DIVISION *of* EPIDEMIOLOGY, STATISTICS *and* PREVENTION RESEARCH

2012 Annual Report

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


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

As the Director of the Division *of* Epidemiology, Statistics *and* Prevention Research, I have the distinct privilege of working with esteemed public health scientists who are committed to improving the health and well being of populations. The Division's research spans from the earliest stages of human reproduction and development through adulthood, and focuses on healthy outcomes to help define normal human variation, disease etiology and prevention research. Collectively, this avenue of research facilitates our understanding of disease occurrence and accompanying attributable risks that may be amenable to population-level interventions aimed at promoting healthy lifestyles and behaviors that maximize well being. Our research is also designed to include vulnerable population subgroups, such as pregnant women, fetuses, children, adolescents, and individuals affected by chronic diseases. Examples of key research findings published in 2012 for these various population subgroups include the following, though further details and other discoveries are reported in the individual reports for Division scientists:

- First evidence suggesting that labor is longer for contemporary cohorts of pregnant women
- Identification of genes associated with birth defects
- Development of first successful clinic-linked behavioral intervention promoting healthful lifestyles demonstrating improved glycemic outcomes among children with type 1 diabetes
- First evidence that teenagers drive in a more risky manner on their own compared with when observed by their parents
- New information about the high rate of teenagers driving after drinking or riding with a drinking driver
- First evidence from a prospective cohort study that chemicals at environmentally relevant concentrations and nutrition affect both male and female fecundity, as measured by reproductive hormonal profiles and time-to-pregnancy

A particularly unique aspect of the Division's research is its commitment to the development of novel methods for improving study design and the analysis of complex population health data. Examples of our methodological discoveries include:

- Development of joint models for assessing menstrual cycles and time-to-pregnancy
- Development of novel methods for pooling biospecimens and combining biomarkers for risk prediction
- Development of risk models for predicting car crashes based upon adolescents' prior g-force event data
- New methods for predicting binary pregnancy outcomes from multivariate longitudinal fetal growth data

As a Division, we explore the feasibility and utility of new research paradigms that might transform our understanding of the dynamic forces underlying population health. For example, scientists are actively conducting research focusing on the early origins of health and disease hypothesis, including potential trans-generational effects of environmental exposures. Recently, the Division implemented a proof-of-concept study focusing on the newly developed exposome paradigm, whose aim is to assess the totality of environmental exposures during sensitive windows of human reproduction and development. Our research continues to explore the impact of genes and environment from preconception through pregnancy and childhood in recognition of the interrelated nature of health and disease across the lifespan. In 2012, the Division successfully completed enrollment for two large population studies: 1) the Upstate KIDS Study, which is an observational prospective birth cohort study; and 2) the Effects of Aspirin in Gestation and Reproduction (EAGeR) Study, which is a randomized trial assessing the efficacy of low dose aspirin for the prevention of miscarriage. Investigators are actively analyzing data from these studies and hope to have answers about the effect(s) of infertility and its treatment on children's growth and development through three years of age, and in determining the potential effect of low dose aspirin in preventing miscarriage, respectively. During this past year, Division scientists gave numerous scientific presentations to varied audiences and published over 100 scientific papers. Of note is the utilization of the Division's research findings for public dissemination such as in the trademarking of the Checkpoint Young Drivers™, a body of research aimed at reducing car crashes amongst teen drivers. Division scientists remain committed to the translation of our findings to ensure that populations have up-to-date information for maximizing their well-being.

Our mission also includes mentoring and professional service. In 2012, the Division mentored 11 postdoctoral fellows, 3 predoctoral fellows, 7 postbaccalaureate fellows, 1 technical fellow, 7 visiting fellows, and 9 summer interns representing 28 academic institutions. In addition, the Division hosted three clinical fellows to further develop their research skills. All fellows are integral members of our research teams and also help to co-mentor summer interns. Our postdoctoral fellows are regularly recruitment targets for tenure track positions across academe and government, as well as for other research positions. Division scientists have been committed to the highly successful NICHD-CIHR Summer Institute in Reproductive and Perinatal Epidemiology, which recently completed its eighth year after having mentored and trained 157 graduate students representing 14 countries and 73 academic institutions.

Division scientists are active members of their professions serving on editorial boards and as elected officers of professional societies, as well as serving as experts for numerous scientific advisory boards and panels. Such service includes The National Academies, the National Institutes of Health, the Centers for Disease Control and Prevention, the U.S. Environmental Protection Agency, the Transportation Research Board, and other private and public institutions and foundations.

Without exception, the Division remains committed to improving the health and well being of populations. We remain good stewards of the resources offered by the NIH intramural community, as we seek novel ways to conduct research and translate important findings to populations across the globe. Our research benefits from our collaborations with other

intramural and extramural NIH scientists, as well as our colleagues at the 17 academic institutions with whom we have had research and development contracts in 2012. We are appreciative of the support we receive from our Institute's Director, Dr. Alan E. Guttmacher, and Scientific Director, Dr. Constantine A. Stratakis. The Division welcomes comments and opportunities for collaborations (comments: louisg@mail.nih.gov).

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

Office of the Director

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


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

The Division *of* Epidemiology, Statistics *and* Prevention Research comprises the Office of the Director and three research Branches - Epidemiology Branch, Biostatistics and Bioinformatics Branch and Prevention Research Branch – and the Computer Sciences Section. In keeping with the Intramural mission of the National Institutes of Health, the Division conducts innovative population health research, trains and mentors professional and graduate students, and provides professional service for governmental agencies, professional societies and other entities. The Office of the Director provides administrative, computing, programming, and research support for all population scientists and mentees. In addition, Dr. Buck Louis maintains an active research program focusing on environmental influences on human reproduction and development.

In 2012, The Division comprised approximately 31 scientific and support positions and a comparable number of fellows. A more complete description of Branch investigators is provided in their individual reports.

Staff

- Germaine M. Buck Louis, Ph.D., M.S., *Senior Investigator & Director*
- Kaye Beall, *Program Analyst*
- Adrienne Lonaberger, *Program Analyst*
- Patricia Moyer, *Computing Specialist*
- Ann Trumble, Ph.D., *Computing Specialist*
- Jennifer Weck, Ph.D., *Laboratory Health Specialist*

Awards

- Germaine Buck Louis, NICHD Merit Award, 2012.

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 adversely impact reproduction and development, and to identify population level interventions. The ultimate goal of our research is to prevent the occurrence of adverse reproductive or developmental outcomes in populations.

Recently, three creative epidemiologic studies have been successfully conducted. Each of these studies is unique and has generated some of the first empirical data regarding the environmental determinants of reproduction. Two of these studies – the LIFE Study and the ENDO Study – were original research initiatives designed by Division investigators, while the Oxford Conception Study was a collaborative investigation under the leadership of Dr. Cecila Pyper, Oxford University.

Longitudinal Investigation of Fertility and the Environment (LIFE Study)

The overarching 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 (LIFE Study). A spectrum of reproductive endpoints have been captured in the LIFE Study, allowing for eventual study of 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 and urine samples were taken to quantify 3 heavy metals (cadmium, lead, mercury); 9 organochlorine pesticides (OCPs); 7 perfluorochemicals (PFCs), 1 polybrominated biphenyls, 10 polybrominated diphenyl ethers (PBDEs), 36 polychlorinated biphenyls (PCBs), and 7 perfluorchemicals (PFCs). 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.

Following publication of the study design and methods paper in 2011, two substantive papers were published in 2012. In our first paper, blood cadmium (μg/L), lead (μg/dL) and mercury (μg/L) concentrations in each partner were analyzed in relation to couple fecundity as measured by time-to-pregnancy (Buck Louis et al., 2012). Female cadmium concentrations were associated with fecundability odds ratios (FORs) below one indicative of a longer time to pregnancy (0.78; 95% CI 0.63–0.97), as was male lead concentration (0.85; 95% CI 0.73–0.98). When jointly modeling couples' exposures, only male blood lead concentration significantly reduced the FOR (0.82; 95% CI 0.68, 0.97), though the FOR remained <1 for female cadmium (0.80; 95% CI 0.64, 1.00). These are the first finding based upon prospective cohort designs that suggest the potential reproductive toxicity of cadmium and lead at environmentally relevant concentrations.

A second paper reported a reduction in fecundability per 1-standard deviation increase in chemical concentration for a number of persistent chemicals (Buck Louis et al. 2012). Reductions in fecundability ranged between 18%-21% for female PCB congeners #118, 167, 209 and perfluorooctane sulfonamide, along with a reduction ranging between 17%-29% for male *p,p'*-DDE, PCB congeners #138, 156, 157, 167, 170, and 172. The strongest associations were observed for female PCB #167 (FOR 0.79; 95% CI 0.64, 0.97) and male PCB #138 (FOR=0.71; 95% CI 0.52, 0.98). Of note is that the magnitude of effect for select chemicals and couple fecundity is within the range reported for age and cigarette smoking.

Collaborators

- Dr. Germaine M. Buck Louis, NICHD, Principal Investigator
- Dr. Dana Barr, Emory University (formerly at the CDC)
- Dr. Zhen Chen, DESPR, NICHD
- Dr. Robert Gore-Langton, EMMES Corporation
- Dr. Kurunthachalam Kannan, Wadsworth Center
- Dr. Sungduk Kim, DESPR, NICHD
- Dr. Courtney Lynch, Ohio State University, College of Medicine
- Dr. Patrick Parsons, Wadsworth Center
- Dr. Enrique Schisterman, DESPR, NICHD
- Dr. Steven Schrader, NIOSH
- Dr. Rajeshwari Sundaram, DESPR, NICHD
- Dr. Anne Sweeney, Texas A & M University, Rural School of Public Health

2012 Publications

1. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Chen Z, Kim S, Caldwell K, Boyd Barr D. *Heavy metals and couple fecundity, the LIFE Study*. Chemosphere 87:1201-1207, 2012.

2. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Maisog J, Kim S, Chen Z, Barr DB. *Persistent environmental pollutant and couple fecundity, the LIFE Study*. Environmental Health Perspectives 2012; Nov 14 online.

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

Endometriosis is a gynecologic disorder affecting menstruating women resulting in the implantation of endometrial glands and stroma outside the uterine cavity. The etiology of endometriosis is unknown, but increasing evidence suggests that environmental chemicals may play an important role. Moreover, recent findings suggest that women with endometriosis may be at increased risk of reproductive site cancers and autoimmune disorders than unaffected women, underscoring the interrelatedness between gynecologic disorders and later onset disease. The overarching 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 (ENDO Study). 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 for the diagnosis of endometriosis. Blood and urine samples were collected for the quantification of bisphenol A (BPA), metals, organochlorine pesticides (OCPs), phthalates, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and perfluorchemicals (PFCs). A proteomic follow on study with the operative cohort (n=63) at the UCSF site also was completed in 2012 to explore fat, peritoneal and urine proteomes that may be informative for endometriosis status.

Several key research findings following the publication of the baseline ENDO Study paper in 2011 were published in 2012. With regard to persistent lipophilic chemicals, we found that the pesticide hexachlorocyclohexane (HCH) was significantly associated with an increased odds of an endometriosis diagnosis per 1-standard deviation increase in the log-transformed concentration in both cohorts, though different HCH isomers emerged (Buck Louis et al., 2012). Specifically, γ-HCH in fat increased the odds (1.27; 95% CI 1.01, 1.59) in the operative cohort, while serum β-HCH was associated with an increased the odds in the population cohort (1.72; 95% CI 1.09, 2.72). Our findings were largely robust in the many sensitivity analyses performed to aid interpretation. These findings underscore the importance of cohort- and biologic medium-specific effects when interpreting results. An increased odds of an endometriosis diagnosis in the operative cohort was observed for one of five measured BP derivatives, viz., 2,4OH-BP (AOR=1.19; 95% CI 1.01, 1.41; Kunisue et al., 2012), and also for perfluorooctanoate (PFOA, AOR=1.89; 95% CI 1.17, 3.06) and perfluorononanonoate (PFNA, AOR=2.20; 95% CI 1.02, 4.75; Buck Louis et al., 2012).

Other findings from the ENDO Study beyond chemicals include evidence that self reported body size and shape is consistent with anthropometric measurements (Thoma et al., 2012), and that the diagnosis of endometriosis within and across surgeons was good (κ=0.69; 95% CI 0.64, 0.74)

and moderately good for disease severity (κ=0.44; 95% CI 0.41, 0.47; Schliep et al., 2012). Research continues to focus on short lived chemicals (BPA and phthalates) and endometriosis, and will culminate in the analysis of chemical mixtures.

Collaborators

- Dr. Germaine M. Buck Louis, NICHD – Principal Investigator
- Dr. Zhen Chen, DESPR, NICHD
- Dr. Mary Croughan, UCSF
- Dr. Victor Fujimoto, UCSF
- Dr. Linda Giudice, UCSF
- Dr. Mary Hediger, DESPR, NICHD
- Dr. K. Kannan, Wadsworth Center, NYSDOH
- Dr. C. Matthew Peterson, University of Utah
- Dr. Patrick Parsons, Wadsworth Center, NYSDOH
- Dr. Karen Schliep, DESPR, NICHD
- Dr. Joseph Stanford, University of Utah
- Dr. Rajeshwari Sundaram, DESPR, NICHD
- Dr. Marie Thoma, NICHD
- Dr. Michael Warner, University of Utah

2012 Publications

1. Buck Louis GM, Chen Z, Peterson CM, Hediger ML, Croughan MS, Sundaram R, Stanford JB, Varner MW, Fujimoto VY, Giudice LC, Trumble A, Parsons PJ, Kannan K. *Persistent lipophilic environmental chemicals and endometriosis: The ENDO Study, 2007-2009*. Environmental Health Perspectives 120:811-816, 2012.

2. Kunisue T, Chen Z, Buck Louis GM, Sundaram R, Hediger ML, Sun L, Kannan K. *Urinary concentrations of benzophenone-type UV filters and endometriosis, the ENDO Study.* Environmental Science and Technology 46:4624-4632, 2012.

3. Schliep KC, Stanford JB, Zhang B, Chen Z, Dorais JK, Johnstone EB, Hammoud AO, Varner MW, Buck Louis GM. *Inter- and intra-reliability in the diagnosis and staging of endometriosis: the ENDO Study.* Obstetrics and Gynecology 120:104-112, 2012.

4. Buck Louis GM, Peterson MC, Chen Z, Hediger ML, Croughan MS, Sundaram R, Stanford JB, Fujimoto V, Varner MB, Giudice, LC, Kennedy A, Sun L, Parsons P, Kannan K. *Perflurochemicals and Endometriosis: The ENDO Study*. Epidemiology 23:799-805, 2012.

5. Thoma M, Hediger M, Sundaram R, Stanford J, Peterson CM, Croughan M, Chen Z, Buck Louis GM. *Comparing "Apples and Pears": How well do women perceive their body size and shape?* Journal of Women's Health 21:1074-1081, 2012.

6. Wolff EF, Hediger ML, Sundaram R, Peterson CM, Chen Z, Buck Louis GM. *In utero exposures and endometriosis, the ENDO Study*. Fertility and Sterility 2012; Dec 1 online.

Stress and Time-to-Pregnancy, Oxford Conception Study

Stress has long been suspected to impact women's ability to conceive or carry a pregnancy to term. However, no prospective longitudinal cohort research has been done. In collaboration with colleagues at Oxford University, we developed a novel protocol to measure two biomarkers of stress in relation to time-to-pregnancy, pregnancy loss and secondary sex ratios. We enrolled 410 women who were participating in the Oxford Conception Study to collect basal saliva samples on day 6 of each menstrual cycle they were attempting pregnancy for the quantification of salivary alpha amylase and cortisol concentrations. These biomarkers were chosen as measures of the hypothalamic pituitary adrenal axis and sympathetic adrenomedullary system, respectively. In 2011, we reported a 12% reduction in fecundity each day during the estimated fertile window for women in the highest quartile of alpha amylase relative to women in the lowest, with no association for cortisol and time-to-pregnancy (Buck Louis et al., 2011). In our second paper, no association was observed between perceived psychosocial measures of stress and fecundability odds ratios or the day specific probabilities of pregnancy (Lynch et al., 2012). However, we did observe a reduced odds of a male birth for women in the 3rd (AOR=0.31; 95% CI 0.11, 0.93) and 4th (AOR=0.25; 95% CI 0.08, 0.74) quartiles of alpha amylase relative to women in the 1st quartile (Chason et al., 2012). This unique database was used to develop flexible Bayesian and joint models models for estimating human fecundity led by our statistical colleagues (Kim et al., 2012; McLain et al., 2012).

Collaborators

- Dr. Germaine Buck Louis, NICHD - Principal Investigator
- Dr. Rebecca Chason, DIR, NICHD
- Dr. Sungduk Kim, NICHD
- Dr. Courtney Lynch, Ohio State University
- Dr. Alexander McLain, University of South Carolina - Columbia
- Dr. Cecilia Pyper, Oxford University – Principal Investigator Oxford Conception Study
- Dr. Rajeshwari Sundaram, NICHD

2012 Publications

1. Lynch CD, Sundaram R, Buck Louis GM, Lum KJ, Pyper C. *Are increased levels of self-reported psychosocial stress, anxiety and depression associated with fecundity?* Fertility and Sterility 98:453-458, 2012.

2. Kim S, Sundaram R, Buck Louis GM, Pyper C. *Flexible Bayesian human fecundity models.* Bayesian Analysis 7:771-800, 2012.

3. Chason R, McLain A, Sundaram R, Chen Z, Segars JH, Pyper C, Buck Louis GM. *Preconception stress and the secondary sex ratio: A prospective cohort study*. Fertility and Sterility 98:937-941, 2012.

4. McLain AC, Lum K, Sundaram R. *A joint mixed effects dispersion model for menstrual cycle length and time-to-pregnancy*. Biometrics 68:648-656, 2012.

Biostatistics & Bioinformatics Branch

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


Paul Albert, Ph.D.

The mission of the Biostatistics and Bioinformatics Branch (BBB) is to: 1) conduct both collaborative and methodological research that is important to the mission of the Division and Institute, 2) provide 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 2012 has been on statistical modeling of time-to-pregnancy, which poses new analytic challenges since, unlike with traditional survival analysis, it must account for the fact that there is no risk of pregnancy without intercourse during a particular window in time.

BBB investigators have developed new statistical methods for analyzing biomarker data. For example, in 2012 we have developed optimal pooling strategies for reducing the expense of assay measurements in longitudinal studies and supervised latent-class models for examining the effects of a large number of biomarkers on the incidence of disease. BBB investigators have developed new methodology for assessing agreement from longitudinally collected ratings and scores. In addition to assessing agreement, BBB investigators have new approaches for assessing the accuracy of ratings or tests when no gold standard test is available.

During 2012, BBB investigators have developed new statistical methodology for analyzing quantitative traits when the outcomes are longitudinal and have developed entropy-based methods for detecting gene-gene and gene-environmental interactions of complex diseases.

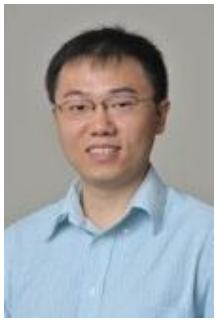
Staff

- 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*
- Sundaram Rajeshwari, Ph.D., *Investigator*
- SungDuk Kim, Ph.D., *Staff Scientist*
- Yunlong Xie, Ph.D., *Postdoctoral Fellow*
- Kirsten J. Lum, M.S., *Predoctoral Fellow*
- Kara Fulton, B.S., *Postbaccalaureate Fellow*

Awards and Accomplishments

- Aiyi Liu, Ph.D., Elected Fellow of the American Statistical Association, 2012

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 Longitudinal Investigation of Fertility and the Environment (LIFE) Study as well as to the NICHD Fetal Growth Study; 2) characterizing longitudinal menstrual cycle and circadian rhythm patterns in longitudinal data with applications to the BioCycle Study and the NEXT Study, 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.

2012 Publications

1. Albert PS. *A linear mixed model for predicting a binary event under random effects misspecification*. Statistics in Medicine 31(2):143-54, 2012.

2. Bhadra D, Daniels M J, Kim SD, Ghosh M, Mukherjee B. *A Bayesian semiparametric approach for incorporating longitudinal information on exposure history for inference in case-control studies.* Biometrics 68:361-370, 2012.

3. Cheon K, Albert PS, Zhang Z. *The impact of random effect misspecification on percentile estimation for longitudinal growth data*. Statistics in Medicine 31:3708-3718, 2012.

4. Malinovsky Y, Albert PS, Schisterman EF. *Pooling designs for outcomes under a Gaussian random effects distribution.* Biometrics 68:45-52, 2012.

5. Ogbagaber S, Albert PS, Lewin D, Iannotti R. *Summer activity patterns among teenage girls: Harmonic shape invariant modeling to estimate circadian cycles*. Journal of Circadian Rhythms 10(1):2, 2012.

6. Roy A, Danaher M, Mumford S, Chen Z. *A Bayesian order restricted model for hormonal dynamics during biocycles in healthy women*. Statistics in Medicine 31:2428-2840, 2012.

7. Wu MX, Yu KF, Liu A, Ma TF. *Simultaneous optimal estimation in linear mixed effects models*. Metrika 75:471–489, 2012.

8. Zhang Z, Albert PS, Simons-Morton B. *Marginal analysis of longitudinal count data in long sequences: methods and applications to a driving study*. Annals of Applied Statistics 6:27-54, 2012.

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

10. 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: Series C (In press).

11. 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).

12. Sun W, McLain AC. *Multiple testing of composite null hypotheses in heteroscedastic models.* Journal of the American Statistical Association, Theory and Methods (In press).

13. Zhang B, Chen Z, Albert PS. *Estimating diagnostic accuracy of raters without a gold standard by exploiting a group of experts.* Biometrics (In press).

14. Zhang Z, Chen Z, Troendle J, Zhang J. *Causal inference on quantiles with application to safe labor*. Biometrics (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 pre-term birth due to preeclampsia) and modeling the gap times between pregnancies.

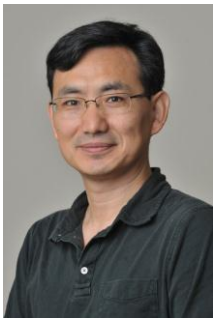
2012 Publications

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).

2. Sundaram R, McLain A, Louis Buck G. *A survival analysis approach to modeling human fecundity*. Biostatistics 13:4-17, 2012.

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 when there is no gold standard test available. Many of the methods developed for assessing agreement and diagnostic accuracy were developed from collaborative research in the Endometriosis: National History, Diagnosis, and Outcome (ENDO) Study, which is focused on comparing and evaluating different measures for diagnosing endometriosis in the absence of a gold standard.

2012 Publications

1. Albert PS, Schisterman EF. *Novel Statistical methodology for analyzing longitudinal biomarker data*. Statistics in Medicine 31:2457-2460, 2012.

2. Buck Louis GM, Sundaram R. *Exposome: time for transformative research: invited commentary.* Statistics in Medicine 31:2569-2575, 2012.

3. Liu A, Liu C, Zhang Z, Albert PS. *Optimality of group testing in the presence of misclassification*. Biometrika 99: 245-251, 2012.

4. Malinovsky Y, Albert PS, Schisterman EF*. Pooling designs for outcomes under a Gaussian random effects distribution*. Biometrics 68:45-52, 2012.

5. Roy A, Danaher M, Mumford S, Chen Z. *A Bayesian order restricted model for hormonal dynamics during biocycles in healthy women*. Statistics in Medicine 31:2428-2840, 2012.

6. Schisterman EF, Albert PS. *The biomarker revolution.* Statistics in Medicine 31:2565-2568, 2012.

7. Tang LL, Liu A, Schisterman EF, Zhou X, Liu CL. *Homogeneity tests of clustered diagnostic markers with applications to the BioCycle Study*. Statistics in Medicine 31:3638-3648, 2012.

8. Zhang B, Chen Z, Albert PS*. A supervised latent class model for high dimensional biomarker data*. Biostatistics 13:74-88, 2012.

9. Zhang Z, Albert PS, Simons-Morton B. *Marginal analysis of longitudinal count data in long sequences: methods and applications to a driving study*. Annals of Applied Statistics 6:27-54, 2012.

10. Zhang Z, Liu A, Lyles RH, Mukherjee B*. Logistic regression analysis of biomarker data subject to pooling and dichotomization*. Statistics in Medicine 31:2485-2497, 2012.

11. Jin M, Liu, A, Chen Z, Li ZH. *Group sequential design in inter-rater reliability study*. Statitica Sinica (In press).

12. Sun W, McClain AC. *Multiple testing of composite null hypotheses in herteroscedastic models*. Journal of the American Statistical Association, Theory and Methods (In press).

13. Tang LL, Liu A, Chen Z, Schisterman, EF, Zhang B, Miao Z. *Nonparametric ROC summary statistics for diagnostic marker data*. Statistics in Medicine (In press).

14. Zhang B, Chen Z, Albert PS. *Estimating diagnostic accuracy of raters without a gold standard by exploiting a group of experts*. Biometrics (In press).

15. Zhang Z, Chen Z, Troendle J, Zhang J. *Causal inference on quantiles with application to safe labor*. Biometrics (In press).

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 that are being addressed by BBB investigators. BBB investigators are also developing new methodology for analyzing quantities and qualitative traits when the outcomes are longitudinal and developing entropy-based methods for detecting gene-gene and gene-environmental interactions of complex diseases. Of particular interest in the Division is accounting for measurement error in environmental exposures. BBB investigators have developed methodology for estimating gene-environment interactions in the presence of measurement error in the environmental factors.

2012 Publications

1. Danaher MR, Schisterman EF, Roy A, Albert PS. *Estimation of gene-environment interaction by pooling biospecimens*. Statistics in Medicine 31:3241-3252, 2012.

2. Fan R, Albert PS, Schisterman. *A discussion of gene-gene environment interaction and longitudinal genetic analysis of complex traits*. Statistics in Medicine 31:2565-2568, 2012.

3. Fan R, Zhang Y, Albert PS, Liu A, Wang Y, Xiong, M. *Longitudinal genetic analysis of quantitative traits.* Genetic Epidemiology 36:856-869, 2012.

Collaborative Research

BBB investigators are essential members of the research team on all major projects in the Epidemiology Branch (EB) and Prevention Research Branch (PRB), with a primary and a

secondary statistical investigator being on most projects. The 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 IRB, the NIH Biometry and Epidemiology Tenure Committee, and numerous NIH DSMBs.

2012 Publications

1. Bobe G, Murphy G, Albert PS, Sansbury LB, Lanza E, Schatzkin A, Cross AJ. *Dietary Lignan and proanthocyanidin consumption and colorectal adenoma recurrence in the Polyp Prevention Trial*. International Journal of Cancer 130:1649-1659, 2012.

2. Brown DA, Hance KW, Rogers CJ, Sansbury LB, Albert PS, Murphy G, Laiyemo A, Wang Z, Cross AJ, Schatzkin A, Danta M, Srasuebkul P, Amin J, Law M, Breit SN, Lanza E. *Serum macrophage inhibitory cytokine-1 (MIC-1jGDF15) for screening and prevention of colon cancer*. Cancer Epidemiology Prevention and Biomarkers 21:337-348, 2012.

3. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Chen Z, Kim S, Caldwell K, Barr DB. *Heavy Metals and Couple Fecundity, the LIFE Study*. Chemosphere 87:1201-1207, 2012.

4. Carter TC, Kay DM, Browne ML, Liu A, Romitti PA, Kuehn D, Conley MR, Caggana M, Druschel CM, Brody LC, Mills JM. *Hirschsprung's disease and variants in genes that regulate enteric neural crest cell proliferation, migration, and differentiation*. Journal of Human Genetics 57(8):485-93, 2012.

5. Hartman TJ, Mahabir S, Stevens RG, Albert PS, Dorgan JF, Kesner J, Meadows JS, Shields R, Taylor PR. *Moderate alcohol consumption and 24-hour urinary levels of melatonin in postmenopausal women*. Journal of Clinical Endocrinology and Metabolism 97:E65-68, 2012.

6. Kunisue T, Chen Z, Louis GMB, Sundaram R, Hediger ML, Sun L, Kannan K. *Urinary concentrations of benzophenone-type UV filters in the US women from two cities and their association with endometriosis*. Environmental Science and Technology 46:4624-4632, 2012.

7. Laughon SK, Zhang J, Grewal J, Sundaram R, Beaver J, Reddy U. *Induction of labor in contemporary obstetric practice*. American Journal of Obstetrics & Gynecology 206:486.e1-9, 2012.

8. Buck Louis GM, Chen Z, Peterson CM, Hediger ML, Croughan MS, Sundaram R, Stanford JB, Varner MW, Fujimoto VY, Giudice LY, Trumble A, Parsons PJ, Kannan K. *Persistent*

lipophilic environmental chemicals and endometriosis: The ENDO Study, 2007-2009. Environmental Health Perspectives 120:811-816, 2012.

9. Lynch CD, Sundaram R, Buck Louis GM, Lum KJ, Pyper C. *Are increased levels of self-reported psychosocial stress, anxiety, and depression associated with fecundity?* Fertility and Sterility 98:453-458, 2012.

10. Mechanic LE, Chen HS, Amos CI, Chatterjee N, Cox NJ, Divi RL, Fan R, Harris EL, Jacobs K, Kraft P, Leal SM, McAllister K, Moore JH, Paltoo DN, Province MA, Ramos EM, Ritchie MD, Roeder K, Schaid DJ, Stephens M, Thomas DC, Weinberg CR, Witte JS, Zhang S, Zöllner S, Feuer EJ, Gillanders EM. *Next generation analytic tools for large scale genetic epidemiology studies of complex diseases*. Genetic Epidemiology 36:22-35, 2012.

11. Mills JL, Carter TC, Kay DM, Browne ML, Brody LC, Liu A, Romitti PA, Caggana M, Druschel CM. *Folate and vitamin B12 related genes and risk for omphalocele*. Human Genetics 131:739–746, 2012.

12. Nansel TR, Iannotti RJ, Liu A*. Clinic-integrated behavioral intervention for families of youth with type 1 diabetes: A randomized clinical trial.* Pediatrics 129: 866-873, 2012.

13. Simons-Morton BG, Cheon K, Guo F, Albert P. *Trajectories of kinematic risky driving among novice teenagers*. Accident Analysis and Prevention 51:27-32, 2012.

14. Thoma M, Hediger M, Sundaram R, Stanford J, Peterson CM, Croughan M, Chen Z, Buck Louis GM. *Comparing "Apples and Pears": How well do women perceive their body size and shape?* Journal of Women's Health 21(10):1074-1081, 2012.

15. Winer KK, Zhang B, Shrader J, Peterson D, Sinaii N, Smith M, Albert PS, Cutler G. *Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism*. The Journal of Clinical Endocrinology & Metabolism 97:391-399, 2012.

16. Zhang J, Kim SD, Grewal U, Albert PS. *Predicting large fetuses at birth: Do multiple ultrasound examinations and longitudinal statistical modeling improve prediction?* Paediatric and Perinatal Epidemiology 26:199-207, 2012.

17. 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 (In press).

18. 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 (In press).

19. Erickson HS, Canales JR, Albert PS, Yala K, Mukherjee S, Hu N, Goldstein AM, Chuaqui RF, Hewitt SA, Taylor PR, Emmert O, Buck MR. *Interrogation of chromosome 13q12-14 esophageal squamous cell carcinoma.* The Open Pathology Journal (In press).

20. Buck Louis GM, Chen Z, Peterson CM, Hediger ML, Croughan MS, Sundaram R, Stanford JB, Varner MW, Fujimoto VY, Giudice LY, Trumble A, Parsons P J, Kannan K. *Perfluorochemicals and endometriosis: The ENDO Study.* Epidemiology 23:799-805, 2012.

21. 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*. The Journal of Clinical Endocrinology & Meta*bolism* (In press).

22. Mitchell JB, Anvers MR, Sowers AL, Rosenberg PS, Figueroa M, Thetford A, Albert PS, Cook JA. *The antioxidant tempol reduces carcinogenesis and enhances survival in mice when administered after non-lethal total body radiation.* Cancer Research (In press).

23. Schliep KC, Stanford JB, Zhang B, Chen Z, Dorals JK, Johnstone EB, Hammoud AO, Varner MW, Louis BG. *Inter- and intra-reliability in the diagnosis and staging of endometroiosis: the ENDO Study*. Obstetrics and Gynecology 120:104-112, 2012.

24. 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 Jan 3. doi: 10.1016/j.fertnstert.2012.11.037.

25. Wolff EF, Hediger ML, Sundaram R, Peterson CM, Chen Z, Buck Louis GM. *In utero exposures and endometriosis, the ENDO Study*. Fertility and Sterility 2012 Dec 1. doi: 10.1016/j.fertnstert.2012.11.013.

26. 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*. The International Journal of Obesity (In press).

27. Waldman TA, Colon KC, Steward DW, Worthy TA, Janik JE, Fleischer TA, Albert, PS, Figgg WD, Spencer SD, Decker JR, Goldman CK, Bryant BR, Petrus MN, Creekmore SP, 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 (In press).

Epidemiology Branch

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


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

The Epidemiology Branch's mission is threefold: 1) to plan and conduct investigator-initiated original epidemiologic research focusing on reproductive, perinatal, and pediatric health endpoints to identify etiologic mechanisms, at risk subgroups, and interventions aimed at maximizing health and preventing, diagnosing, and/or treating disease; 2) to provide service to the Division, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health (NIH), Department of Health and Human Services, and the profession via consultation, collaboration, and assistance to advance the scientific discipline of epidemiology and the goals of the Institute; and 3) to recruit highly qualified students 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 forward the Division and Institute's mission. The Branch conducts team science and is committed to using trans-disciplinary, cutting-edge science to address critical data gaps throughout the life course.

Staff

- Enrique F. Schisterman, Ph.D., M.A., *Senior Investigator and Chief*
- James L. Mills, M.D., M.S., *Senior Investigator*
- S. Katherine Laughon, M.D., M.S., *Investigator*
- Pauline Mendola, Ph.D., M.S., *Investigator*
- Sunni L. Mumford, Ph.D., M.P.H., *Investigator*
- Edwina H. Yeung, Ph.D., M.P.H., *Investigator*
- Cuilin Zhang, M.D., Ph.D., M.P.H., *Investigator*
- Jagteshwar (Una) Grewal, Ph.D., M.P.H., *Staff Scientist*
- Mary L. Hediger, Ph.D., *Deputy Director and Staff Scientist*
- Michele Kiely, Dr.P.H., *Staff Scientist*
- Neil J. Perkins , Ph.D., *Staff Scientist*
- Katherine A. Ahrens, Ph.D., M.P.H., *Postdoctoral 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*
- Stefanie Hinkle, Ph.D., *Postdoctoral Fellow*
- Tuija Mannisto, M.D., Ph.D., *Postdoctoral Fellow*
- Anna Z. Pollack, Ph.D., M.P.H., *Postdoctoral Fellow*
- Candace Robledo, Ph.D., M.P.H., *Postdoctoral Fellow*
- Lindsey A. Sjaarda, Ph.D., M.S., *Postdoctoral Fellow*

- Karen C. Schliep, Ph.D., M.S.P.H., *Postdoctoral Fellow*
- Marie Thoma, Ph.D., M.S., *Postdoctoral Fellow*
- Kerri Kissell, M.D., *Clinical Fellow*
- Ankita Prasad, B.A., *Postbaccalaureate Fellow*
- Devon Kuehn, M.D.**,** *Special Volunteer*
- Shannon Rigler, M.D., *Special Volunteer*

Awards and Accomplishments, 2012

- Mary L. Hediger, Ph.D., ***Deputy Director and Staff Scientist***, NICHD Merit Award
- Devon Kuehn, M.D., ***Special Volunteer,*** Southern Society for Pediatric Research Young Investigator's Award
- Michelle Danaher, M.S., *Predoctoral Fellow,* International Biometric Society's Eastern North American Region Distinguished Student Paper Award
- Enrique F. Schisterman Ph.D., *Senior Investigator and Chief,* NICHD Mentoring Award
- Sunni L. Mumford, Ph.D., *Investigator*, Earl Stadtman Tenure Track Investigator

Reproductive Epidemiology

Reproductive Epidemiology specifically investigates the various factors that affect both male and female reproductive health, and the processes that affect conception, reproduction, and infertility. The Epidemiology Branch has several key studies in this area: the BioCycle Study, the Effect of Aspirin in Gestation and Reproduction (EAGeR) Study, and the Folic Acid and Zinc Supplementation Trial (FAZST) Trial. 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

BioCycle

Principal Investigator: Enrique F. Schisterman, Ph.D.

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

Division Collaborators:

- Paul S. Albert, Ph.D.
- Katherine Ahrens, Ph.D., M.P.H.
- Michelle Danaher, Ph.D., M.S.
- Kerri Kissell, M.D.
- Pauline Mendola, Ph.D., M.P.H.
- Sunni L. Mumford, Ph.D., M.P.H.
- Neil J. Perkins , Ph.D.
- Anna Z. Pollack, Ph.D., M.P.H.
- Ankita Prasad, B.A.

- Karen C. Schliep, Ph.D., M.S.P.H.
- Edwina H. Yeung, Ph.D., M.P.H.
- 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 251 women aged 18 to 40 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 dianes, as well as fasting glucose, total cholesterol and serum antioxidant vitamins. At each of the 16 clinic visits, we prospectively collected data on diet, physical activity and other environmental exposures.

Since completion of the study much progress has been made in the analysis of the BioCycle Study data. With regards to the main question under study, we found a significant positive association between F2-Isoprostanes (a marker of oxidative stress) and estrogen which calls into question the hypothesis of estrogen serving as an antioxidant. We have also shown that metabolic markers such as oxidative stress, lipoprotein cholesterol, inflammation, glucose metabolism, 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. The hypothesized cardioprotective effects of estrogen in premenopausal women may actually be partially explained by hormonal variability. While the best time to measure biomarkers during a woman's cycle has yet to be established, measurements should be made during the same cycle phase for consistent comparisons. Further, biomarker variability was observed among healthy women, and it is possible that other populations have even greater variability. These findings have implications for clinical practice (i.e., doctor visits should be timed to menstrual cycle phase) and for study designs among women of reproductive age.

2012 Publications

1. Gaskins AJ, Mumford SL, Wactawski-Wende, Schisterman EF. *Effect of daily fiber intake on luteinizing hormone levels in reproductive-aged women*. European Journal of Nutrition 51(2):249-53, 2012.

2. Gaskins AJ, Wilchesky M, Mumford SL, Wactawski-Wende J, Perkins NJ, Schisterman EF. *Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle study*. American Journal of Epidemiology 175(5): 423-31, 2012.

3. Dasharathy S, Mumford SL, Pollack AZ, Perkins NJ, Mattison D, Wactawski-Wende J, Schisterman EF. *Menstrual bleeding patterns among regularly menstruating women*. American Journal of Epidemiology 175(6): 536-45, 2012.

4. Pollack AZ, Schisterman EF, Goldman LR, Mumford SL, Wactawski-Wende J. *Relation of blood cadmium, lead, and mercury levels to biomarkers of lipid peroxidation in premenopausal women*. American Journal of Epidemiology 175(7):645-52, 2012.

5. Schliep K, Schisterman EF, Mumford SL, Pollack AZ, Zhang C, Ye A, Stanford JB, Hommoud AO, Porucznik CA, Wactawski-Wende J. *Caffeinated beverage intake and reproductive hormones among premenopausal women in the BioCycle Study*. American Journal of Clinical Nutrition 95(2):488-97, 2012.

6. Zhang B, Shen X, Mumford SL. *Generalized degrees of freedom and adaptive model selection in linear mixed-effects models.* Computational Statistics and Data Analysis 56(3):574-86, 2012.

7. Gaskins AJ, Mumford SL, Chavarro J, Zhang C, Pollack AZ, Wactawski-Wende J, Perkins NJ, Schisterman EF. *The impact of dietary folate intake on reproductive function in premenopausal women: a prospective cohort study*. Public Library of Science ONE 7(9):e46276, 2012.

8. Tang LL, Liu A, Schisterman EF, Zhou XH, Liu CC. *Homogeneity tests of clustered diagnostic markers with applications to the BioCycle Study*. Statistics in Medicine 31(28):3638-48, 2012.

9. Yeung EH, Zhang C, Albert PS, Ye A, Mumford SL, Perkins NJ, Hediger ML, Wactawski-Wende J, Schisterman EF. *Adiposity and sex hormones across the menstrual cycle: the BioCycle Study*. International Journal of Obesity (In press).

10. Roy A, Danaher MR, Chen Z, Mumford SL, Schisterman EF. *A Bayesian order restricted model for hormonal dynamics during menstrual cycles of healthy women*. Statistics in Medicine (In press).

11. Schildcrout JS, Mumford SL, Chen Z, Heagerty PJ, Rathouz PJ. *Outcome dependent sampling for longitudinal binary response data based on a time-varying auxiliary biomarker*. Statistics in Medicine (In press).

12. 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 (In press).

13. Schliep KC, Schisterman EF, Mumford SL, Perkins NJ, Ye A, Pollack AZ, Zhang C, Porucznik CA, VanDerslice JA, Stanford JB, Wactawski-Wende J. *Caffeine validation using different instruments in the BioCycle Study*. American Journal of Epidemiology (In press).

14. Danaher MR, Roy A, Chen Z, Mumford SL, Schisterman EF. *Minkowski-Weyl Priors for models with parameter constraints: An analysis of the BioCycle Study*. Journal of the American Statistical Association (In press).

15. Mumford SL, Steiner AZ, Pollack AZ, Perkins NJ, Filiberto AC, Albert P, Mattison DR, Wactawski-Wende J, Schisterman EF. *The utility of menstrual cycle length as an indicator of cumulative hormonal exposure*. The Journal of Clinical Endocrinology & Metabolism (In press).

16. 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 (In press).

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

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

Division Collaborators:

- Paul S. Albert, Ph.D.
- Katherine Ahrens, Ph.D., M.P.H.
- Michelle Danaher, Ph.D., M.S.
- Kerri Kissell, M.D.
- S. Katherine Laughon, M.D., M.S.
- Sunni L. Mumford , Ph.D., M.S.
- Pauline Mendola, Ph.D., M.S.
- Neil J. Perkins , Ph.D.
- Ankita Prasad, B.A.
- Karen Schliep, Ph.D. , M.S.P.H.
- Edwina Yeung, Ph.D., M.P.H.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

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

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

The EAGeR Trial is a multi-site prospective double-blind trial designed to assess the effects of low-dose aspirin on 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/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 what was referred to as active follow-up for two menstrual cycles. In this phase, women kept daily diaries and visited the clinic four times, where they filled out questionnaires and provided blood samples, in addition to daily urine samples. After this, they 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 four weeks post-conception and passively through parturition. Pregnancy loss, pregnancy complications, and perinatal outcomes were monitored throughout pregnancy. Trial recruitment began June 15, 2007, and ended in July 2011, with the last screening done on July 14, 2011, and the last randomization on July 15, 2011. Follow-up has been completed as of September 2012 and results of the trial are pending.

Perinatal Epidemiology

Perinatal epidemiologic research focuses on parturient women and their pregnancy outcomes. There are several studies in the Epidemiology Branch that fall into the category of perinatal epidemiology, such as the: 1) Consortium on Safe Labor; 2) Diabetes and Women's Health (DWH) Study; 3) Gestational Diabetes Mellitus: Epidemiology, Etiology and Health Consequences; and the 4) NICHD Fetal Growth Studies. A brief description of each study follows.

Consortium on Safe Labor

Principal Investigators:

- Jagteshwar (Una) Grewal, Ph.D., M.P.H.
- S. Katherine Laughon, M.D., M.S.

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

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

Division Collaborators:

- Zhen Chen, Ph.D.
- Stefanie Hinkle, Ph.D.
- Tuija Mannisto M.D., Ph.D.
- Pauline Mendola, Ph.D., M.S.
- Yunlong Xie, Ph.D.
- Cuilin Zhang M.D., Ph.D., M.P.H.

Pauline Mendola, Ph.D. M.S.

The Consortium on Safe Labor (CSL) was a multicenter retrospective observational study of 228,562 deliveries at 12 clinical centers across the U.S. The CSL team identified several key findings regarding contemporary clinical obstetrical management. These include: 1) identification of factors contributing to the high 33% U.S. cesarean delivery rate (viz., a high percentage of intrapartum cesarean deliveries being performed too soon or before women achieved active labor and that a prior history of a cesarean delivery accounted for most repeat cesarean sections); 2) labor patterns are longer now than approximately 50 years ago; and 3) 7% of neonates delivered late preterm or at 34 – 36 weeks of gestation were either elective or delivered based on clinical judgment instead of "hard" indications. The implications of these findings are that preventing cesarean delivery is especially important in the first pregnancy. Since providers are using definitions of abnormal labor developed in a population of women different from the contemporary obstetrical population, the CSL findings suggest that routine interventions such as the use of oxytocin and timing of cesarean delivery as well as modern-day labor process management warrant reconsideration. Collectively, this body of research is providing data to develop clinical guidance regarding the management of contemporary parturient women based upon empirically supported guidance.

In addition to multiple studies being published in high impact journals, few studies have been the focus of two NICHD Research Perspectives monthly podcast series hosted by the NICHD Director.

2012 Publications:

1. Reddy UM, Zhang J, Sun L, Chen Z, Raju TNK, Laughon SK. *Neonatal mortality by attempted route of delivery in early preterm birth*. American Journal of Obstetrics & Gynecology 207(117):1-8, 2012.

2. Laughon SK, Zhang J, Grewal J, Sundaram R, Beaver J, Reddy UM. *Induction of labor in contemporary obstetrical practice*. American Journal of Obstetrics & Gynecology 206(486):1-9, 2012.

3. Laughon SK, Branch DW, Beaver J, Zhang J. *Changes in labor patterns over 50 years*. American Journal of Obstetrics & Gynecology 206:419.e1-9, 2012.

4. Zhang Z, Chen Z, Troendle JF, Zhang J. *Causal Inference on quantiles with an obstetric application*. Biometrics 68(3):697-706, 2012.

5. 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 (In press).

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

Principal Investigator: Cuilin Zhang M.D., Ph.D, M.P.H.

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

Division Collaborators:

- Paul Albert, Ph.D.
- Wei Bao, M.D., Ph.D.
- Ruzong Fan, Ph.D.
- Michele Kiely, Dr.P.H.
- Aiyi Liu, Ph.D.
- Germaine Buck Louis, Ph.D., M.S.
- James L. Mills, M.D., M.S.
- Enrique F. Schisterman, Ph.D., M.A.
- Edwina Yeung, Ph.D., M.P.H.

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 2015.

2012 Publications:

1. Tobias DK**,** Hu FB, Chavarro J, Rosner B, Mozaffarian, Zhang C. *Healthful dietary patterns and type 2 diabetes risk among women at high risk*. Archives of Internal Medicine 2012; Sept 17 online.

Gestational Diabetes Mellitus - Epidemiology, Etiology, and Health Consequences

Principal Investigator: Cuilin Zhang M.D., Ph.D.

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

DESPR Collaborators:

- Wei Bao, M.D., Ph.D.
- Jagteshwar (Una) Grewal, Ph.D., M.P.H.
- Enrique F. Schisterman, Ph.D., M.A.
- Edwina Yeung, Ph.D., M.P.H.

Gestational diabetes mellitus (GDM), one of the most common complications of pregnancy, is related to substantial short-term and long-term adverse health outcomes for both women and their offspring. Understanding the epidemiology and etiology of GDM is critical for the development of effective and targeted intervention strategies to prevent GDM and to interrupt the vicious cycle across generations involving maternal GDM, childhood obesity 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 Nurses' Health Study II.

- Investigation of the pathogenesis of GDM using prospectively and longitudinally collected biospecimens from pregnancy cohorts, such as the NICHD Fetal Growth Studies and the EAGeR Study. 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.

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

2012 Publications

1. Bowers K, Tobias DK, Yeung E, Hu FB, Zhang C. *A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes*. American Journal of Clinical Nutrition 95(2):446-453, 2012.
2. Chen L, Hu FB, Yeung E, Tobias DK, Willett WC, Zhang C. *Prepregnancy consumption of fruits and fruit juices and the risk of gestational diabetes mellitus: a prospective cohort study*. Diabetes Care 35(5):1079-1082, 2012.
3. Tobias DK, Zhang C, Chavarro J, Bowers K, Rich-Edwards J, Rosner B, Mozaffarian D, Hu FB. *Prepregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus*. American Journal of Clinical Nutrition 96(2):289-295, 2012.

NICHD Fetal Growth Study

Principal Investigator: Germaine M. Buck Louis, Ph.D., M.S.

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

Division Collaborators:

- Paul S. Albert, Ph.D.
- Jagteshwar (Una) Grewal, Ph.D., M.P.H.
- Mary L. Hediger, Ph.D.
- Sung Duk Kim, Ph.D.
- S. Katherine Laughon, M.D., M.S.
- Cuilin Zhang, M.D., Ph.D., M.P.H.

Determining optimal fetal growth remains a key research priority, as alterations in growth are associated with various pregnancy disorders and also infant/child morbidity and mortality. Moreover, the early origins of health and disease hypothesis posits that decrements in fetal size may be associated with various chronic diseases such as heart disease later in life. Thus, delineating optimal fetal growth has implications for clinical care and population health. The NICHD Fetal Growth Study is an ambitious observational epidemiologic study that is recruiting 2,400 low risk pregnant women from 12 clinical sites in the United States (Fetal Growth Studies). Study participants undergo longitudinal 2D- and 3D- ultrasounds at *a priori* defined gestational ages during pregnancy. The overarching goal of the Study is to determine the optimal fetal growth for four race/ethnic groups of women, and to develop methods for the accurate clinical estimation of birth size with the eventual goal of predicting the optimal timing

of delivery. A second pregnancy cohort comprises approximately 150 pregnant women carrying dichorionic twins with the goal of establishing growth trajectory for contemporary twin populations. A third pregnancy cohort comprised 450 obese pregnant women. Follow-up of women in all cohorts will be completed in 2013.

Pediatric Epidemiology

Pediatric epidemiology focuses on the factors that affect the growth, development and health of children from infancy through adulthood. The Epidemiology Branch has three research projects, including the Birth Defects Research Group, Genetic factors in Birth Defects and the Upstate Kids Study. A brief summary of each of the studies follows.

Birth Defects Research Group

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

Division Collaborators:

- Mary Conley, M.A.
- Ruzong Fan, Ph.D.
- Shannon Rigler, M.D.
- Devon Kuehn, M.D.
- Aiyi Liu, Ph.D.

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

The Birth Defects Research Group is a multi-center multi-disciplinary 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 and 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. Recently, Branch investigators published a paper focusing on 82 candidate genes associated with folate and related compound metabolism. This is the largest neural tube defect genetic association study to date. Ten genes were nominally associated with neural tube defects; but findings should be considered preliminary given the large sample size.

Ongoing research involves examining quantitative traits in a genome wide association study given the genetic analysis is complete. Collected samples have been stored for further analysis of genetic factors as is the case with von Willebrand factor (in press). Additional analyses are ongoing.

2012 Publications:

1. Pangilinan F, Molloy AM, Mills JL, Troendle JF, Parle-McDermott A, Signore C, O'Leary VB, Chines P, Seay JM, Geiler-Samerotte K, Mitchell A, Vandermeer JE, Krebs KM, Sanchez A, Cornman-Homonoff J, Stone N, Conley M, Kirke PN, Shane B, Scott JM, Brody LC. *Evaluation of common genetic variants in 82 candidate genes as risk factors for neural tube defects*. BMC Medical Genetics 13:62, 2012.

2. Minguzzi S, Molloy AM, Kirke PN, Mills JL, Scott JM, Troendle J, Pangilinan F, Brody LC, Parle-McDermott A. *Development of a melting curve assay to genotype a tri-allelic polymorphism of MTHFD1L: an association study of nonsyndromic cleft in Ireland*. BMC Medical Genetics 13:29, 2012.

Genetic Factors in Birth Defects Study

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

Division Collaborators:

- Nansi Boghossian, Ph.D., M.P.H.
- Mary Conley, M.A.
- Devon Kuehn, M.D.
- Shannon Rigler, M.D.
- Edwina Yeung, Ph.D., M.P.H.

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

The Genetic Factors in Birth Defects Study is a multi-center multi-disciplinary study led by NICHD to identify genetic risk factors for a wide range of major birth defects. The collaborating institutions are the NICHD and National Human Genome Research Institute, the New York State Department of Health, and the University of Iowa. 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. To date, genetic variants (single nucleotide polymorphisms) have been identified and the reported results include:

- Omphalocele

- Hirschsprung's disease
- Limb defects
- Ano-rectal atresia

Because of the very large number of affected children included in this study, it has been possible to examine relatively rare conditions such as non-syndromic omphalocele. Folic acid-containing vitamins taken during the periconception period and the consumption of food fortified with folic acid have both been reported to reduce omphalocele rates. We found that a gene involved in vitamin B12 transport was strongly associated with omphalocele, suggesting that both folate and B12 status may influence omphalocele risk.

Our investigation of genetic factors associated with abnormal limb development identified a variant in the gene FGF 10 that was strongly associated with abnormal limb development. This gene plays a role in the embryonic development of bones (formation of the apical epidermal ridge). Our finding suggests that this variant could be an important factor in abnormal development of many bones.

We investigated the role of genes involved in neuronal migration in Hirschsprung's disease, since it is known that abnormal innervation is critical in this disorder. Our research showed that there are more variants in a key gene, RET, than had been previously appreciated involved in Hirschsprung's disease, and that the risk associated with RET may vary by ethnic background.

Because we are one of the few groups with sufficient cases to study the disorder, we investigated genetic factors at regulatory sites as possible risk factors for anorectal atresia in an exploratory study. This study demonstrated that several factors related to transcription factor binding, splicing, and DNA methylation were associated with anorectal atresia. However, the findings await confirmation.

The large number of cases has also enabled the group to make substantial contributions to consortia performing genome wide association studies. The group is currently collaborating in one such study examining craniosynostosis. This investigation has identified two new gene risk factors for craniosynostosis that are related to skeletal development. The group is interested in exploring collaborations with investigators conducting such studies.

2012 Publications:

1. Browne ML, Carter TC, Kay DM, Kuehn D, Brody LC, Romitti PA, Liu A, Caggana M, Druschel CM, Mills JL. *Evaluation of genes involved in limb development, angiogenesis, and coagulation as risk factors for congenital limb deficiencies*. American Journal of Medical Genetics 158A:2463-72, 2012.

2. Carter TC, Kay DM, Browne ML, Liu A, Romitti PA, Kuehn D, Conley MR, Caggana M, Druschel CM, Brody LC, Mills JL. *Hirschsprung's disease and variants in genes that*

regulate enteric neural crest cell proliferation, migration and differentiation. Journal of Human Genetics 57:485-93, 2012.

3. Mills JL, Carter TC, Kay DM, Browne M, Brody LC, Liu A, Romitti PA, Caggana M, Druschel C. *Folate and vitamin B12 related genes and risk for omphalocele*. Human Genetics 131:739-46, 2012.

4. Justice CM, Yagnik G, Kim Y, Peter I, Jabs EW, Erazo M, Ye X, Ainehsazan E, Shi L, Cunningham ML, Kimonis V, Roscioli T, Wall SA, Wilkie AO, Stoler J, Richtsmeier JT, Heuzé Y, Sanchez-Lara PA, Buckley MF, Druschel CM, Mills JL, Caggana M, Romitti PA, Kay DM, Senders C, Taub PJ, Klein OD, Boggan J, Zwienenberg-Lee M, Naydenov C, Kim J, Wilson AF, Boyadjiev SA. *A genome-wide association study identifies susceptibility loci for nonsyndromic sagittal craniosynostosis near BMP2 and within BBS9*. Nature Genetics 44(12):1360-4, 2012;

5. Carter TC, Kay DM, Browne ML, Liu A, Romitti PA, Kuehn D, Conley MR, Caggana M, Druschel CM, Brody LC, Mills JL. *Anorectal atresia and variants at predicted regulatory sites in candidate genes*. Annals of Human Genetics (In press).

Upstate KIDS Study

Principal Investigators:

- Mary L. Hediger, Ph.D. (retired)
- Edwina Yeung, Ph.D.

Edwina Yeung, Ph.D., M.P.H.

Division Collaborators:

- Germaine M. Buck Louis, Ph.D., M.S.
- Nansi S. Boghossian, Ph.D., M.P.H., *Postdoctoral Fellow*
- Patricia Moyer, M.S.
- Candace Robledo, Ph.D., M.P.H., *Postdoctoral Fellow*
- Rajeshwari Sundaram, Ph.D.
- Ann Trumble, Ph.D.

The Upstate KIDS Study was designed in response to growing albeit equivocal evidence suggesting that pregnancies conceived with assisted reproductive technologies (ART) were at increased risk for pregnancy complications, perinatal and infant mortality, and decrements in gestation and birth size in both singletons and twins (Upstate Kids Study). 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 three 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 3-5 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.

Parental participation includes completion of: 1) a baseline questionnaire on reproductive and medical history, environmental exposures and infant characteristics; 2) parental developmental rating instruments (i.e., Ages & Stages at 4, 8, 12, 18, 24, 30, 36 months of age and the Modified Checklist for Autism in Toddlers at 18 and 24 months) and 3) children's longitudinal growth and medical history as recorded in journals. All infants or children who screen positive for developmental delays are referred to their primary health provider or for clinical assessment. The Upstate KIDS Cohort has been linked with the Society for Assisted Reproductive Technologies' database for the capture of ART treatment. 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 samples (punches) from Guthrie cards were harvested and analyzed for 5 panels of inflammatory and environmental chemical biomarkers. Such exposures are associated with alterations in child growth and development.

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 that the Epidemiology Branch is conducting research on include the Modeling of Menstrual Cycle Function, Gene Environment Interactions and Pooling of Biological Specimens. A brief description of each research area follows.

Modeling of Menstrual Cycle Function

Principal Investigator:

- Enrique F. Schisterman, Ph.D., M.A.
- Paul S. Albert, Ph.D.

Division Collaborators:

- Sunni L. Mumford, Ph.D., M.P.H.
- Neil J. Perkins, Ph.D.

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

- Anna Z. Pollack, Ph.D., M.P.H.
- Edwina Yeung, Ph.D., M.P.H.

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, statistical models are needed which appropriately account for the intricacies of the menstrual cycle biology. Our methodologic research is aimed at developing various approaches for modeling menstrual cycle function 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 inter-relationship between multiple hormones across the menstrual cycle?

Current topics of interest include the application of harmonic models to model menstrual cycle function, as well as the use of joint-models to model the four reproductive hormones simultaneously.

2012 Publications:

1. Dasharathy SS, Mumford SL, Pollack AZ, Perkins NJ, Mattison DR, Wactawski-Wende J, Schisterman EF. *Menstrual bleeding patterns among regularly menstruating women*. American Journal of Epidemiology 175(6):536-545, 2012.

2. Gaskins AJ, Wilchesky M, Mumford SL, Whitcomb BW, Browne RW, Wactawski-Wende J, Perkins NJ, Schisterman EF. *Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study*. American Journal of Epidemiology 175(5):423-431, 2012.

3. Roy A, Danaher M, Mumford SL, Chen Z. *A Bayesian order restricted model for hormonal dynamics during menstrual cycles of healthy women*. Statistics in Medicine 31(22):2428-2440, 2012.

4. 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 (In press).

Gene-Environment Interactions

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

DESPR Collaborators:

- Paul S. Albert, Ph.D.
- Michelle Danaher, Ph.D., M.S.
- Ruzong Fan, Ph.D.
- Neil J. Perkins, Ph.D.
- Zhen Chen, Ph.D.

Genes and environment are important for complex disease such as gestational diabetes, birth defects and miscarriages. One important implication of unmasking gene-environment interactions is to identify highly susceptible populations, such that modifiable exposures associated with disease can be prevented or minimized. However, genetically susceptible individuals cannot be identified without a better understanding of gene-environment interactions.

One complication in studying gene-environment interactions is the high cost due to genotyping the large number of people necessary to have sufficient power to detect an interaction. Additional considerations include insufficient volume of biospecimens for genotyping, or restrictions on genotyping for privacy and confidentiality reasons. Division researchers are examining a new study design to increase statistical power by strategically pooling biospecimens. Pooling can reduce overall costs, while requiring less biospecimen volume from each individual. Therefore by using a pooling strategy, previously underpowered or abandoned gene-environment hypotheses can be explored.

These issues have been 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 gene-environment interactions.

2012 Publications:

1. Chen J, Kang G, VanderWeele T, Zhang C, Mukherjee B. *Efficient designs of gene-environment interaction studies: implications of Hardy-Weinberg equilibrium and gene-environment independence.* Statistics in Medicine 31(22):2516-2530, 2012.

2. Danaher MR, Schisterman EF, Roy A, Albert PS. *Estimation of gene-environment interaction by pooling biospecimens*. Statistics in Medicine 31(26):3241-3252, 2012.

3. Roy A, Danaher MR, Mumford SL, Chen Z. *A Bayesian order restricted model for hormonal dynamics during menstrual cycles of healthy women*. Statistics in Medicine 31(22):2428-2440, 2012.

4. Fan R, Albert PS, Schisterman EF. *A discussion of gene-gene and gene environment interactions and longitudinal genetic analysis of complex traits*. Statistics in Medicine 31(22):2565-2568, 2012.

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

Pooling of Biological Specimens

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

Division Collaborators:

- Paul S. Albert, Ph.D.
- Michelle Danaher, Ph.D., M.S.
- Aiyi Liu, Ph.D.
- Sunni L. Mumford, Ph.D., M.P.H.
- Neil J. Perkins, Ph.D.

Biomarkers of exposure and disease status play a critical role in epidemiological research, but fiscal limitations and the high cost of assays often require that investigators choose a subset of potential markers. Less often but equally of concern, samples may physically lack the volume necessary to perform a particular assay. Such issues may impact the ability to design the work or carry it through.

Pooling biospecimens is a technique in which samples from different individuals are physically combined and measured. This approach reduces the amount of each sample necessary for the assay and makes each assay more informative, thus reducing the number of tests required and overall cost. Division researchers have shown that a wide variety of statistical analyses (hypothesis testing, regression, ROC curves, semi and fully parametric methods) can be applied to pooled data, often with only minor adjustments to standard practice. Additional benefits of pooling have been demonstrated, such as increasing efficiency while limiting the impact of the limit of detection. A hybrid pooled-unpooled design also was developed by Division researchers and offers considerable cost savings when pooling, with the added ability to assess and address measurement error without the need for replicate assays.

2012 Publications:

1. Whitcomb BW, Perkins NJ, Zhang Z, Ye A, Lyles RH. (2012). *Assessment of skewed exposure in case-control studies with pooling*. Statistics in Medicine 31(22):2461-2472, 2012.

2. Malinovsky Y, Albert PS, Schisterman EF. *Pooling designs for outcomes under a Gaussian random effects model.* Biometrics 68(1):45-52, 2012.

3. Roy A, Perkins NJ, Buck Louis G. *Assessing chemical mixtures and human health: Use of Bayesian Belief Net Analysis*. Journal of Environmental Protection 3(6):462-468, 2012.

4. Danaher MR, Schisterman EF, Roy A, Albert PS. *Estimation of gene-environment interaction by pooling biospecimens*. Statistics in Medicine (In press).

Prevention Research Branch

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


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

The mission of the Prevention Research Branch includes the following: 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 Prevention Research 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 Ronald Iannotti, 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*
- Ronald Iannotti, Ph.D., *Staff Scientist*
- Leah Lipsky, Ph.D*., Staff Scientist*
- Kaigang Li, Ph.D., *Research Fellow*
- Johnathan Ehsani, Ph.D., *Postdoctoral Fellow*

- Anuj Pradhan, Ph.D., *Postdoctoral Fellow*
- Ashley Russell, Ph.D., M.P.H., *Postdoctoral Fellow*
- Virginia Quick, Ph.D., *Postdoctoral Fellow*
- Brittney Barbieri, B.S., *Postbaccalaureate Fellow*
- Faith Summersett-Ringgold, B.S., *Postbaccalaureate Fellow*
- Jessamyn Perlus, B.A., *Postbaccalaureate Fellow*

Research on Young Drivers

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


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

Division Collaborators:

- Paul S. Albert, Ph.D., *Senior Investigator*
- Kaigang Li, Ph.D., *Research Fellow*
- Johnathan Ehsani, Ph.D., *Postdoctoral Fellow*
- Anuj Pradhan, Ph.D., *Postdoctoral Fellow*
- Ashley Russell, Ph.D., M.P.H., *Postdoctoral Fellow*
- Brittney Barbieri, B.S., *Postbaccalaureate Fellow*

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 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 fMRI and executive functioning into this research. Thus, we employ the best methodology available to answer key research questions about teenage driving (Teen Driving Risk Studies).

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

The NTDS is one of the first studies to assess driving risk objectively among teenage drivers. The purpose was to assess the prevalence and determinants of crash/near crash and 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, 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 CPU in the vehicles' trunks with removable hard drives.

Data were successfully collected from 41 of 42 study participants. We have published papers on methods, driving exposure, crash risk, and risky driving. Elevated g-force event rates predict the likelihood of a crash or near crash (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 crash/near crash events) and data on few subjects (Zhang, Albert, Simons-Morton, 2012; Jackson, Albert, Zhang, Simons-Morton., in press). Regarding driving risk, we found that crash/near crash 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 (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.

The Supervised Practice Driving Study (SPD): 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 supervised practice driving prior to licensure while other adolescents for whom managing the vehicle is more difficult receive a great deal of supervise practice driving prior to licensure. Only one previous naturalistic study of supervised practice driving has been conducted (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 December 2013. We have developed data reduction protocols, including procedures for evaluating audio recordings of teen-parent verbal communications during instructional drives.

The Effect of Teenage Passengers on Teenage Simulated Driving Performance

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 provided a slightly protective effect on crash/near crash 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 4-5 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 2 conditions (passenger: risk-accepting vs. risk-averse) X 2 drive orders (driving alone first vs. driving with the passenger first). T-test comparisons of difference scores (passenger minus solo) 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.

Further analyses are planned, including the fMRI, executive function, and psycho-social tasks such as Cyberball, an exclusion task, and Go No, a risk tolerance task. The TPS2, now underway, tests 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 serves 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 psycho-social tasks will also be conducted. TPS3, planned for 2012-13, will involve actual peers rather than confederates.

The Effect of Feedback About Elevated G-Force Events on Risky Driving Among Novice Teenage Drivers

Elevated g-force event rates are associated with motor vehicle crashes (Simons-Morton, Zhang, Albert, 2012) and novice teenage drivers have high rates that persist at least through 18 months after licensure (Simons-Morton et al., 2011). Feedback about elevated g-force events has been shown to reduce event rates among young drivers in several pre-post, non-randomized studies using the DriveCam, a commercial event recorder marketed to the families

of young drivers. The DriveCam includes an accelerometer connected to small cameras directed at the vehicle occupants and forward roadway. Data are continually recorded, but only the few seconds before and after an event were stored for retrieval. The study evaluated the effect of two forms of feedback from the DriveCam device on risky driving behavior. A sample of 90 novice teenage drivers was recruited and randomized to one of two treatment conditions. The DriveCam device was installed (near the rear view mirror) of the study participants' vehicles. For the first two weeks the devices provided no feedback to the participants. Thereafter, for those assigned to the Lights Only condition, the device was set to provide immediate feedback in the form of a blinking red and green light each time the threshold of 0.5 g was exceeded. Similarly, for those assigned to the Lights Plus condition, the device was set to provide immediate feedback in the form of the blinking light and delayed feedback in the form of a weekly report card and access to video footage of each event on a secure website by teens and parents. DriveCam, Inc. coders blinded to the study evaluated each event according to standard procedures to derive the risk scores. The findings indicate that immediate feedback only had no effect on event rates. However, event rates among those who received immediate plus family feedback declined immediately and substantially. The effect size of 1.67 favored the Lights Plus group.

NEXT Naturalistic Driving Study

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 the 12th grade (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 crash/near crash)? and 2) What individual and driving condition factors are associated with risky driving and crashes/near crashes? Recruitment and installation of the data acquisition systems are underway. Study participants will be followed for a period of 4 years.

2012 Publications

1. 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-Series C, Applied Statistics 62, Part 3, 2012.

2. Simons-Morton BG, Ouimet MC, Wang J, Chen R, Klauer SG, Lee SE, Dingus T. *Psychosocial factors associated with speeding among teenage drivers*. Journal of Safety Research 2012; Nov 13 online.

3. Simons-Morton BG, Zhang Z, Jackson JC, Albert PS. *Do elevated gravitational-force*

events while driving predict crashes and near crashes? American Journal of Epidemiology 175(10):1075-1079, 2012.

4. Simons-Morton BG, Cheon K, Guo F, Albert P. *Trajectories of kinematic risky driving among novice teenagers*. Accident Analysis & Prevention 51C:27-32, 2012.

5. Simons-Morton BG, Bingham R, Ouimet MC, Pradhan A, Chen R, Wang J. *The effect on teenage risky driving of feedback from a safety monitoring system: A randomized controlled trial*. Journal of Adolescent Health (In press).

6. Zhang Z, Albert PS, Simons-Morton BG. *Marginal analysis of longitudinal count data in long sequences: Methods and application to a driving study*. Annals of Applied Statistics 6 (1):27–54, 2012.

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. T he 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), 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 NEST Study promises to be among the most important longitudinal studies since the Add Health.

Health Behavior in School Children Survey (HBSC)

The HBSC is a national probability survey of adolescent health behavior in the U.S, which has been conducted every 4 years since 1998. The U.S. HBSC complements the Youth Risk Behavior Survey (YRBS) in that it is the only survey simultaneously conducted in approximately 40 European countries. As a result, it is the only survey that permits comparisons of U.S. adolescents with adolescents throughout Europe. The aims of the survey are to assess the prevalence of health behaviors and identify contextual factors associated with them in a national probability sample of 6th to 10th grade students, allowing for trend analyses and cross-national comparisons among participating countries involved in the quadrennial international HBSC surveys. Because core survey items have remained consistent both nationally and internationally since 2001, HBSC surveys provide essential data for examining and comparing national and international trends. Participating countries may also collect data on approved optional measures that are unique topics, for example, injury, or more in depth assessments, for example, substance use. The US HBSC has concentrated assessments on diet, physical activity, bullying and substance use. It also includes measures of medication taking, mental health, school functioning, social relations, and socio-economic status. Public access HBSC datasets are made available three years after they are available to DESPR scientists.

The NEXT Generation Health Study

The NEXT Generation Health Study is a longitudinal survey of adolescent health and behavior. A nationally representative cohort of 2770 adolescents, approximately 16 years of age, was recruited in 2010 and is assessed annually up to age 22. 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 2770 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 the Wave 3 assessments is 92%.

In collaboration with colleagues at NIDA (which co-sponsors NEXT), we have under review a paper 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.

2012 Publications

1. Bjarnason T, Bendtsen P, Arnarsson AM, Borup I, Iannotti RJ, Löfstedt P, Haapasalo I, Niclasen B. *Life satisfaction among children in different family structures: A comparative study of 36 western societies*. Children & Society 26:51-62, 2012.

2. Bogt TF, Gabhainn SN, Simons-Morton BG, Ferreira M, Hublet A, Godeau E, Kuntsche E, Richter M. *Dance is the new metal: adolescent music preferences and substance use across Europe*. Substance Use & Misuse 47(2):130-42, 2012.

3. Caccavale LJ, Farhat T, Iannotti R J. *Social engagement in adolescence moderates the association between weight status and body image*. Body Image 9(2):221-226, 2012.

4. Divekar G, Pradhan AK, Pollatsek A, Fisher DL. *External distractions: Evaluation of their effect on younger novice and experienced drivers' behavior and vehicle control*. Transportation Research Record (In press).

5. Farhat T, Simons-Morton BG, Kokkevi A, van der Sluijset W, Fotiou A, Kuntsche E. *Early adolescent and peer drinking homogeneity: Similarities and differences among European and North American countries*. Journal of Early Adolescence 32(1): 81-103, 2012.

6. Hingson R, Zha W, Iannotti RJ, Simons-Morton BG. *Physician advice to adolescents about drinking and other health behaviors*. Pediatrics (In press).

7. Iannotti R J, Chen R, Kololo H, Petronyte G, Haug E, Roberts C. *Motivations for adolescent participation in leisure-time physical activity: international differences*. Journal of Physical Activity and Health (In press)

8. Kuntsche E, Rossow I, Simons-Morton BG, ter Bogt T, Kokkevi A, Godeau E. *Not early drinking but early drunkenness is a risk factor for problem behaviors among adolescents from 38 European and North American countries*. Alcoholism: Clinical and Experimental Research (In press)

9. Lipsky LM, Iannotti RJ. *Associations of television viewing with eating behaviors in the 2009 Health Behavior in School-Aged Children study (HBSC)*. Archives of Pediatrics & Adolescent Medicine 166:465-472, 2012.

10. Luk JW, Farhat T, Iannotti RJ, Simons-Morton BG. *Parent-child communication and substance use among adolescents: Do father and mother communication play a different role for sons and daughters?* Addictive Behaviors (In press)

11. Luk JW, Wang J, Simons-Morton BG. *A latent class analysis of bullying victimization among U.S. adolescents: Associations with demographic characteristics and psychosomatic symptoms*. Journal of Adolescence (In press)

12. Mikolajczyk RT, Iannotti RJ, Farhat TM, Thomas V. *Ethnic differences in perceptions of body satisfaction and body appearance among U.S. schoolchildren: A cross-sectional study*. BMC Public Health 12(1):425, 2012

13. Ogbagaber S, Albert PS, Lewin D, Iannotti RJ. *Summer activity patterns among teenage girls: harmonic shape invariant modeling to estimate circadian cycles*. Journal of Circadian Rhythms (In press)

14. Simoes C, Gaspar Matos M, Moreno C, Rivera F, Bastiste-Foguet J, Simons-Morton BG. *Substance use in Portuguese and Spanish adolescents: highlights from differences and similarities and moderate effects*. Spanish Journal of Psychology 15(3):1024-37, 2012.

15. Simons-Morton BG, Kuntsche E. *Adolescent estimation of peer substance use: Why it matters (Commentary)*. Addiction 107:885-891, 2012.

16. Wang J, Iannotti RJ, Luke JW. *Patterns of adolescent bullying behaviors: Physical, verbal, exclusion, rumor, and cyber*. Journal of School Psychology (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 recently completed Family Management of Childhood Diabetes and the ongoing Cultivating Healthy Eating in Families of Youth with Type 1 Diabetes, and a forthcoming intervention trial on diet among pregnant women. The future course of this area of research will be: 1) to determine the effect of a clinic-linked intervention on the diet and disease management practices of families with children with type 1 diabetes mellitus and 2) to examine diet and weight gain among pregnant women and test an intervention to foster healthy eating and weight gain.

Family Management of Type 1 Diabetes in Youth

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, including diabetic ketoacidosis and damage to the heart, kidneys, nerves, eyes, blood vessels, and other organs. Successful management of diabetes in youth is heavily dependent upon family adaptation to the affective, behavioral, and cognitive demands imposed by the disease. The transfer of diabetes management responsibilities from parents to adolescents is a particularly important process. Although many youths and parents negotiate this transition effectively, it is also a period when many other youths take costly, self-destructive paths resulting in preventable health care costs and psychological suffering in the short-term and accelerated onset and progression of long-term complications of the disease. 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. Research to date on behavioral interventions for youth with type 1 diabetes suggest that adherence, quality of life, and glycemic control could be enhanced if behavioral interventions were routinely implemented as part of standard care. Yet there are many barriers to the translation of these interventions into routine clinical practice, including cost, access, third party coverage, availability of qualified clinicians, convenience and social stigma. 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.

Family Management of Diabetes Multi-site Trial

Families receiving care at one of four geographically disperse clinical sites were randomized to receive either standard care or a clinic-integrated behavioral intervention, in which a trained non-professionals delivered the semi-structured approach based on applied problem-solving at each routine clinic visit. A sample of 390 families was followed for two years. Biomedical and self-report data were collected during clinic visits, as well as in-home and by telephone. The intervention tested in this study was based on both individual and family system theoretical perspectives, including social cognitive theory, self-regulation, and authoritative parenting. It was designed to provide experiential training for families in the use of a problem solving approach (represented by the acronym "WE*CAN") to promote improved parent-child teamwork and more effective problem-solving skills for diabetes management. The intervention was designed to be applicable to the broad population of youth with diabetes and their families, flexibly implemented and tailored to the varying needs of families, and delivered at a low intensity over time to meet the changing families' needs and roles during the period in which responsibility for diabetes management typically undergoes transition. Intervention components included a preparation telephone contact prior to clinic visits, an action session during clinic visits designed to assist the family in setting specific goals for diabetes management and problem-solving to facilitate goal attainment, and follow-up telephone contacts to reinforce effort and further assist progress. Findings from the Family Management of Diabetes Multisite Trial demonstrated an intervention effect on glycemic control at two-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.

Dietary Intake in Youth with Type 1 Diabetes

Nutrition guidelines for children with type 1 diabetes are similar to those for the general population, and nutrition education for families of children with type 1 diabetes includes recommendations for general healthful eating and efforts to achieve and maintain optimal weight for height. A primary component of medical nutrition therapy in type 1 diabetes is carbohydrate estimation, especially in the current era emphasizing physiologic insulin replacement, as carbohydrates are the principal macronutrient affecting glycemic excursions. As such, a major focus 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. Limited

research has examined relations between usual dietary intake and diabetes management in type 1 diabetes. However, there is a growing body of evidence indicating that dietary intake, particularly carbohydrate quality, may affect blood sugar control, insulin demand, and weight management. To date, research has not examined individual and family determinants of dietary intake in youth with type 1 diabetes. Further, excepting one study using only a nutrition education approach, no intervention studies to improve dietary quality among this population have been conducted. Research within the general population indicates a complex interplay of socio-environmental and personal factors impacting children's dietary intake. The family plays a critical role in influencing children's eating habits, both through regulating food availability as well as by shaping food attitudes, preferences and values through modeling and food-related parenting practices. Challenges to healthful eating faced by families include perceived time constraints, perceived cost of healthful eating, increase in food consumed away from home, and a food environment characterized by an abundance of unhealthful options. 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.

Eating Behaviors Among Youth with Type 1 Diabetes

This study enrolled 291 families (parent-youth dyads) in a cross-sectional study of 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 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 disordered eating behaviors with diet quality, and significant associations of youth food preferences and the family food environment with dietary intake. We have developed measures for assessing nutrition knowledge, diabetes management adherence, and intake of whole plant foods. We have demonstrated the utility of a random effects model for examining dietary intake by weekends and weekdays, providing a method for improved data analysis when differential constellations of weekdays and weekend days are obtained across subjects or over time. 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.

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

This 18-month study, which is currently in the field, 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 is underway; 96% of participants who completed baseline assessment have been retained through the 6-month assessment, encompassing the majority of intervention visits.

2012 Publications

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2. Lipsky LM, Cheon K, Albert P, Nansel TR. *Candidate measures of whole plant food intake are related to biomarkers of nutrition and health in the US population (NHANES 1999-2002)*. Nutrition Research 32(4):251-259, 2012.

3. Nansel TR, Iannotti RJ, Liu A. *Clinic-integrated behavioral intervention for families of youth with type 1 diabetes: RCT*. Pediatrics 129:e866-e873, 2012.

4. Nansel TR, Haynie DL, Lipsky LM, Laffel L, Mehta SN. *Multiple indicators of poor diet quality in youth with type 1 diabetes are associated with higher weight status but not glycemic control*. Journal of the Academy of Nutrition and Dietetics 112(11):1728-1735, 2012.

5. Rovner AJ, Nansel TR, Mehta SN, Higgins LA, Haynie DL, Laffel LMB. *Development and validation of the type 1 diabetes nutrition knowledge survey*. Diabetes Care 35:1643-1647, 2012.

6. Tse J, Nansel TR, Haynie D, Laffel L, Mehta S. *The relationship of diet quality and disordered eating behaviors in adolescents with type 1 diabetes*. Journal of the Academy of Nutrition and Dietetics 112(11):1810-1814, 2012.

7. Williams J, Nansel TR, Weaver NL, Tse J. *Safe N' Sound: an evidenced based tool to prioritize injury messages for pediatric healthcare.* Family and Community Health 2012, 35(3):212-224, 2012.

8. Weaver NL, Brixey S, Williams S, Nansel TR. *Promoting correct car seat use in parents of young children: challenges and recommendations*. Health Promotion Practice, 2012; Sept 17 online.