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Annual Reporting Form for SCEDDBO Projects and Cores

Center Overview

Period covered by the report: 5/1/2012 – 4/30/2013
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Allison Ashley Koch, Richard Auten, W. Michael Foster, Alan Gelfand, Pamela Maxson, Evan Myers, Jerome Reiter, Geeta Swamy, Redford Williams
Project Period: Year 6

Objectives of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO)

The central mission of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes is to determine how environmental, social, and host factors jointly contribute to health disparities. Specific aims of the Center are:

1. *To develop and operate an interdisciplinary children's health research center with a focus on understanding how biological, physiological, environmental, and social aspects of vulnerability contribute to health disparities;*
2. *To enhance research in children's health at Duke by promoting research interactions among programs in biomedicine, pediatric and obstetric care, environmental health, and the social sciences and establishing an infrastructure to support and extend interdisciplinary research;*
3. *To develop new methodologies for incorporating innovative statistical analysis into children's environmental health research and policy practice, with a particular emphasis on spatial, genetic and proteomic analysis;*
4. *To serve as a technical and educational resource to the local community, region, the nation, and to international agencies in the area of children's health and health disparities; and,*
5. *To translate the results of the Center into direct interventions in clinical care and practice.*

SCEDDBO leverages and promotes active partnerships among the Nicholas School of the Environment, the Duke University Medical Center, Trinity College of Arts and Sciences, as well as the School of Natural Resources and Environment and the Children's Environmental Health Initiative at the University of Michigan and Durham County Public Health (DCPH) and the Lincoln Community Health Center (LCHC). The Center brings together the expertise of obstetricians, pediatricians, genetic epidemiologists, spatial statisticians, environmental scientists, social epidemiologists, social psychologists, geographers, and community organizations.

Synthesis across SCEDDBO. **Research Project A: Mapping Disparities in Birth Outcomes** provides population-level research on health disparities in birth outcomes. Spatially-linking 1.7 million birth records with environmental, social, and host factor data layers allows for population-level analysis of potential co-factors identified in both the clinical obstetrics **Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes** and mouse model **Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health** studies. The data from Research Project A is spatially linked in GIS to the data from Research Project B.

The two neighborhood assessments (2008 and 2011) undertaken in Research Project B continue to provide important neighborhood-level environmental and social data to Research Project A. In addition, the environmental data developed for Research Project A works synergistically with the mouse model work in Research Project C. For example, the air quality data from Research Project A is being used to further refine experimental dose design in Research Project C. In turn, results from Research Project C regarding experimental effects of multiple environmental agents on fetal growth restriction and postnatal somatic and lung development help point to locations in North Carolina where we are looking more closely at air quality impacts on birth outcomes in Research Project A.

Thus Research Project A is an epidemiological study, while Research Project B is a complementary clinical obstetrics project. Both projects focus on how combined environmental, social, and host factors shape disparities in birth outcomes. Research Project B also allows for additional host factor analysis. Research Project C uses a mouse model system to explore how disparities in exposure and response to exposure initiate and/or enhance disparities in birth outcomes and subsequent neonatal respiratory health. Like Research Projects A and B, Project C explores the effects of *combined* environmental exposures to prototypical air pollutants common in North Carolina (particulate matter and ozone) and non-chemical stressors on fetal growth restriction, neonatal somatic growth, and subsequent lung development and function.

The synergy among the research projects is facilitated by the GIS and Statistical Analysis (GISSA) Core. The GISSA Core allows for data analysis of the very large amount of data through the use of high-end GIS applications in combination with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, thus permitting multi-level analysis. Research Projects A and B both apply a Bayesian spatial hierarchical modeling approach to capture uncertainties in pregnancy outcomes and to elucidate the contributions of economic, sociocultural, and environmental stressors on health disparities in pregnancy outcomes. State-of-the-art GIS methods allow for sophisticated spatial statistical analyses at highly resolved spatial scales.

The GISSA Core also provides the analysis of the biological response and genetic data generated in Research Projects B and C. The rich source of social, environmental, and host data in Project B, coupled with sophisticated statistical genetic approaches for identifying gene-gene and gene-environment interactions, provides the opportunity to make important discoveries of how these higher order interactions may be working together to promote or prevent adverse birth outcomes. By serving as a central clearinghouse for statistical analysis, the GISSA Core tracks outcomes in each project and uses these discoveries to guide the analysis in each of the other projects.

The Community Outreach and Translation Core (COTC) facilitates the communication of findings from all three projects. The COTC continues to communicate the results of the neighborhood assessment to community partners and stakeholders. In addition, the COTC draws on the GISSA Core to develop materials that communicate the results of the research projects in formats and applications that are immediately accessible to the lay public.

Administrative Core

Period covered by the report: 5/1/2012– 4/30/2013
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Richard Auten, Pamela Maxson
Project Period: Year 6

Objectives of Core

The Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) is governed through an Administrative Core that includes an Executive Committee composed of the Director, a Co-Director, and the Project Manager; an Internal Steering Committee composed of members of the Executive Committee and the Directors of the Research Projects and the Facility and Community Outreach Cores; and an External Advisory Committee composed of senior environmental health scientists, as well as community representatives, with expertise relevant to SCEDDBO, who provide informal consultation, as well as annual formal evaluation of Center research and outreach activities.

The specific aims of the Administrative Core are to:

a. Provide scientific direction and leadership;

b. Coordinate and foster interactions among research project and facility core investigators;

c. Provide administrative services for the Center;

d. Direct the Young Investigators program; and

e. Represent Duke's SCEDDBO to the university, the community, the NIH, other Children's Environmental Health Centers across the United States, and the policy and scientific community interested in children's environmental health more broadly.

In all activities, SCEDDBO emphasizes the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social, and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators are all indicative of the importance that we place on fostering environments where all people can prosper.

Progress Report/Summary of Accomplishments

Quality Management Plan. The Administrative Core continued to distribute the Quality Management Plan (QMP) to all new SCEDDBO collaborators. These individuals are required to sign the cover sheet thereby agreeing to abide by the policies laid out in the QMP. The Administrative Core keeps a copy of these signed forms in its files.

Despite quality management oversight, a research technician from Project C was dismissed for cause and investigations show that some of her data reports do not match the original data generated by the instruments. The office of research integrity at Duke University is investigating the matter. One SCEDDBO publication has been retracted, with experiments currently being repeated to determine the validity of our previous findings. We hope to have these finished and analyzed in the next six months. We are not using SCEDDBO funds to repeat these experiments.

Young Investigators Program. Marie Lynn Miranda continued to serve as a mentor to Dr. Heather Stapleton and Dr. Rebecca Fry during year 6.

Year Six Expenditures. As SCEDDBO is in a no-cost extension period, expenditures are mostly in personnel and laboratory categories to allow continuation of our ongoing work. Most costs were associated with maintaining and expanding the animal models and continuing statistical and GIS analysis of the data. Dissemination costs were also incurred for conference presentation and publication costs.

IRB Certification. A centralized database on IRB and IACUC certification and continuing education requirements is maintained through the Administrative Core. Twice a year, Dr. Pamela Maxson, the QA Manager, verifies that all researchers associated with SCEDDBO have completed their basic certification and continuing education requirements (one credit of continuing education is required each year to maintain certification). Reminders are sent to investigators when they are due for additional training. In addition, Dr. Maxson is responsible for ensuring IRB and IACUC Protocols are renewed and updated as necessary. All of these documents are posted to the SCEDDBO internal website, and paper copies are centrally maintained by Dr. Maxson.

Website. The Administrative Core provided material on SCEDDBO to the EPA for uploading to the EPA children's centers website. In addition, we updated our SCEDDBO website, linked off the website for the Children's Environmental Health Initiative (cehi.snre.umich.edu). We continue to use our secure internal website that allows for discussion boards, email communication, and document storage associated with the work of each of the SCEDDBO components.

Dissemination. Numerous talks were given throughout the year by SCEDDBO investigators at a variety of different conferences as described in the research project write-ups below.

New Collaborations. In our no-cost extension period, as part of our mission to both support the work of young investigators and advance the research mission of SCEDDBO, we continue our collaborations with Dr. Staci Bilbo, Assistant Professor, Department of Psychology and Neuroscience, Duke University and Dr. Rebecca Fry, Associate Professor, Gillings Global School of Public Health, UNC. We continue working with Dr. Bilbo on mouse models to explore the joint impact of environmental and social stressors on birth and developmental outcomes. We are working with Dr. Fry to explore combined chemical and non-chemical stressors, with a particular emphasis on cadmium and cotinine exposure. In addition, we continue our work with Dr. Heather Stapleton, Associate Professor, Nicholas School of the Environment, Duke University. We are leveraging our completed clinical obstetrics project to assess *in utero* exposures to brominated flame retardants, as well as the relationship between brominated flame retardant body burden and maternal thyroid function. Multiple papers are in progress or have been published on this work in year 6.

Personnel. Our personnel consisted primarily of project management, laboratory technicians, and GIS and statistical analysts.

National Service. Duke continued to organize and host the Children's Environmental Health Centers' monthly conference calls during year 6. In addition, Dr. Miranda continues to serve as a standing member of the Children's Health Protection Advisory Committee. Multiple SCEDDBO investigators help to review proposals for federal funding agencies, as well as review manuscripts for peer-reviewed journals.

Research Project A: Mapping Disparities in Birth Outcomes

Period covered by the report: 5/1/2012 – 4/30/2013
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda (PI), Alan Gelfand, Pamela Maxson, Evan Myers
Project Period: Year 6

Objectives of Research

Project A utilizes the conceptual framework of the "weathering hypothesis," which posits that chronic and persistent stressors lead to accelerated biological aging of women, which in turn accounts for adverse birth outcomes among certain subpopulations. The central objective is to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in fetal growth restriction.

Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims are to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than percentile cut points; and
3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

This project evaluates a large number of factors in diverse populations, providing broad relevance for birth outcomes across time, space, and demography. Identifying social and environmental factors contributing to fetal growth restriction will improve our understanding of disease etiology and explain the racial disparity in disease incidence, leading to effective interventions against poor outcomes in all population groups.

Progress Report/Summary of Accomplishments Progress Report/Summary of Accomplishments

Over the past year, the Project A research team has moved forward within small groups to discuss research ideas, review progress of current analysis and identify next steps, and work on manuscript preparation.

A continuing goal is the linking of the detailed birth record data to USEPA PM_{10}, $PM_{2.5}$, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birth weight. To this end, in year 6 we were invited to write a review of air pollution effects on birth outcomes which will be completed in year 7. We are especially focused on incorporating refined

exposure metrics to most effectively characterize meaningful exposures. Significant progress has been made on the relationships between air pollution exposures, socioeconomic status, and birth outcomes. We have extended our methodological work with *spatial downscalers* to conduct an applied analysis on racial and socioeconomic disparities in exposure to air pollution across the State of North Carolina (See Gray et al.). While previous studies of the environmental justice dimensions of air pollution limit analysis of populations living near air quality monitoring stations, we use space-time downscaling methods that we previously developed to output predictive surfaces of ozone (O_3) and particulate matter < 2.5 μm in aerodynamic diameter ($PM_{2.5}$) at the census-tract level covering all of North Carolina. This analysis seeks to provide a better understanding of the environmental justice dimension of air pollution exposure across the entire North Carolina population. Moreover, in an additional forthcoming work (see Gray et al.), we link the downscaled output to the detailed birth record in order to examine the joint effects of socioeconomic status and air pollution on birth outcomes, using the highly resolved estimated pollution exposures. The downscaled output allowed us to estimate the association between air pollution exposure and birth outcomes for times and locations where exposure data was otherwise unavailable.

Having linked the North Carolina statewide detailed birth record and educational record databases, we have begun examining the impact of pregnancy-related events and exposures on neurodevelopmental outcomes in early childhood. Two manuscripts have recently been accepted for publication. The first, forthcoming in JAMA Pediatrics, (See Gregory et al. 2013), investigates whether induction and/or augmentation during labor may be associated with autism diagnosis in children in grades 3-8. In this work, we use logistic regression modeling for rare events data to first establish an association between labor induction/augmentation and autism diagnosis and then examine whether the association is robust to controlling for successive sets of potential confounders related to maternal demographics, maternal health conditions, and events of labor and delivery, as recorded in the detailed birth record. The second is forthcoming in Pediatric and Perinatal Epidemiology, examining the joint effect of birth outcomes and maternal prenatal smoking on educational test scores in reading and math (See Anthopolos et al. 2013). This study finds that maternal prenatal smoking may interact with birth outcomes on reading and mathematics test scores, particularly among non-Hispanic white children. Additionally, improvements in birth outcomes, even within the clinically normal range, may be associated with improved academic performance.

We have synthesized our hypotheses concerning the adverse effects of *racial residential segregation* on the one hand, and *poor quality built environment* on poor birth outcomes on the other, which we previously examined in separate published research articles (indicated on the Project A report for 2012). Using advanced mediation models as the basis for our analytical approach, we examine whether poor quality built environment acts as a mediator in the relationship between racial residential segregation and preterm birth. Currently in submission, this work develops a novel method to maintain an additive scale in estimating natural direct and indirect effects from non-linear models (e.g., logistic regression). Additivity is required for interpreting the proportion of the total effect (i.e., the effect of the exposure, racial residential segregation, on the outcome) explained by the mediator (i.e., the poor quality built environment) in a causal framework. In addition, we developed a summary poor built environment index to avoid violating assumptions of no unmeasured confounding in the mediation model.

We have also continued building joint models in order to examine correlated outcomes. Joint modeling eliminates potential causal inference concerns. In work under preparation, we examine the association between features of the built environment with the bivariate outcome of preterm birth and low birthweight see Messer et al.). Additionally, we have developed multivariate spatial modeling to accommodate correlated continuous outcomes (currently in

submission – see Neelon et al.). This latter work incorporates correlation not only between jointly modeled outcomes but also among mothers living in nearby neighborhood units

Our methodological work on expected performance accruing to *synthesizing categorical datasets*, with the objective of enhancing inference, has been accepted for publication at *Statistical Methodology* (See Berrocal et al., 2012). This work deals with a collection of datasets of varying sizes that are all relevant to a particular scientific question, but which include different subsets of the relevant variables, with some overlap. We synthesize cross-classified categorical datasets drawn from a common population where many of the sets are incomplete (i.e., one or more of the classification variables is unobserved), but at least one is completely observed. The method is expected to reduce uncertainty about the cell probabilities in the associated multi-way contingency table as well as for derived quantities such as relative risks and odds ratios.

Collaborations with other SCEDDBO Components

We continue our engagement with the other two research projects, as well as a strong connection with the GISSA and COTC.

Future Activities

Achieving a better understanding of exposure to air toxins, particularly particulate matter and ozone, is a central focus of our future efforts. Areas of investigation will include space time analysis of trends in births across North Carolina, an investigation of linked births (same mother) using suitable random effects models, and a more thorough investigation of the impact of introducing spatial random effects in regression modeling to explain birth outcomes.

We are continuing the process of linking participants in Project B with their associated birth certificate record. We are excited to begin exploring the additional insights into the detailed birth record data that can be gleaned by linking these data with the rich dataset collected in Project B. This linkage will not only allow us to explore issues of data accuracy in the detailed birth record, but will also allow us to begin implementing the methods of synthesizing categorical data discussed above.

We seek to leverage the fact that we have linked births to the same mothers in our data architecture. This is particularly pertinent to analyses where genetic factors may play a confounding role. For example, we seek to replicate our study on birth outcomes, maternal prenatal smoking, and educational test scores in reading and mathematics accounting for siblings in our dataset.

We continue to target various professional audiences for dissemination of our work. Recent presentations have been at the following conferences: the Society of Epidemiological Research and the 2012 Summit on the Science of Eliminating Health Disparities.

Publications

Anthopolos, R., Edwards, S.E., and Miranda, M.L. "Effects of Maternal Prenatal Smoking and Birth Outcomes Extending into the Normal Range of Academic Performance in 4th Grade in North Carolina, USA." *Paediatric and Perinatal Epidemiology.* Forthcoming.

Berrocal, V., Gelfand, A., Holland, D. 2012. "Space-time Data Fusion under Error in Computer Model Output: an Application to Air Model Quality." *Biometrics.*

Berrocal, V., Miranda, M.L., Gelfand, A.E., and Bhattacharya, S. "Synthesizing Categorical Datasets to Enhance Inference." *Statistical Methodology.* Forthcoming.

Chang H.H., Reich B.J., and Miranda M.L. "A Spatial Time-to-Event Approach for Estimating Associations between Air Pollution and Preterm Birth." *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 62(2):167-179.

Gray, S., Edwards, S.E., and Miranda, M.L. "Race, Socioeconomic Status, and Air Pollution Exposure in North Carolina." *Environmental Research*. Forthcoming.

Gray, S., Edwards, S., Schultz, B., Miranda, M.L. "Assessing the Impact of Race, Social Factors, and Air Pollution on Birth Outcomes: A Population-based Study." *Environmental Health*. Forthcoming.

Gregory, S.G., Anthopolos, R., Osgood, C., Grotegut, C.A., and Miranda, M.L.. "Association of Autism with Induced or Augmented Childbirth in North Carolina Birth Record (1990-1998) and Education Research (1997-2007) Databases." *JAMA Pediatrics*. Forthcoming.

Miranda, M.L., Edwards, S.E., Chang, H.H., and Auten, R.L. "Proximity to Roadways and Pregnancy Outcomes." *Journal of Exposure Science and Environmental Epidemiology*. Forthcoming. PMID: 22805991.

Montagna S, Tokdar ST, Neelon B, and Dunson D. "Bayesian Latent Factor Regression for Functional and Longitudinal Data." *Biometrics*. Forthcoming.

Publications – In Preparation/Submission

Anthopolos, R., Messer, L.C., Kaufman, J.S., Miranda, M.L. "The Built Environment as a Mediator in the Relationship between Racial Residential Isolation and Preterm Birth in Durham, North Carolina." In submission.

Edwards, S.E., Maxson, P.J., Sandberg, N., and Miranda, M.L. "Air Pollution and Pregnancy Outcomes" in Air Pollution and Health Effects, John Hollingsworth, editor. Springer Publishers: New York, NY. In preparation.

Messer, LC, Neelon, B, Anthopolos, R., Kaufman, JS. "The Built Environment and Adverse Birth Outcomes: An Analysis using Biprobit Modeling to Account for Correlated Outcomes." In revision.

Neelon, B., Gelfand, A.E., Miranda, M.L. 2012. "A Multivariate Spatial Mixture Model for Areal Data." In submission.

Presentations

Miranda, ML., Anthopolos, RA, Edwards, SE., and Kim, D. "Impact of Pregnancy-Related Exposures on Educational Test Scores." Summit on the Science of Eliminating Health Disparities, National Harbor, MD, December 2012.

Supplemental Keywords

Data fusion, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation, built environment, birth outcomes

Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes

Period covered by the report: 5/1/2012 – 4/30/2013
EPA Agreement Number: RD83329301-0
Investigators: Redford Williams (PI), Allison Ashley-Koch, Richard Auten, Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy
Project Period: Year 6

Objectives of Research

The central objective of the Healthy Pregnancy, Healthy Baby Study is to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There are four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
    a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
    b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and
    c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

Progress Report/Summary of Accomplishments

Participant recruitment has been completed, with 1889 women successfully completing participation. Women were recruited from Duke University Medical Center (DUMC) and Lincoln Community Health Center. Demographic data indicate that we were highly successful recruiting women most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women.

The following information was collected from participants in the Healthy Pregnancy, Healthy Baby Study:

- Psychosocial measures include: CES-D, perceived stress, self-efficacy, interpersonal support, paternal support, perceived racism, perceived community standing, pregnancy intention, John Henryism Active Coping Scale, NEO Five Factor Inventory of personality.
- Environmental exposure survey measures include: short survey on fish consumption, smoking pattern and exposure to second-hand smoke, and drinking water source.
- Maternal and neonatal medical record abstraction includes: detailed pre-pregnancy medical and social history, antepartum complications, birth outcomes, and neonatal complications.
- Blood samples for genetic and environmental analysis to assess candidate genes related to environmental contaminant (nicotine, cotinine, cadmium, lead, mercury, arsenic, and manganese) metabolism, inflammation, vascular dysfunction, and stress response.
- Cord blood and placental samples are currently being stored for future genetic analysis and evaluation of activity at the maternal-fetal interface.

We were highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 944 delivery samples collected.

All maternal data are georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Healthy Baby Study also includes two in-depth neighborhood assessments designed to capture both built environment and community-level social stressors and community resources. In order to increase the participant capture rate (first assessment 40%), we expanded our second assessment area, successfully capturing approximately 70% of the participants. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

The bulk of our focus during the no-cost extension has been on data analysis and manuscript preparation. To that end, we detail our most recent work.

Cadmium. Cadmium is prevalent in the environment and understudied as a developmental toxicant. We conducted an analysis of maternal cadmium exposure and leukocyte DNA methylation patterns in 17 mother-newborn pairs. A methylated cytosine-guanine (CpG) island recovery assay was used to assess over 4.6 million sites spanning 16,421 CpG islands. Exposure to cadmium and cotinine was classified for each mother-newborn pair according to maternal blood levels. Comparative methylation analysis was performed to identify genes with differential methylation levels. DNA motifs that were overrepresented among the differentially methylated genes were identified. Subsets of genes were identified that showed altered DNA methylation levels in fetal DNA associated with exposure to cadmium (n=61), cotinine (n=366), or both (n=30). In maternal DNA, subsets of cadmium-associated (n=92) and cotinine-associated (n=134) genes were identified. While the gene sets were largely distinct between mothers and newborns, functional similarities at the biological pathway level were identified including transcriptional regulation and apoptosis. Furthermore, conserved DNA motifs with sequence similarity to specific transcription factor binding sites were identified within the CpG islands of the gene sets. This pilot investigation provides evidence for distinct patterns of DNA methylation alterations in fetal and maternal DNA associated with exposure to cadmium. The genes with differential methylation share common motifs at the sequence level suggesting that structural commonalities in DNA sequence may affect environmentally-related DNA methylation status. This manuscript has been submitted.

Psychosocial Indicators. Analyses have been completed on psychosocial influences on birth outcomes. In order to reduce the number of psychosocial variables, cluster analysis has been performed, resulting in three distinct clusters of women. Cluster analysis on personality was also performed, and a paper is in preparation. A paper examining the relationship between the built environment as measured through the Community Assessment Project and women's psychosocial health was published in year 6 (Messer et al. 2012). Analysis on cadmium exposure and psychosocial stress has been conducted and is being prepared for publication in the coming year. Future analyses will continue with a focus on the concomitant exposure to risk from chemical and non-chemical stressors and resulting pregnancy outcomes.

Maternal Medical Complications. Fetal health is not only individually determined, but is also influenced by maternal health and well-being. We continue our emphasis on maternal outcomes. In particular, we have focused on hypertensive disorders during pregnancy. As a first step, we are trying to identify factors that affect maternal blood pressure during pregnancy. In order to make use of the entirety of blood pressure readings collected across the pregnancy, we have considered a variety of statistical approaches, including latent trajectory and sparse functional data models. Our goal is to use environmental, social, and genetic data (such as GRK5 polymorphisms) to predict these blood pressure trajectories. A manuscript involving GRK5 polymorphisms and pregnancy-related hypertensive disorders is in preparation. Ultimately we hope these predicted trajectories will aid us in predicting birth outcomes; for example, women with monotone-increasing blood pressure trajectories may exhibit poorer birth outcomes than women with U-shaped curves. This work has been done in collaboration with the GISSA core. We have also conducted preliminary genetic association analyses involving obesity and gestational weight gain, an issue that has come to the forefront of maternal conditions affecting not only the maternal health but also appears to have long-term effects on childhood health.

Statistical Methods Development. We have been developing new statistical methodologies designed to improve analysis of the Project B data, as well as to advance statistical analysis more broadly. A paper detailing statistical methodology developed in year 5 for accounting for mid-study changes in measurement scales won the Youden award for the best paper in interlaboratory testing methods this past year (Burgette & Reiter. 2012). These methods were needed because the Project B investigators switched laboratories for measuring blood levels of heavy metals midway through data collection in order to take advantage of finer measurement scales. Exploratory analysis indicated that the distributions of levels for several exposures were markedly different across the labs, so that analyses based on a simple concatenation of the two labs' data would be biased. Using the second lab scale as the standard, so that effectively measurements before the lab switch are treated as missing, we developed general purpose methodology for imputing plausible values of the missing exposure measurements. The methods are based on assumptions about the relative ranks of measurements in the two scales, e.g., a measurement in the 10th percentile in one scale should be at the 10th percentile in the other scale. We implemented this methodology on the Project B data to provide the investigative team with improved data product.

In addition, we developed and implemented methods for finding important predictors in quantile regression when there are a very large number of covariates. These methods adapted the lasso and elastic net penalties for quantile regression. We applied the methods on a mid-study sample of women to uncover a previously unreported interaction: women who smoke and who have high blood lead levels tend to have babies with lower birth weights. An article on this research has been accepted for publication by *Epidemiology* (Burgette et al. 2012).

We developed and implemented methods for using factor analysis models in the context of

quantile regression. The investigative team believes that many of the predictors can be grouped into underlying factors. For example, the Project B data contain several variables that measure maternal stress, and arguably we should connect birth outcomes to the underlying factor of stress rather than its individual indicators. As another example, the data contain several imperfect indicators of smoking status, and we would like to connect birth outcomes to the underyling factor of true smoking status. We implemented the model on a mid-study sample of women from Project B, and we found that the smoking factor was a strong predictor of low birth weight. An article on this research was accepted for publication in *Biometrics* (Burgette & Reiter, 2012).

We also developed statistical methods for the genetic data. The first statistical innovation involving the genetic data is the adverse sub-population regression (ASPR) for multi-variate outcomes with high dimensional predictors. The ASPR is a two component latent class model, with the dominant component corresponding to (presumed) healthy individuals and the risk of falling in the minority component characterized via a logistic regression. The logistic regression model is designed to accommodate high-dimensional predictors, as occur in studies with a large number of gene by environment interactions, through use of a flexible nonparametric multiple shrinkage approach. The Gibbs sampler is developed for posterior computation. The method was evaluated with the Project B data and has been published in *Statistics in Medicine* (Zhu et al. 2012).

Collaborations with other SCEDDBO Components

The collaborative efforts across the SCEDDBO components have continued over the past year. The entire SCEDDBO team prioritized air pollution as one of the primary environmental contaminants to be examined across projects. This has involved significant discussions between members of Project B with members in Project A to construct viable markers of air pollution, including proximity to major roadways, and NATA data. Project B continues to consult with Project C to make more biological synergies across the two projects. Project C introduced a nest-deprivation model into the ongoing animal experiments in an attempt to better replicate the more complex psycho-social stressors experienced by the mothers in Project B. And finally, the statistical team for the GISSA Core has worked hard to develop more innovative statistical approaches to disentangling the complex web of interactions that are driving the birth outcomes. These innovations have been motivated by specific questions across all three projects.

Future Activities

In the next year, we will focus on data analysis and manuscript completion. We will continue to explore means to reduce the dimensionality of the genetic, psychosocial, and other data, as well as impute missing data. Our overall goal is to identify complex interactions amongst the three sides of the triangle we hypothesize influence pregnancy outcomes: host, social, and environmental contributors. We anticipate preparing and publishing several manuscripts in the next year. With the data collection complete, we are well-positioned to examine and identify combinations of factors that lead to health disparities in birth outcomes. We are particularly interested in identifying chemical and non-chemical environmental risk factors given that they are actionable to improve birth outcomes.

Publications

Chang HH, Reich BJ, and Miranda ML. Spatial Time-to-Event Analysis of Air Pollution and Preterm Birth. *Journal of the Royal Statistical Society Series C*. Forthcoming.

Messer LC, Miranda ML, Maxson P. 2012. The Built Environment and Women's Psychosocial Health. *Journal of Urban Health*. 1-15. PMID: 22907713.

Miranda, M.L., Edwards S., Chang, H., Auten, R. Proximity to Roadways and Pregnancy Outcomes. *Journal of Exposure Science and Environmental Epidemiology*. 23: 32-38. PMID: 22805991.

Zhu, B., Ashley-Koch, A.E., and Dunson, D.B. Generalized Admixture Mapping for Complex Traits. G3 (Bethesda). 2013 Jul 8;3(7):1165-75. doi: 10.1534/g3.113.006478. PMID: 23665878

Zhu B, Dunson D, Ashley-Koch AE. 2012. "Adverse Sub-population Regression for Multivariate Outcomes with High-dimensional Predictors." *Stat.Med.*

Publications – In Preparation/Submission

Laine, J., Sanders, A., Garrett, M., Miranda, M.L., Ashley-Koch, A., Fry, R. "Genes and the Environment: Genetic Variants of Th1/Th2 Cytokines Associated with Cd-induced Racial Differences in Birth Weight." In preparation.

Maxson, P., Edwards, S., Reiter, J., Miranda, M.L. "Psychosocial Health Typologies in Pregnant Women." In preparation.

Maxson, P., Edwards, S., Williams, R., Miranda, M.L. "Personality Profiles in Pregnant Women: Associations with Pregnancy Outcomes, Risk Behaviors, and Psychosocial Health." In preparation.

Miranda, M.L., Anthopolos, R., Wolkin, A., Stapleton, H.M. "Relationships between Maternal PBDE levels during Pregnancy and Birth Outcomes." In preparation.

Sanders, A., Smeester, L., Rojas, D., DeBussycher, T., Wu, M., Wright, F., Zhou, Y., Laine, J., Rager, J., Swamy, G., Ashley-Koch, A., Miranda, M.L., Fry, R. "Cadmium-associated Patterns of DNA Methylation in Mother-Baby Pairs: Enrichment of Common CpG Island Motifs." In preparation.

Swamy GK, Garret ME, Ashley-Koch AE, Miranda ML, "Genetic Variation in G-Protein Coupled Receptor Kinase-5 and Preeclampsia Among Black Women." In preparation.

Zhu, B., Garrett, M., Saldono, K., Swamy, G., Miranda, M.L., Ashley-Koch, A. "NOS1 is Associated with Preterm Birth and Birthweight among White Mothers." In preparation.

Supplemental Keywords

Pregnancy, preterm birth, low birth weight, preeclampsia, gestational hypertension, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms, genetic admixture

Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Period covered by the report: 5/1/2012 – 4/30/2013
EPA Agreement Number: RD83329301-0
Investigators: P.I.: Richard L. Auten, Co-Inv: W. Michael Foster
Project Period: Year 6

Objectives of Research: Specific Aims

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure 're-programs' maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

Progress Report/Summary of Accomplishments

Progress has been stalled. The technician who was employed by W. Michael Foster was dismissed for cause and investigations of her reports to collaborating investigators, including us, show that her reports do not match the original data generated by the instruments. The office of research integrity at Duke University is investigating the matter which has affected numerous projects. As a result, we have retracted one publication that had been accepted at the *J. Appl. Physiol* and are now repeating the experiments.

The Project C PI acquired a new instrument to perform pulmonary function testing in mice and is presently repeating the pivotal exposures and measurements to determine the validity of previous findings. No SCEDDBO funds are being used to support the repeat of these experiments. We have obtained supplemental funding from our dean to support performance of the pivotal studies for this project which are in question: the ascertainment of maternal diesel effects on postnatal ozone-induced airway hyperreactivity and the determination that neonatal ozone exposure produces long-lasting airway hyperreactivity. We hope to have these finished and analyzed in the next six months. The effects of prenatal diesel on neurocognitive development appear to be robust: postnatal high fat diet or pre-natal maternal social stress demonstrate synergistic effects on impairment of affective and cognitive behaviors in mice, and the effects on microglial activation appear to be TLR4 dependent. We plan to repeat the studies on the effects on respiratory function to determine if the perinatal pollution effects on lung structure and function in offspring are TLR4 dependent.

Future Activities

These will depend on the reproducibility of our previous findings.

Publications

Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, Cory-Slechta DA, Costa D, Diaz-Sanchez D, Dorman DC, Gold DR, Gray K, Jeng HA, Kaufman JD, Kleinman MT, Kirschner A,

Lawler C, Miller DS, Nadadur SS, Ritz B, Semmens EO, Tonelli LH, Veronesi B, Wright RO, Wright RJ. The outdoor air pollution and brain health workshop. Neurotoxicology. 2012. 3395)972-84.

Bolton JL, Huff NC, Smith SH, Mason SN, Foster WM, Auten RL, Bilbo SD. Maternal Stress and Effects of Prenatal Air Pollution on Offspring Mental Health Outcomes in Mice. 2013. *Environmental Health Perspectives*. In press.

Presentations

Bolton JL, Huff NC, Smith SH, Mistry RS, Potts-Kant EN, Auten RL, Bilbo SD. "Maternal Stress Exacerbates the Effects of Prenatal Air Pollution Exposure on Brain & Lung Cytokine Expression and Cognitive and Affective Outcomes in Offspring in a Sex-Specific Manner" Society for Neuroscience, New Orleans LA, October 13-17, 2012.

Bolton JL, Mason SN, Potts EN, Gilmour MI, Foster WM, Auten RL, Bilbo SD. "Sexually dimorphic placental responses to maternal air pollutant exposure: the root of sex differences in behavioral and metabolic outcomes of adult offspring?" Organization for the Study of Sex Differences, Baltimore, June 7-9, 2012.

Auten, RL. "Embracing Complexity: Animal Models of Environmental Health." EPA/NIEHS 2012 Webinar Series: Protecting Children's Health for a Lifetime.

Supplemental Keywords

Neuroinflammation, air pollution, maternal stress

Community Outreach and Translation Core

Period covered by the report: 5/1/2012 – 4/30/2013
EPA Agreement Number: RD83329301-0
Investigators: Pamela Maxson (PI)
Project Period: Year 6

Objectives of Research

The central objective of the Community Outreach and Translation Core (COTC) is to create, implement, and assess strategies to translate and apply the findings of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) into relevant information for women of childbearing age, families, community groups, policy makers, and health care professionals. The COTC conducts environmental health outreach and education directed at low income and minority women and their children; enhances the capacity of disadvantaged communities to understand threats posed by environmental contaminants and non-chemical stressors; and provides a bridge between campus research, communities and policy makers. The specific aims of the COTC are:

1. Support the community-based neighborhood assessment being undertaken as part of Research Projects A and B;
2. Partner with nursing programs at Duke-affiliated hospitals to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes;
3. Develop culturally-appropriate advisory materials on environmental contaminants for low-income expectant or nursing mothers with low English proficiency;

4. Deliver training to local health department personnel focused on environmental factors related to maternal health and pregnancy outcomes;
5. Participate in regional, state and federal policy dialogues to provide decision makers with policy-relevant science-based information concerning environmental exposures and health disparities related to maternal and child health and well-being; and
6. Increase awareness of maternal health and health disparities by facilitating bi-directional exchanges between Center investigators, community members, public health advocacy groups, and policy makers.

Progress Report/Summary of Accomplishments

The overall goals for COTC in year 6 were to continue to expand communication and translation efforts to specific audiences. The COTC utilized various communication tools appropriate to a variety of audiences. Collaboration with researchers and groups external to SCEDDBO continued to evolve and the COTC welcomed and responded to requests for environmental health information from community groups and the general public.

The Community Assessment Project (CAP) Phase 2 report was completed and disseminated to community partners in year 6. This phase expanded the geographic area so it included roughly 30,700 tax parcels. This second phase captured nearly 70% of the physical addresses for participants in the Project B cohort, providing a detailed characterization of the local neighborhood environment for a significant subset of participants. Built environment data were combined with Durham crime data and tax assessor data. In collaboration with the GISSA Core, CAP data were summarized into seven Neighborhood Health Indices. These indices have been linked to outcomes from Projects A and B. Our collaboration with community partners at all stages of the tool development, data collection, and dissemination of results provides a model for engaging the community in an active research program. The COTC will continue to disseminate the CAP results to multiple audiences (community members, public health professionals, and government officials).

Specific Aim 2 of the COTC is to partner with nursing programs to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes. Implementing activities to address this Specific Aim continued as a focus of COTC efforts in Year 6. A comprehensive project was designed to develop environmental health curricula for nursing students, nursing faculty, and practicing nurses. Supplemental funding from EPA's Environmental Education Grant Program has enabled collaborations with the Ecology Center in Ann Arbor, MI to produce this curriculum. The curriculum will be piloted and evaluated in the upcoming year.

COTC staff continues to collaborate with a variety of regional, state, and federal advisory groups including the American Lung Association Advisory Group, the Durham County Public Health Community Health Assessment Working Group, and the Obesity and Chronic Disease Committee of the Partnership for a Healthy Durham. In addition, SCEDDBO Director Marie Lynn Miranda serves on the EPA's Children's Health Protections Advisory Committee (CHPAC). The CHPAC is a federal advisory committee established in 1998 to provide independent advice to the EPA Administrator on regulations, research, and communications issues relevant to children's environmental health.

Collaborations with other SCEDDBO Components

COTC staff continues to meet with the SCEDDBO investigators to keep apprised of research developments and findings, translation opportunities, and scientific outreach activities (e.g., meetings, presentations and manuscripts) of the SCEDDBO investigators. The COTC staff also

provides the investigators with updates on COTC activities and opportunities to participate in outreach activities. During Year 6, as part of the communication strategy, COTC staff received a periodic update from each SCEDDBO investigator detailing any presentations, conferences, or other issues or occasions that might constitute a research translation opportunity. These regular and frequent communications enable COTC staff to keep abreast of research progress, update the website, and plan for translation efforts.

External Collaborations

The COTC has developed a wide and diverse network of collaborators among federal, state, and local agencies, universities, and community groups. Activities with these diverse partners cover a broad spectrum of children's environmental health issues, ranging from birth outcomes to lead poisoning prevention, environmental exposures, and obesity.

COTC staff has developed working relationships with scientists at the U.S. EPA representing a wide variety of disciplines. These relationships have allowed for exchange of research findings and data in a number of areas including distance-to-roadway analyses, air pollution impacts on birth outcomes, community engagement, and using GIS for environmental justice analysis. In terms of formal meetings, activities with multiple state and local agencies continue to cover a wide variety of topics including the impact of the built environment on obesity and pregnancy outcomes, mapping environmental exposures and built environment variables, as well as other topics related to school-aged children.

For the 5th consecutive year, COTC investigators mentored a student in the "Break the Cycle" project sponsored by the Region 4 of the U.S. EPA, Emory University and the Southeast Pediatric Environmental Health Specialty Unit. The selected student presented the built environment data from our Community Assessment Project and its relationship with pediatric asthma. The conference was held in Atlanta, GA, in May 2012. Dr. Pamela Maxson accompanied the student as her mentor.

Finally, the COTC continues to respond with detailed information to numerous requests from private citizens about a variety of environmental health concerns. These requests were received through both the CEHI toll-free number and via the CEHI website.

Future Activities

During the final year of the no-cost extension, the COTC will continue to expand communication and translation efforts to specific audiences. We will also continue our efforts to incorporate environmental health topics into continuing nursing education and sustain established collaborations with researchers within and external to SCEDDBO.

Publications

Kroeger G.L., Messer L., Edwards S.E., and Miranda M.L. 2012."A Novel Tool for Assessing and Summarizing the Built Environment." *International Journal of Health Geographics,* 11:46. PMID: 23075269.

Publications – In Preparation/Submission

Martz, M., Geller, M., Anthopolos, R., and Maxson, P. "Pediatric Obesity and Food Access in Durham, NC." In submission.

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Presentations

Henry, H., and Maxson, P. "Traffic-related Air Pollution and Pediatric Asthma in Durham County, North Carolina." Break the Cycle Conference. Emory University, Atlanta, GA. May 2012.

Supplemental Keywords

Risk communication, outreach, translation, participatory research, built environment

Geographic Information System and Statistical Analysis Core

Period covered by the report: 5/1/2012 – 4/30/2013
EPA Agreement Number: RD83329301-0
Investigators: Alan Gelfand (PI), Allison Ashley-Koch, Marie Lynn Miranda, Jerome Reiter
Project Period: Year 6

Objectives of Research

The overall objective of the GIS and Statistical Analysis Core is to **support spatial and quantitative analysis needs of the Center research projects, as well as the Community Outreach and Translation Core.** Our specific aims include:

1. Providing support for the development of environmental and social data layers needed to implement data analyses required for the research projects and the Community Outreach and Translation Core;
2. Providing statistical analysis, advice, and consulting on the broad range of statistical issues that arise in conjunction with the research projects, with a particular emphasis on data reduction methods and modeling spatial and spatio-temporal data within a Bayesian framework; and,
3. Providing analysis for the unique needs of genetic data arising from the clinical and animal studies of the center.

This support core facilitates the development of innovative quantitative methodology for children's environmental health research associated with the projects and cores. Equally important, it will enhance substantive collaboration between statisticians and scientists involved in the research projects yielding improved analyses of research core data, as well as novel statistical modeling.

Progress Report/Summary of Accomplishments

The GISSA Core has continued to build and maintain a spatially and temporally linked data architecture for maternal and child health outcomes from the prenatal period to early childhood. The central objective is to track mothers and offspring in their residential environments at varying time slices. While capitalizing on the extensive data warehouse that we have assembled since the Center's inception, we have continued to integrate data layers into the architecture such as metrics from the EPA's Air Quality System, National-Scale Air Toxics Assessment, fused air pollution data combining modeled and monitored data, and in-house constructed road proximity measures, in addition to the most recently available years of North Carolina statewide administrative data on births, educational outcomes, and blood lead levels. Based on linking methods described in previous reporting periods, the unique individual-level identifying record now enables connections across multiple administrative databases on births, blood lead surveillance, deaths, and educational outcomes. These datasets can each be examined separately and in various combinations according to the master linking file.

Moreover, with the completion of participant recruitment in Project B in August 2011, GISSA staff has focused on data quality control/quality assurance, along with finalizing the project analysis dataset and planning related studies with the participants. All of the participants have

been integrated into a geographic information system with information on environmental exposures, factors of the built environment, and standard demographic data.

In addition to data acquisition, management, and georeferencing, the GISSA Core has continued to provide innovative statistical support to each of the Projects. In Project A, the GISSA Core has continued to develop spatial models to better characterize associations between birth outcomes and environmental exposures, including air pollution and the built environment. In Project B, the GISSA Core supports multiple imputation efforts to construct finalized imputed datasets based on the full study population.

Collaborations with other SCEDDBO Components

By its nature, the GISSA Core is highly involved in collaborations across all Center components. On an ongoing basis, we work with the investigators of Project A and Project B to determine the relevant spatial and temporal data layers for upcoming analyses. We also remain actively involved in analysis planning in order to identify opportunities for statistical methods development. Overarching the Center, the GISSA Core is tasked with determining synergistic research areas across projects.

Future Activities

We will continue developing and expanding the geospatial data warehouse that supports analysis among various projects. The GIS team will continue working with investigators in Projects A and B to identify additional environmental layers to integrate into our data architecture. With the construction of the spatio-temporal data architecture, we will conduct analyses that leverage the spatial and longitudinal nature of the data, focusing on the quantile and multivariate approaches already developed by our team.

We will continue analyses on approximately 1,600 Project B participants with complete pregnancy data, genetic results, and environmental results. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity. We will also continue to generate imputed datasets based on the methodology developed by the GISSA Core, in order to handle missing data and error in laboratory measurements.

Publications

All manuscripts supported by the GISSA Core are listed under the individual research projects.

Supplemental Keywords

Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling