; Jackson, Albert, Zhang, Simons-Morton, 2013; Kim, Chen, Zhang, Simons-Morton, Albert, 2013). Regarding driving risk, we found that CNC risk was 3.91 times higher and elevated g-force event rates were 5.08 times higher among teenagers compared with adults (Simons-Morton et al., 2011). Curiously, CNC rates among teen drivers declined over time, but risky driving did not. Furthermore, we reported that CNC rates were 75% lower and risky driving was 67% lower among teenage drivers in the presence of adult passengers; and risky driving was 18% lower in the presence of teen passengers, suggesting that the presence of teen passengers does not always increase risk. However, having risky friends (i.e., those who smoked, drank alcohol, used marijuana, engaged in risky driving) increased CNC rates by 96% and risky driving by 109% (Simons-Morton et al., 2011). The publications from this study provide some of the best information available on key aspects of teenage driving.

Supervised Practice Driving (SPD) Study: The Effect of Supervised Practice Driving on Independent Driving Performance

It is logical that more supervised practice driving leads to improved independent driving outcomes. It may be that at least some adolescents who quickly learn to manage the vehicle receive little SPD prior to licensure, while other adolescents for whom managing the vehicle is more difficult receive a great deal of SPD prior to licensure. Only one previous naturalistic study of SPD has been conducted (Goodwin, Margolis, Waller, 2010), but has not reported 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 are following them for 12 months after licensure. Data collection is expected to be completed by June, 2014. We have developed data reduction protocols, including procedures for evaluating audio recordings of teen-parent verbal communications during instructional drives. Analyses of the practice driving period are underway.

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 et al., (2010) reported that male teenage passengers increased fatal crash risk not only among teenage but also among 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 CNC and 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 to 5 year period, incorporating what is learned from each study into the next study.

The Teen Passenger Study 1 (TPS1), completed in the spring of 2012, 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 two conditions (passenger: risk-accepting vs. risk-averse) and two drive orders (driving alone first vs. driving with the passenger first). T-test comparisons of difference scores (passenger minus alone) were

in the expected direction favoring greater driving risk in the risk-accepting passenger group. We concluded that teenage drivers exposed to a risk-accepting teenage passenger were less likely to stop at red lights (p=0.04) while driving in a simulator, and this risky behavior was greater in the presence of a risk-accepting than a risk-averse peer passenger (Simons-Morton et al., in press).

In other analyses of TPS1 neuroimaging data we found participants who were sensitive to social exclusion, measured by the Cyberball task, in which confederate peers play cyber catch with the participant while he is being imaged. Gradually, the confederates exclude the participant and the imaging indicates painful exclusion. 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 et al., in press).

The TPS2 tested the effect of teenage peer pressure on 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 encourages 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 psychosocial tasks will also be conducted. Preliminary analyses indicated that the study participant drove in a more risky manner in the presence of a peer exerting mild pressure to engage in risk compared with in the presence of a confederate passenger who exerted mild pressure not to take risk.

TPS3, which is underway, evaluates the effect of pre-drive mood on risky simulated driving in the presence of a peer passenger. Participants are 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.

Uniform Naturalistic Driving Study (UNDS)

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 UNDS will obtain data from the SHRP2 Naturalistic Driving Study, which used the same instrumentation as the Naturalistic Teenage Driving Study and Supervised Practice Driving Study. SHRP2 obtained driving data from over 200 novices and another 600 adult drivers, which we plan to combine with the data from the NICHD Naturalistic Teenage Driving Study (n-42) and SPD Study (N=90). The large combined data set 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 study is in the planning stages, developing the protocol and obtaining institutional approvals.

SHRP2 data will be available starting in April, and data from SHRP2 and SPD will be ready for analyses by December 2014.

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 150 young drivers starting in grade 12 (ages 17-18) and ending when the participants are ages 21-22. Assessment is done using the DriveCam driving assessment device. The sample is drawn from the NEXT Study and will also have completed 7 years of annual assessments on their health behaviors. The research questions of interest include: 1) What is the variability within the sample and over time in driving performance (elevated g-force events and CNC)? 2) What individual and driving condition factors are associated with risky driving and CNC? Data collection is ongoing and study participants will be followed for a period of 4 years, concluding in 2016.

2013 Research on Young Drivers Publications

1. Klauer S, Guo F, Simons-Morton, BG, Dingus T. (2013). The effect of distraction on CNC among novice teen and adult drivers. *New England Journal of Medicine*, 370(1):54-59.

2. Simons-Morton BG, Bingham R, Ouimet MC, Pradhan A, Chen R, Barretto A, Shope J. (2013). The effect on teenage risky driving of feedback from a safety monitoring system: A randomized controlled trial. *Journal of Adolescent Health*, 53(1):21-26, 2013.

3. Guo F, Klauer SG**,** Simons-Morton BG, Ouimet MC, Dingus T. (2013). Variability in crash and near crash risk among novice teenage drivers: A naturalistic study. *Journal of Pediatrics*, 163(6):1670-1676.

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11. Simons-Morton BG, Guo F, Klauer SG, Ehsani JP, Pradhan AK. Keep your eyes on the road: Young driver crash risk increases according to duration of distraction. *Journal of Adolescent Health* (In press).

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13. Lambert AE, Simons-Morton BG, Cain SA, Weisz S, Cox DJ. Considerations of a dual-systems model of cognitive development and risky driving. *Journal of Research on Adolescence* (In press).

14. Simons-Morton BG, Li K, Russell A, Ehsani J, Pradhan A, Ouimet M C, Klauer S. Validity of the C-RDS self-reported risky driving measure. Proceedings of the Seventh International Driving Symposium on Human Factors in Driver Assessment, Training and Vehicle Design. *Driving Assessment* (In press).

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16. Pradhan A, Li K, Simons-Morton BG, Ouimet MC, Klauer S. Measuring Young drivers' behaviors during complex driving situations. *Proceedings of the Seventh International Driving Symposium on Human Factors in Driver Assessment*, Training and Vehicle Design, *Driving Assessment* (In press).

Adolescent Health Behavior

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Adolescence is a critical period for the development of unhealthy behavioral patterns that may be associated with subsequent adolescent and adult morbidity and mortality. Adolescence is also a critical period for physiological and behavioral changes and for the onset of obesity and substance use. The influence of peers and physical environment (e.g., community programs, policies, and resources) increase during this period as adolescents spend more time outside the family. As adolescents move from high school to post-secondary education or new places of work, their personal, social, and physical environments change. These transitions impact their health and behavior. Currently, we are conducting the NEXT Longitudinal Study of Adolescent Health Behavior (NEXT Study), which follows a nationally representative sample during the transition from high school to early adulthood. The NEXT Study captures assessments of cardiovascular risk factors, adolescent problem behaviors (substance use and dating violence), and novice driving. With funding from outside groups, the study has a number of subsamples on which in-depth behavioral and biomedical data are collected. The NEXT Study promises to be among the most important longitudinal studies since the National Longitudinal Study of Adolescent Health (Add Health).

NEXT Generation Health Study

The NEXT Generation Health Study is a longitudinal survey of adolescent health and behavior. A nationally representative cohort of 2,770 adolescents, approximately 16 years of age, was recruited in 2010 and is assessed annually up to age 22. 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 study focuses on the following areas of adolescent risk: substance use, driving, and cardiovascular disease risk factors and biomarkers. At the end of the recently completed Wave 3 survey, we have a retention rate of 86% of the original 2,770 10th graders recruited at Wave 1. In addition to annual surveys conducted with the entire sample, a subsample of 540 (NEXT Plus) of the 2,770 provide additional data, including diet and physical activity recalls, accelerometers to measure activity and sleep, biospecimens to assess cardiovascular risk, saliva for genetic analyses, peer networks, and driving. Retention among the NEXT Plus subsample at Wave 3 assessments is 92%.

In collaboration with colleagues at the National Institute on Drug Abuse (which co-sponsors NEXT), we published one paper and have another under review on the prevalence of substance use, including poly-drug users (tobacco, alcohol, marijuana, medication misuse, and other illicit drugs). Using a Latent Class Analysis approach, we found approximately 8% of 10th grade students were characterized as poly-substance users. An analysis of peer influences on alcohol use using the first two waves of data revealed that descriptive norms regarding alcohol use mediated the relationship between adolescent exposure to peer drinking at Wave 1 and adolescent drinking at Wave 2. Furthermore, the NEXT Study provides unique data on alcohol/drug impaired driving and riding with an impaired driver. In the first of these analyses, we found that approximately 12.5% of licensed 11th grade students reported driving while alcohol/drug impaired at least once; and 23.9% of all 11th graders reported riding with an impaired driver.

In the past year, based on data from NEXT, we have published papers on the failure of physicians to advise adolescent patients on drinking alcohol (Hingston et al., 2013), poly-substance use among adolescents (Conway et al., 2013); the relationship between alcohol use and drinking with peers (Brooks-Russell et al., 2013); impaired driving among adolescents (Li et al., 2013); and the association of parenting practices with impaired driving (Li et al., in press). Analyses are underway of trajectories of physical activity and diet, and of changes in health behavior the first year after high school.

2013 NEXT Generation Study Publications

1. Hingson, R., Zha, W., Iannotti, R.J., Simons-Morton, B.G. (2013). Physician advice to adolescents about drinking and other health behaviors. *Pediatrics*, 131(2):249-57.

2. Conway K, Vullo GC, Nichter B, Wang J, Compton W, Iannotti RJ, Simons-Morton B. (2013). Prevalence and patterns of polysubstance use in a nationally representative sample of 10th graders in the United States. *Journal of Adolescent Health,* 52: 716-723.

3. Li K, Simons-Morton BG, Hingson R. (2013). Impaired-driving prevalence among U.S. high school students: Associations with substance use and risky driving behavior*s. American Journal of Public Health*, 103(11):e71-7, 2013.

4. Haynie, DL, Farhat, T, Brooks-Russell, A, Wang, J, Barbieri, B., Iannotti, RJ. (2013). Dating violence perpetration and victimization among U.S. adolescents: Prevalence, patterns, and associations with health complaints and substance use. *Journal of Adolescent Health,* 53(2):194-201.

5. Russell A, Farhat T, Wang J, Simons-Morton, BG. Trends in adolescent substance use among 6-10th grade students from 1998 to 2010: Findings from a national probability study. *Journal of Early Adolescence*, doi: 10.1177/0272431613501409 (In press).

6. Brooks-Russell, A, Simons-Morton, B, Haynie, D, Farhat, T, and Wang, J. Longitudinal relationship between drinking with peers, descriptive norms, and adolescent alcohol use. *Prevention Science,* PMID 2356529 (In press).

7. Li K, Simons-Morton BG, Hingson R. Drinking and parenting practices as predictors of impaired driving behaviors among U.S. adolescents. *Journal of Studies on Alcohol and Drugs* (In press).

8. Summersett-Ringgold F, Li K, Haynie DL, Iannotti RJ. Are school resources influencing the relationship between high versus low income adolescents and their school perceptions? *Journal of School Health* (In press).

Behavioral Intervention in Health Care

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Chronic disease and other behavior-related or behavior-managed conditions account for the majority of morbidity, mortality, and health care costs; yet the health care system is based on an acute care model that cannot adequately assist individuals to engage in the health behaviors required to prevent or manage these conditions. The behavioral sciences offer a substantial knowledge base in mechanisms of promoting behavior change; thus integration of the behavioral and medical sciences in clinical practice offers great potential for improving health and decreasing the burden of illness. Our research in this area includes a series of studies involving children and adolescents with type 1 diabetes, including the Family Management of Childhood Diabetes study and the recently completed Cultivating Healthy Eating in Families of Youth with Type 1 Diabetes study, and a forthcoming observational study on diet among pregnant women.

Family Management of Type 1 Diabetes in Youth

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Management of type 1 diabetes is a complex, intensive task, including multiple daily insulin injections or use of an insulin pump, multiple daily blood glucose testing, regulation of carbohydrate intake, regular physical exercise, and problem-solving to correct excessive blood

glucose fluctuations. Careful management 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 2 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.

Findings from the Family Management of Diabetes Multisite Trial demonstrated an intervention effect on glycemic control at 2-year follow-up. This intervention effect was observed only among adolescents. Given the well-documented deterioration in glycemic control that occurs during adolescence, the development of an effective approach for this age group is of particular clinical significance. Analysis of hypothesized behavioral mediators of the intervention effect on glycemic control, however, indicated no significant differences between groups. These findings are highly informative for guiding future research. Previous research has focused on family conflict and responsibility-sharing as key family behaviors impacting diabetes management. Our findings suggest an additional unmeasured behavioral pathway for successfully impacting glycemic control.

Cultivating Healthful Eating in Families of Youth with Type 1 Diabetes (CHEF)

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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, youth's 3-day diet records, parent food frequency questionnaire. Two-week retest data were also obtained from youth and parents on select self-report survey items developed by the investigators. Key findings include the poor dietary quality of youth with type 1 diabetes and associations with BMI, the direct association of parental modeling and attitudes on healthy eating with youth diet quality, the inverse association of food neophobia and pickiness with dietary variety and quality, and significant associations of meal contextual factors with dietary intake. 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.

The 18-month CHEF trial tests 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, which are 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 collected include medical record abstraction, parent-youth interview, youth self-report surveys, parent self-report surveys, youth 3-day diet records, parent 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. Conduct of the CHEF efficacy trial was recently completed; analyses of findings are underway.

Diet, Weight Change, and Obesity in Pregnancy

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The rising prevalence of obesity in the United States over the past several decades and the accompanying spread of adverse long-ranging health effects pose serious public health and economic consequences. At least one-half of women of reproductive age now enter pregnancy at a high BMI (kg/m2), and the majority experience pregnancy-associated weight gains in excess of Institute of Medicine 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, this quickly expanding body of work has not been incorporated into population-based research to date. 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.

2013 Behavioral Intervention in Health Care Publications

1. Nansel TR, Lipsky L, Haynie D, Mehta S, Laffel L. (2013). Relationships among parent and youth healthful eating attitudes and youth dietary intake in a cross-sectional study of youth with type 1 diabetes. *International Journal of Behavioral Nutrition and Physical Activity*, 10: 125. doi:10.1186/1479-5868-10-125

2. Nansel TR, Lipsky L, Iannotti R. (2013). Cross-sectional and longitudinal relationships of body mass index with glycemic control in children and adolescents with type 1 diabetes mellitus. *Diabetes Research and Clinical Practice*, 100(1): 126-32.

3. Sands A, Higgins L, Mehta S, Nansel T, Lipsky L, Laffel L. (2013). Associations of youth and parent weight status and reported vs. predicted daily energy intake in families of youth with type 1 diabetes. *Journal of Diabetes Science and Technology*, 7(1): 263-70.

4. Abraham SB, Abel BS, Nansel TR, Rubino D, Ramsey S, Nieman LK. (2013). A direct comparison of quality of life in Cushing's syndrome and obese patients. *European Journal of Endocrinology*, 168(5): 787-93.

5. Weaver NL, Brixey S, Williams S, Nansel TR. (2013). Promoting correct car seat use in parents of young children: Challenges and recommendations. *Health Promotion Practice*, 14(2): 301-7.

6. Quick V, Lipsky LM, Laffel LMB, Mehta SN, Quinn H, Nansel TR. Relationships of neophobia and pickiness with dietary variety, dietary quality, and diabetes management adherence in youth with type 1 diabetes. *European Journal of Clinical Nutrition* (In press) doi: 10.1038/ejcn.2013.239.

7. Albert P, Liu A, Nansel T. Efficient logistic regression designs under an imperfect population identifier. *Biometrics* (In press) doi: 10.1111/biom.12106.

8. Tse J, Nansel TR, Weaver NL, Williams J. Botello-Harbaum M. Implementation of a tailored kiosk-based injury prevention program in pediatric primary care. *Health Promotion Practice* (In press) doi: 10.1177/1524839913504586.

9. Kornides M, Nansel TR, Haynie D, Lipsky L., Laffel L, Mehta S. Family sociodemographics, eating environment, and meal characteristics: Associations with frequency of family meals. *Child: Care Health and Development* (In press) doi: 10.1111/cch.12078.

10. Nansel TR, Lipsky L, 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* (In press).