Mid-Atlantic Nutrition Obesity Research Center (NORC)
Start Date: 2005
Status: Ongoing
Funding Agency: NIDDK
Website: http://medschool.umaryland.edu/norc/

Organization and Goals

The mission of the Mid-Atlantic Nutrition and Obesity Research Center (Mid-Atlantic NORC) is to foster multidisciplinary research that leads to discoveries that enhance our knowledge of how nutrition impacts risk for chronic disease, including obesity, type 2 diabetes, hypertension, hyperlipidemia, cardiovascular disease (CVD), sleep disordered breathing, and osteoporosis, and to translate this knowledge into effective clinical treatments and prevention efforts. The Mid-Atlantic NORC brings together resources at the University of Maryland, Johns Hopkins University, the U.S. Department of Agriculture (Beltsville), and the Geisinger Health System, as well as cross-cutting expertise in molecular genetics and genomics, genetic epidemiology and statistical genetics, functional genomics, basic adipose cell biology, and applied physiology and clinical investigation that addresses the basic mechanisms that determine individual responses to nutrient intake and energy imbalance. Major themes include nutrigenomics and gene x environment interactions, adipose biology, aging, and exercise and muscle physiology.

In its first five years, the Mid-Atlantic NORC has been extremely successful. The Research Base has grown from 51 (39 funded members and 12 associate members) to 104 (76 funded members and 28 associate members). Mid-Atlantic NORC investigators have made seminal discoveries that have been published in high-profile journals, successfully garnered new research support, and have initiated efforts to translate their findings into new treatment and prevention paradigms for chronic nutrition related diseases. The Mid-Atlantic NORC has helped launch the careers of young investigators in obesity and nutrition science through its Pilot and Feasibility (P/F) Program. The Enrichment Program has improved education in nutrition science in the medical and graduate school and promoted outreach in the community.

The Mid-Atlantic NORC is organized into three interacting Focus Groups (Genetics and Nutrigenomics, Interventions, and Adipose Biology). There are three Research Cores: Molecular Genetics and Nutrigenomics (MGN) Core, Adipose Biology and Basic Mechanisms (ABBM) Core, and Clinical and Translational Research (CTR) Core. A fourth Core, the Administrative, Bioinformatics and Enrichment (ABE) Core, organizes seminars, journal clubs, symposia and other activities; oversees the P/F Program, which fosters multidisciplinary efforts and training of young investigators in nutrition-related science; and offers support in biostatistics to its members. By providing infrastructure that facilitates the work of our already highly interactive members, the Mid-Atlantic NORC enables progress toward the goal of establishing the scientific and clinical evidence base for effective new treatment and prevention paradigms, including personalized nutrition.

Objectives of the Mid-Atlantic NORC

1. To enable inter- and multidisciplinary efforts to identify genes and nutrient-gene interactions that influence nutrient metabolism and the risk of chronic diseases (particularly obesity, type 2 diabetes, CVD, stroke, and osteoporosis), and to determine the role of the gut microbiome in these and other nutrition-related diseases.

2. To understand the mechanisms by which weight loss through caloric restriction and exercise reduce risk factors for type 2 diabetes and CVD (e.g., hypertension, dyslipidemia, insulin resistance) in obese Americans and to understand the effect of aging on these nutrition and obesity-related chronic diseases.

3. To translate new discoveries in nutrition science by testing the effectiveness of lifestyle intervention strategies (diet and/or exercise) to:

    a. Prevent and treat obesity and its co-morbidities in at-risk groups (middle aged/older individuals, urban minorities, and youth);

    b. Prevent and treat sarcopenia and osteopenia associated with deconditioning and suboptimal nutrition in the elderly, as well as improving rehabilitation after hip fracture.

4. To expand the four Mid-Atlantic NORC Cores (ABE Core, MGN Core, ABBM Core, and CTR Core) to provide state-of-the-art and cost-effective services to a growing Mid-Atlantic NORC research base to enhance nutrition and obesity research and its translation to patient care.

5. To attract young investigators from different fields of biomedicine to apply innovative methods that address important questions in the field of nutrition through the P/F Grant mechanism.

6. To increase awareness of researchers and practicing health professionals in the Mid-Atlantic region about the important role of nutrition in human health by:

    a. Enriching and promoting nutrition education for medical, graduate, and allied health professional students, house staff, and physicians.

    b. Disseminating new developments in the area of nutrition science to the public through outreach programs in public schools and the community

Core Laboratories

Administrative, Biostatistics and Enrichment (ABE) Core: Alan R. Shuldiner, M.D., Director; Andrew P. Goldberg, M.D., Co-Director; Pilot and Feasibility Grant Program Co-Directors: Andrew P. Goldberg, M.D., and Gabriele Ronnett, Ph.D.; Enrichment Program Director: Nanette Steinle, M.D.

Biostatistics and Medical Informatics SubCore: John Sorkin, M.D., Ph.D., Director; Les Kirchner, Ph.D, Site Leader, Geisinger Health System

Molecular Genetics, and Nutrigenomics (MGN) Core: Braxton Mitchell, Ph.D., Director; Alan Shuldiner, M.D., Co-Director; Glenn Gerhard, M.D., Site Leader, Geisinger Health System

Clinical and Translational Research (CTR) Core: Andrew Goldberg, M.D., Director; Alice Ryan, Ph.D., Co-Director; Christopher Still, D.O., Director, Geisinger Health Center Satellite; Alan Shuldiner, M.D., Director, Amish Research Clinic Satellite; William Rumpler, Ph.D., Director, United States Department of Agriculture Satellite

Adipose Biology and Basic Mechanisms (ABBM) Core: Carole Sztalryd, Ph.D., Director; John McLenithan, Ph.D., Co-Director; Da-Wei Gong, Ph.D., M.D., Co-Director; George Argyropoulos, Ph.D., Site Director, Geisinger Health System

Executive Committee:

Drs. Alan R. Shuldiner, Andrew P. Goldberg, Carole Sztalryd, Alice Ryan, Nanette Steinle, Gabriele Ronnett, Braxton Mitchell, Da-Wei Gong, John McLenithan, Heidi Ortmeyer, John Sorkin, and Glenn Gerhard

Program Coordinator: Sara Sturgess, M.S., R.D., L.D.N., C.N.S.

External Advisory Committee:

Currently, the External Advisory Committee consists of the following individuals:

- Alan Attie, Ph.D., Professor of Biochemistry, University of Wisconsin
- Barbara Corkey, Ph.D., Professor of Medicine and Director, Boston Obesity and Nutrition Center, Boston University
- Michael Jensen, M.D., Professor, Department of Endocrinology, Diabetes, Metabolism, and Nutrition, and Director, Metabolic Studies Core, Minnesota Obesity and Nutrition Center, Mayo Clinic
- Jesse Roth, M.D., F.A.C.P. (*ad hoc*), Professor of Medicine, Albert Einstein College of Medicine, and Yeshiva University Investigator, Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System
- Steven C. Elbein, M.D. (*ad hoc*), Professor of Medicine, University of Arkansas for Medical Sciences, Endocrinology

With the new grant period to begin in September 2010, we plan to reconstitute the External Advisory Committee (members to be named). This will ensure the infusion of new ideas and critical insights to continue to improve our program.

Pilot and Feasibility Studies

Current Pilot and Feasibility (P/F) Project Descriptions

The Role of Nutrition in Acute Lung Injury-Associated Skeletal Muscle Wasting. Principal Investigator (PI): Michael Crow, Ph.D., Associate Professor, Director, Basic & Translational

Research, Division of Pulmonary & Critical Care, Johns Hopkins University. Funded 9/09. Eligibility: Senior investigator initiating novel nutrition research.

Muscular weakness is increasingly recognized as a serious complication of acute lung injury (ALI). It contributes to increased mortality, increased length of hospitalization, prolonged ventilator dependence, and markedly reduced quality of life. Muscle weakness is closely associated with muscle atrophy, a process that involves reduced protein synthesis and increased protein degradation and is driven by changes in the expression of genes that collectively are known as atrogenes. Dr. Crow has developed a mouse model of ALI that induces muscle wasting/dysfunction that mimics many of the unique features of a human muscle wasting syndrome in the context of ALI. His model shows (1) marked up-regulation (5–25 fold) of muscle atrogenes that is associated with loss of muscle mass and impairment of muscle function during the period of active lung injury and (2) markedly reduced food (but not water) consumption during the period of active lung injury that is coupled with a maladaptive increase in whole-body metabolism.

Based on the work of others in other muscle-wasting models, it is generally thought to involve the release of cytokines or other substances from the lung that then trigger activation of atrogenes in skeletal muscle. ALI also suppresses food intake, and reduced food intake in its extreme state (starvation) has been shown to directly trigger muscle atrogene expression through the up-regulation of the transcription factor, FOXo3a. It is possible then that the extreme reduction in food intake that occurs early in ALI could play an important and perhaps singular role in the activation of atrogene expression. To test this hypothesis, Dr. Crow proposes to (1) determine whether reduced food intake/nutrition alone (i.e., in the absence of ALI) can increase atrogene expression and promote muscle wasting and (2) determine whether restoring food uptake/nutrition blocks ALI-induced atrogene expression. To do this in a controlled fashion, he will force-feed each animal using an implanted gastrostomy tube to continuously deliver nutritional fluids before and after intratracheal instillation of lipopolysaccharide (IT-LPS) to induce ALI. This experiment will establish whether the reduction in food uptake is necessary for increased atrogene expression and muscle wasting in ALI mice. Overall, these experiments will establish whether changes in nutrition play a role in the induction of atrogene expression and muscle wasting in the context of ALI. Core facilities used: ABBM Core.

Determining Actical Thresholds for Ankle Accelerometry Among Adolescent Girls. PI: Erin Hager, Ph.D., Assistant Professor, Growth and Nutrition Division, Department of Pediatrics, University of Maryland, Baltimore. Funded 9/09. Eligibility: New investigator.

Accurate assessment of physical activity is necessary to determine level of physical activity, to examine trends and correlates of activity, and to evaluate the effects of physical activity promotion programs. Accelerometry provides a non-invasive method for objectively assessing physical activity that can be used to examine intensity, frequency, duration, and patterns of physical activity. Validation studies are necessary for each brand of accelerometer, placement of the accelerometer (e.g., hip, ankle, wrist), and population to be studied. The purpose of this study is to conduct a validation/calibration study to determine the threshold counts needed to classify activities by intensity (sedentary, light, moderate, and vigorous) for the Actical accelerometer, when placed on the non-dominant ankle of low-income, urban, African American adolescent girls. Three aspects of the proposed investigation are unique: (1) Most calibration studies have

examined waist or hip placement; however, Dr. Hager has found excellent compliance with ankle placement. (2) Validation studies are rarely conducted on low-income, minority samples—a group at high risk for inactivity and overweight/obesity. (3) The Actical, introduced in 2003, is widely used but has not been well studied in pediatric populations. This study will create valid threshold counts using ankle accelerometry, a placement method that Dr. Hager has shown is acceptable and feasible among a low-income, urban adolescent population; will contribute much-needed information to the physical activity literature; and will provide preliminary data for a Career Development Award application. Core facilities used: CTR Core.

Yoga To Improve Psychological and Neuroendocrine Function and Promote Weight Loss in Obesity. PI: Anjeli Inscore, Psy.D., Research Associate, Division of Gerontology, University of Maryland, Baltimore. Funded 9/09. Eligibility: New investigator.

The increased stress and impulsivity associated with obesity after menopause adversely affects metabolism and CVD risk, and can potentiate weight gain by increasing caloric intake, cortisol production, and adipose tissue lipoprotein lipase (ATLPL) activity. The relationship between stress, eating behavior, and obesity is complex. Although not a uniform finding, many individuals, particularly women, increase their food consumption during stress. Although weight loss and exercise interventions are effective in reducing cardiometabolic risk in the short-term, weight regain is common, reestablishing obesity and increasing risk of CVD and diabetes. Yoga, a mind-body intervention, improves psychological health and cognitive, cardiorespiratory, and metabolic functions. Persons participating in yoga interventions report decreased levels of state and trait anxiety and depression, enhanced well-being, neurocognitive benefits, reduced body weight, and improvements in blood pressure and lipid profiles in obese, insulin-resistant, and diabetic subjects. However, many of these studies have methodological flaws, including inadequate descriptions of study sample/subject selection, lack of randomization to experimental versus control comparison groups, limited sample sizes, short duration, poor statistical methods and control for confounders, observational designs without quantitative measurement of outcomes, and lack of follow-up and assessment of compliance. Dr. Inscore hypothesizes that yoga, when combined with caloric restriction (CR) will (a) improve psychological and neurocognitive functioning; (b) reduce activation of neural centers controlling appetite and the reward associated with appealing food; (c) decrease neuroendocrine stressors, insulin resistance, and ATLPL activity and increase muscle LPL; and (d) reduce cardiometabolic risk factors to a greater extent than does a low-intensity exercise (LI-EX; walking) + CR program. Dr. Inscore predicts that longitudinal follow-up of these subjects for 6 months after cessation of yoga + CR will show greater maintenance of weight loss than the LI-EX + CR group. The aims are the following: (1) In a small randomized efficacy study, compare the effects of a 4-month lifestyle intervention involving yoga + CR with behavior modification to an intervention involving LI-EX + CR on (a) mood and self-reported psychological stress, (b) neurocognitive function, (c) neuroendocrine stressors (cortisol) and adipocytokines, and (d) glucose and lipid metabolism, adipose, and muscle LPL activity. (2) Investigate whether these psychological, neuroendocrine, and metabolic changes are associated with changes in neural activation of key brain appetite and reward centers in response to visual images of appetizing foods. Core facilities used: CTR Core; ABBM Core.

Is BRCA1 a Novel Regulator of Adiposity and Energy Balance? PI: Laundette Jones, Ph.D., Assistant Professor, Department of Pharmacology and Experimental Therapeutics, University of Maryland, Baltimore. Funded 9/09. Eligibility: New investigator.

Dr. Jones's research focuses on the mechanisms underlying mammary epithelial cell growth and differentiation in Breast Cancer susceptibility gene 1 (BRCA1)-associated breast cancers using a mouse model of loss of full-length BRCA1. She recognized a unique phenotype within the adult mammary fat pad characterized by high levels of "brown adipocyte-like" cells that was not observed in the mammary gland of other adult female mouse strains. The objective of this study is to determine whether BRCA1 deficiency in mammary epithelial cells affects the differentiation of adipose tissue in the mammary gland. She hypothesizes that the loss of BRCA1 in mammary epithelial cells results in the persistent expression of "brown adipocyte-like" cells in the mammary fat pad. This persistent brown adipose tissue (BAT) may cause a shift in whole body metabolic status.

To test the hypothesis, she proposes to (1) characterize the temporal and spatial appearance of BAT and changes in metabolic parameters in BRCA1 mutant mice compared with wildtype at different ages and (2) determine whether the brown adipocyte phenotype in the mammary fat pad is attributed to loss of BRCA1 in mammary epithelial cells. This research will provide insight into whether white or brown adipose tissue has a role in the development of breast cancer. Core facilities used: ABBM Core.

RUNX2 as a New Molecular Biomarker Involved in the Regulation of Normal Angiogenesis, Possibly Altered with the Acquisition of Diabetic Vascular Complications. PI: Antonio Passaniti, Ph.D., Associate Professor of Pathology, University of Maryland, Baltimore. Funded 9/09. Eligibility: Senior investigator initiating research in nutrition and obesity.

Adiponectin, an anti-angiogenic factor found in fat tissue of lean individuals, declines with obesity, perhaps accounting for increased angiogenesis in fat tissue of obese individuals. Hyperglycemia (HG) along with insulin resistance contributes to the pathological consequences of diabetes, which include endothelial cell (EC) dysfunction, inhibition of angiogenesis, and development of both diabetes-induced microvascular complications (DIMC) and CVD. The runt-related transcription factor 2 (RUNX2) transcription factor, which regulates EC migration, proliferation, survival, and wound healing is activated (DNA binding and transcriptional activity) by euglycemic levels of glucose but inhibited by HG, suggesting a role in normal angiogenesis. However, it is not clear whether regulation of RUNX2 in microvascular EC from adipose tissue will be similar to its regulation in other ECs. Dr. Passaniti's hypothesis is that RUNX2 DNA binding and transcription in adipose-derived EC might be an accurate predictor of functional angiogenesis and that its regulation may be dependent on glucose and expression of adiponectin. The specific objectives are these: (1) to define the glucose-responsive activity of RUNX2 in human adipose-derived EC and (2) to determine whether the antioxidant resveratrol or the adipokine adiponectin regulate RUNX2 activity in response to glucose in human adipose-derived EC.

Since RUNX2 activity is inhibited to HG through the aldose reductase/ROS pathways, the long-term goal of Dr. Passaniti's work is to discover compounds that reduce oxidative stress and prevent or treat the vascular deficits associated with diabetes and/or CVD. These studies will

affect the understanding of how obesity impacts angiogenesis and vascular EC wound healing through HG and adipokine changes. This research will support the hypothesis that RUNX2 is a relevant biomarker of vascular dysfunction in diabetes. Core facilities used: ABBM Core.

Epigenetic Mechanisms for Altered Energy Homeostasis in Offspring Produced by Assisted Reproductive Techniques. PI: Kellie Tamashiro, Ph.D., Postdoctoral Fellow, Psychiatry and Behavioral Sciences, The Johns Hopkins University. Funded 10/08, 9/09. Eligibility: New investigator.

Assisted Reproductive Techniques (ART) bypass several biological processes and interactions that occur with natural *in vivo* fertilization. Although it is now well established that conception and development to full term can occur despite exclusion of these processes and interactions, the possible adverse consequences are not well known. Dr. Tamashiro previously reported that mice produced by somatic cell nuclear transfer (SCNT) become obese in adulthood. SCNT is the most extreme form of ART and is not currently used in humans. However, many of the procedures used in SCNT are also associated with ART and are used to circumvent infertility in humans. The overall scientific objective of this proposal is to determine the possible epigenetic alterations resulting from ART such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in mice that may be responsible for altered metabolic phenotypes using a genome-wide epigenetic approach. While epigenetics is known to play a critical role in the etiology of many cancers, only recently has the involvement of epigenetic mechanisms in other pathophysiological conditions, including the metabolic syndrome, been recognized. Thus, Dr. Tamashiro is in a position to utilize an existing high-throughput platform to identify epigenetic changes that may be associated with altered energy homeostasis in general. She hypothesizes that ART results in adverse metabolic phenotypes, such as obesity and insulin resistance, via epigenetic alterations, DNA methylation (DNAm) in particular, that persist into adulthood resulting in altered gene expression. During this second year of funding, she will run the CHARM assays as described in the initial proposal at the Epigenetic Center at Hopkins, now that the hybridization station is fully functional. She planned to conduct follow-up validation studies, as well as extend her findings to additional tissues in Year 2. Since she revised the research plan for Year 1 to focus on the placenta, she will focus her effort in Year 2 on a thorough characterization of the pancreas using resources provided by the Mid-Atlantic NORC to complement her genome-wide epigenetic assay for DNAm. Thus, she plans to accomplish the following aims: (Aim 1) to further characterize pancreatic tissues using resources provided by the Mid-Atlantic NORC ABBM Core. She will utilize the ABBM Core services for a more comprehensive examination of the pancreas, including determination of islet morphology and cell number and size. These data will complement and facilitate interpretation of the genome-wide methylation data, and facilitate interpretation of Aim 2. (Aim 2) Determine whether ART contributes to increased body weight and impaired glucose tolerance through epigenetic mechanisms using a genome-wide DNAm assay. Once genomic DNA is extracted from pancreatic tissue, the DNA sample is initially sheared randomly by passing it through a laser-drilled hole in a ruby, providing a highly controlled fragment range which is set to 1–3.5 kb. The protocol undergoes continuous optimization, and currently one can obtain sufficient DNA for CHARM without PCR Amplification, obviating any sequence-dependent PCR bias from 5–10 μg DNA. Quality control is ascertained by real-time PCR of known methylated and unmethylated genes. Two-color hybridization is performed using the CHARM array design on the NimbleGen HD2 platform, allowing inclusion of 2.1 million features on each array. The hybridizations are done in 12-side

Maui hybridization chambers and then scanned on an Axon GenePix 4000B scanner. Data are stored and analyzed using the High Performance Scientific Computing Core in the Johns Hopkins Bloomberg School of Public Heath. Dr. Rafael Irizarry, biostatistician for the Epigenetics Center, will provide biostatistics consultation for this project. (Aim 3) Validate top DNAm differences identified in Aim 2 by bisulfate pyrosequencing and RT-PCR. Dr. Tamashiro wants to validate the DNAm differences detected using CHARM with another method that has high precision, and in a replicate set of mice. Bisulfite pyrosequencing is the current gold standard approach to DNA determination in individual genes. Quantitative reproducibility of technical replicates amplified by the same PCR is approximately 2%, while variation induced by different bisulfate treatments and/or separate PCR amplifications is approximately 5%. Thus, she should be able to confidently determine the validity of the CHARM results. These studies appear to be a high priority to the NIH, as NICHD has issued a Program Announcement to examine the long-term consequences of ART on offspring, and NIDDK has a current RFA on *in utero* effects on metabolism with epigenetic mechanisms as a focus. Thus, the data obtained through this proposal will aid Dr. Tamashiro's application for R01 funding and transition to independent investigator. Core facilities used: MGN Core, ABBM Core.

Role of LSDP5, a Lipid Droplet Surface Associated Protein in Regulating Cardiac Myocytes β-oxidation. PI: Hong Wang, Ph.D., Postdoctoral Fellow, Division of Endocrinology, Diabetes and Nutrition, University of Maryland, Baltimore. Funded 9/09. Eligibility: New investigator.

A link between defects in cardiac cellular lipid homeostasis and disease is evidenced by several epidemiologic studies reporting higher rates of heart failure incidence in obese and diabetic patients. Animal models have provided us with some clues to potential underlying mechanisms, highlighting the importance to protect the cardiac mitochondrial function to prevent disease. Because cardiac myocytes have limited capacity for de novo lipogenesis, they are highly dependent on their ability to uptake and oxidize fatty acids (FA) to generate ATP to sustain their high metabolic function. Thus, to develop therapies to prevent heart failure, it is crucial to understand the nature of the mechanisms underlying the lipid droplet role in protecting mitochondrial function. The PAT protein family (Perilipin, ADRP, and Tip47) is the lipid droplet surface key proteome signature, and Lipid Droplet Storage Protein 5 (LSDP5), a recently discovered PAT protein, is highly expressed in oxidative tissues, including heart, and decreases lipid droplet hydrolysis and increases β-oxidation. This study is designed to advance the knowledge of the role of LSDP5 in regulating and protecting the mitochondrial function in cardiac myocytes. The aims of this study are designed to examine the mechanisms by which LSDP5 can protect the mitochondrial function by (1) decreasing the lipid droplet hydrolysis and (2) increasing efficient delivery of FA to the mitochondria by recruiting mitochondria at the lipid droplet surface. Understanding the mechanisms by which the lipid droplet compartment exerts its protective action toward the mitochondria function will help develop new effective drug strategies against cardiac cellular lipotoxicity.

Dr. H. Wang has found that LSDP5 recruits mitochondria at the lipid droplet surface and acts as a scaffolding protein for ATGL and CGI-58, respective lipase and co-lipase also involved in heart lipid droplet hydrolysis and decreases lipolysis. She has now obtained similar data in HL-1 heart cells that LSDP5-YFP over expression in HL-1 heart cells elicits mitochondria recruitment at the lipid droplet surface. Once she has established the protective role of LSDP5 in cardiac

myocytes in cultured cell line (cardiac α myosin heavy chain (MHC) promoter clone 26 has been obtained from Dr. Robbins), Dr. H. Wang plans to test the protective role of LSDP5 in the whole animal and will generate transgenic mice over expressing LSDP5 specifically in heart in a diet-induced model of obesity in C57BL mice and the genetic obesity/diabetic db/db mice. Core facilities used: ABBM Core.

Is the Relationship Between Depressive Symptoms and Obesity Explained by Physical Activity and Diet? A Prospective Study among African American Adolescents. PI: Yan Wang, M.D., Dr.P.H., Epidemiologist/Data Analyst, Division of Growth and Nutrition, Department of Pediatrics, University of Maryland, Baltimore. Funded 9/09. Eligibility: New investigator.

The purpose of this study is to determine the relationship between depressed mood and obesity among adolescents and examine the role of physical activity or diet in the relationship. Prior research indicates that depressed mood might lead to elevations in sedentary behavior and eating in the absence of hunger and leads to obesity. However, due to the lack of prospective studies and the difficulties in assessing physical activity and diet patterns, few studies have examined the pathway linking depressed mood to obesity through physical activity or diet. To fill in the gap in research, Dr. Y. Wang will conduct a prospective study using data retrieved from the Challenge project conducted by the Division of Growth and Nutrition, Department of Pediatrics, University of Maryland School of Medicine, with assessments at three time points. A total of 235 African American adolescents, ages 11 to 16 years old, from low-income, urban communities participated in a randomized health promotion/obesity prevention intervention trial. They were assessed three times: at baseline between July 2002 and May 2004, at post intervention 10 months later, and at delayed follow-up 24 months later.

Specific aims are to evaluate whether antecedent depressed mood and/or obesity are associated with subsequent increase in body mass index (BMI) and depressed mood among adolescents. Dr. Y. Wang will ascertain whether (1) gender modifies the relationship, (2) adolescents' average daily time spent in physical activity mediates the relationship between antecedent depressed mood and/or obesity and later increases in BMI, and (3) adolescents' average daily energy consumption mediates the relationship between antecedent depressed mood, antecedent obesity, and later increase in BMI. The dataset from the Challenge project provides a unique opportunity for mediation analyses due to its prospective design meeting the temporal criteria and having all the variables needed in the mediation model. This investigation will enhance the understanding of the relationship between depressed mood and obesity, and it will inform obesity or depression prevention interventions among children and adolescents by reducing the cost and enhancing the effectiveness. Core facilities used: Biostatistics and Medical Informatics SubCore.

Scientific Advances/Accomplishments

The Mid-Atlantic NORC provides cost-effective, laboratory-based services and hands-on training in specialized methods to new and established investigators. Mid-Atlantic NORC resources contributed importantly to advances and new initiatives of Mid-Atlantic NORC members in the areas of obesity, diabetes, CVD, and osteoporosis.

Mid-Atlantic NORC-supported investigators have made several seminal discoveries in the areas of nutrition, obesity, and nutrition-related chromic diseases that have resulted in publications in excellent journals and appreciable new funding. From 2005 to November 2009, Mid-Atlantic NORC investigators have published more than 1,200 original articles in excellent, peer-reviewed journals, approximately 200 of which were supported by Mid-Atlantic NORC activities. In 2009, 44 NORC-supported articles were published by NORC investigators.

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Educational Activities/Accomplishments

Mid-Atlantic NORC Seminar Series

The 2009–2010 Mid-Atlantic NORC Seminar Series included renowned speakers such as:

- **John Brunzell, M.D.**, Professor Emeritus of Medicine; Division of Metabolism, Endocrinology and Nutrition, University of Washington School of Medicine, Seattle, WA, who presented ***Hepatic Lipase: Genetics, Central Obesity and Premature Cardiovascular Disease*** on October 8, 2009
- **Randy J. Seeley, Ph.D.**, Professor of Psychiatry and Associate Director, Obesity Research Center, University of Cincinnati College of Medicine, Cincinnati, OH, who presented ***How Obesity Went to Our Heads: Novel Aspects of the Regulation of Energy Balance*** on November 2, 2009
- **Nir Barzilai, M.D.**, The Ingeborg and Ira Leon Rennert Chair of Aging Research; Professor of Medicine and Genetics and Director, Institute for Aging Research, Albert Einstein College of Medicine, New York, NY, who presented ***Basic Mechanisms of the Biology of Aging: Genetics and Longevity*** on April 8, 2010
- **Abhimanyu Garg, M.D.**, Professor of Internal Medicine and Chief, Division of Nutrition and Metabolic Diseases and Endowed Chair in Human Nutrition Research, University of Texas Southwestern Medical Center, Dallas, TX, who presented ***Lipodystrophies: Genetic and Acquired Syndromes*** on May 6, 2010
- **Derek LeRoith, Ph.D.**, Professor of Medicine and Chief, Hilda and J. Lester Gabrilove, M.D. Division of Endocrinology, Diabetes and Bone Disease and Director, Metabolism Institute, Mount Sinai Medical Center, New York, NY, who presented ***Increased Risk for Cancer in Obesity and Type 2 Diabetes: Does Hyperinsulinemia Play a Role?*** on June 7, 2010

About 40–50 faculty, postdoctoral fellows, and graduate students attended this seminar series regularly.

The Fat Focus Data Club group continues to meet every other Friday and is regularly attended by well over 20 faculty, fellows, and graduate students. This interest group has grown by a margin of about 50% in the past year, with several collaborations being fostered as a result of the regular meetings/talks.

Minisymposium and Retreat Planning

A minisymposium is being planned for spring 2011, focusing on nutrient/gene interactions. Also, plans are being made for one or more retreats/meetings for all Mid-Atlantic NORC investigators within the coming year.

Medical Education

Dr. Steinle has spearheaded nutrition education for medical students and house staff. Nutrition education for the clinical faculty in the Department of Medicine includes an annual presentation entitled "Popular Diets," given by Dr. Steinle at Ambulatory Grand Rounds. Dr. Steinle has also organized two Nutrition Case Study days per year for medical students as part of their curriculum. The topics are "Nutrition and the Nervous System" and "Nutrition and Immunity." These Case Study days are presented in small groups and are integrated to give students the opportunity to explore the nutritional basis of some conditions that they may encounter. Cases are presented and discussions are supported by the current literature.

To promote nutrition in medical practice and professional education, Mid Atlantic NORC members provide expertise and participate in medical education programs. Nutrition topics are presented to clinical faculty during the Ambulatory Grand Rounds series. Dr. Elizabeth Streeten discusses vitamin D, calcium, and bone health; Dr. Kristi Silver discusses management of diabetes; Dr. Nanette Steinle discusses popular diets and nutrient/drug interactions.

The Mid-Atlantic NORC Enrichment Program has devoted major efforts to incorporate nutrition into the medical curriculum at the University of Maryland. These efforts are supported primarily through coordinating educational efforts and teaching by Mid-Atlantic NORC members. We aim to integrate nutrition into the curriculum at all levels. In year one, medical students receive nutrition didactics in the Cell and Molecular Biology course. In addition to topics addressing cellular metabolism and macronutrients, topics address cellular mechanisms involving fat-soluble vitamins, water-soluble vitamins, minerals and trace elements, and nutrition in the lifecycle. Clinical conferences are devoted to diet assessment and vitamin D. The Introduction to Clinical Medicine course includes diet history and nutrition assessment, and physical manifestations of nutrient deficiency syndromes. Key elements of the nutrition history are being incorporated into standardized patient assessment metrics. Nutrition content in the second year includes calcium and vitamin D metabolism and bone health, obesity and energy homeostasis, dyslipidemias, diabetes, hypertension and micronutrients, hematopoietic disorders and iron, folate, vitamin B12 and pyridoxine, nutritional consequences of chronic renal failure, and nutrition and immunology. In year three, students receive training in critical illness and nutrition support, nutrient/drug interactions, celiac disease and nutritional consequences, and nutrition and chronic disease prevention. Fourth year electives in nutrition and in complementary medicine are

offered. The nutrition elective provides students the opportunity to conduct rounds with clinical nutrition teams and develop nutrition practice behavior skills in a variety of settings. Dr. Streeten participates in the nutrition elective by providing a clinical venue in the Medical Genetics clinic, where students are exposed to diagnosis and treatment of inborn errors of metabolism. Students completing the nutrition elective rotate with Dr. Streeten in the Metabolic Bone clinic as well. Students from throughout the United States have completed this elective. Dr. Steinle is clinical course co-director of the year one Cell and Molecular Biology course and was recently appointed an ad hoc member of the year two Pathophysiology and Therapeutics course committee, roles that facilitate ongoing integration of nutrition education in the medical curriculum. A didactic session created and taught by Dr. Steinle regarding nutrition and dental health is now included in the third year dental school curriculum at University of Maryland, Baltimore (UMB) as well. Dr. Streeten gives a core curriculum lecture to residents in Family Practice and Orthopedics and to Nurse Practitioner students annually, in which calcium and vitamin D metabolism are discussed. She also teaches fellows in Rheumatology and Geriatrics about calcium and vitamin D metabolism in a monthly metabolic bone clinic at the Baltimore VA Medical Center.

As part of the Mid-Atlantic NORC Enrichment Program, several Mid-Atlantic NORC members are involved in teaching obesity-related topics in the UMB curriculum as well.

- Dr. Alan Shuldiner teaches in the School of Nursing, Physiology of Aging course. He also incorporates discussion of the pathophysiology of obesity in the endocrine section in year two of the medical school curriculum.
- Dr. Shuldiner presents Current Topics in Molecular Medicine and Molecular insights in diabetes and obesity in the GPILS.
- Dr. John McLenithan is the section head and instructor for the endocrine physiology section of the first-year medical student's Functional Systems Course. He has developed a lecture for this course titled "Adipose Tissue as an Endocrine Organ and Obesity" that is integrated with his lecture on pathophysiology of obesity-dependent type 2 diabetes.
- Dr. McLenithan also teaches three lectures in the Physiologic Basis of Molecular Medicine, a GPILS course for graduate students, on "whole body metabolism" with emphasis on appetite, obesity, and metabolic disease.
- Dr Sztalryd teaches in the GPILS Core in the fall semester. Her class focuses on the structure and biological function of lipids and lipid metabolism pathways, understanding the regulation of cellular lipid homeostasis, as well as the digestion and absorption of lipids in physiological and pathological conditions (obesity and diabetes type 2).
- Recently, Dr Sztalryd began teaching in the physiology program and presents the regulation of adiposity in physiological and pathological conditions and an application lecture entitled "The Glycemic Clamp and Energy Homeostasis."
- Medical students and residents have an opportunity to complete a research elective of their choosing. Mid-Atlantic NORC members provide research training and mentor medical students and residents who chose to complete a research elective.
- Mid-Atlantic NORC members are also scheduled to meet with students informally throughout the academic year during brown bag lunches to promote exchange among students and Mid-Atlantic NORC members.
- The Mid-Atlantic NORC Enrichment Program has agreed to host, on a limited basis, international nutrition undergraduate students to provide research and clinical nutrition

training as well. To date, one international student from the Medical School of the University of Lisbon has rotated with Mid-Atlantic NORC faculty.

The Mid-Atlantic NORC Summer Research Program

The Mid-Atlantic NORC began a formal 8–10-week summer research internship for undergraduate and medical students in 2009 and continues this program with further development and growth in 2010. The Program is administered by Drs. Nanette Steinle and Alan Shuldiner, with the assistance of Sara Sturgess, Mid-Atlantic NORC Administrative Coordinator. In addition, the Mid-Atlantic NORC Executive Committee provides oversight. As Director of Enrichment, Dr. Steinle is responsible for curriculum development and course evaluation. The Program offers an intensive summer internship experience and mentorship during the formative stage of education that is critical to capturing the most promising motivated and brightest students into careers in nutrition. Students engage in a mentored research project in which students select a research question and are provided with laboratory resources and training. Students present a summary of their work in a peer group setting upon completion of the internship. They attend research conferences and seminars and have a weekly Core lecture by Mid-Atlantic NORC faculty, designed specifically for this Program and covering broad topics in nutrition and obesity-related chronic diseases. Summer interns potentially interested in careers in clinical arenas have the opportunity to shadow clinical faculty at inpatient and outpatient clinics (Joslin Diabetes Center at the University of Maryland, Endocrine Clinic, Surgery, Emergency Medicine, etc.).

Outreach

Dr. Steinle also provides mentorship to a medical student-led initiative, "Healthy Choices Baltimore." This initiative is aimed at reducing childhood obesity through teaching nutrition and lifestyle interventions to elementary school-age children in Baltimore. Medical, pharmacy, nursing, and social work students travel to the school weekly and provide nutrition and healthy lifestyle education for the students. The elementary school students receive nutrition education, which significantly enhances their curriculum and plants seeds toward developing healthy lifestyles. Medical students teach third, fourth, and fifth grade classes every Monday afternoon from 1–2 p.m. during the academic year. The Mid-Atlantic NORC Enrichment Program provides faculty and advising support. Dr. Steinle is faculty advisor to this student organization and meets quarterly with them. This activity is another resource for medical and allied health students to become involved in nutrition activities, to prompt their intellectual curiosities toward nutrition, and to encourage interaction with Mid-Atlantic NORC investigators. This program is also supported by the School of Medicine Office of Student Affairs and local businesses. Lesson plans developed by the medical students will soon be posted on the Mid-Atlantic NORC website.

Mid-Atlantic NORC leaders have engaged in a large number of community outreach programs. A summary of the most notable recent ones includes:

- Sponsored three community health fairs. Mid Atlantic NORC volunteers painted colorful fruits and vegetables on children and adult faces, providing an opportunity to discuss health and nutrition.

- Provided nutrition consultative services to one health club, and discussions are currently ongoing to develop nutrition-based resources for members of the Merritt health clubs.
- Six to 12 medical students volunteered for Healthy Choices Baltimore; 60 to 70 Midtown Academy Students are receiving weekly nutrition education.
- University of Maryland, Eastern Shore Mini-Med School Program, an outreach program focused on members of the Eastern Shore community and created to address disparities in minority and medically underserved populations in our region through improved health literacy, hosted the Mid-Atlantic NORC presentation "Obesity and making better nutrition and lifestyle choices."
- Participants completing the People Reducing Risk and Improving Strength Through Exercise and Diet (PRAISED) program lost an average of 7 lbs and significantly lowered their blood pressure and increased their HDL cholesterol. Significant improvements were also seen in functional tests, such as the 6-minute walk, which demonstrated benefit from increased activity.
- The MOVE! program enrolled 72 older, overweight-obese individuals (BMI 37.0 ± 6.2), high-risk veterans with sub-optimally controlled CAD risk factors. Of the first 18 veterans who completed the program, the average weight loss was 6 lbs, with an 11% decrease in blood pressure, and clinically meaningful (13%) decreases in TG, 4% decline in LDL, and a 3% increase in HDL.
- Dr. McLenithan lectured to three Parkville High School Biology classes in the Baltimore County Science and Mathematics Magnet Program on "Molecular Genetics of Diabetes and Obesity."
- Dr. McLenithan hosted a Howard County Biology Teacher, Dr. Saya Vijily, Ph.D.,for a laboratory internship to further develop her laboratory skills and knowledge of molecular aspects of diabetes and obesity research.
- Dr. Sztalryd presented her research on obesity to students at Baltimore Polytechnic Institute High School.
- Dr. Shuldiner and other Mid-Atlantic NORC leaders hosted 60 high school students for a half-day program that included discussion of Darwin's theory of evolution with a focus on the Thrifty Genotype Hypothesis and the obesity epidemic. Students also had a tour of the laboratories.
- Mypyramid.gov nutrient analysis exercise was completed with local middle schoolers during an aftercare program.
- Small group presentations were conducted by Mid-Atlantic NORC R.D.s about nutrition-related topics presented at Veterans Administration Quarterly Stroke Club meetings.
- Adriane Kozlovsky, M.S., R.D., conducted a supermarket tour and dining out education class at a local restaurant to practice heart healthy menu selection and eating habits.
- Mid-Atlantic NORC R.D.s provided individualized nutrition consultation to UMB faculty/staff through the Get Fit Maryland Program.
- Sara Shaughnessy, M.S., R.D., L.D.N., C.N.S., presented "Nutrition 101" and "Fad Diets: The Good, the Bad and the Ugly" at the 2009 UMB Dental School staff retreat.

Benefits and Interactions Resulting From the Existence of the NORC

Mid-Atlantic NORC Contributions to Bringing New Investigators to Nutrition Research

Through the Core's consultative services and the Mid-Atlantic NORC P/F program, we have attracted several high-quality investigators from outside the field into nutrition and obesity research. Several of these individuals are now funded for these studies. Examples include Gloria Reeves, M.D., Assistant Professor of Child Psychiatry, now studying antipsychotic medications and weight gain; Steven Munger, Ph.D., Associate Professor of Anatomy and Neurobiology, now studying the role of taste receptors in the gut on energy homeostasis; Jia Bei Wang, Associate Professor, UMB School of Pharmacy, studying HINT1 null mice now working on the mechanisms of a newly discovered obese phenotype; Jeffrey Fink, M.D., Associate Professor of Medicine, an expert in progressive renal insufficiency, now interested in the role of nutrition; Claire Fraser-Liggett, Ph.D., Emmanuel Mongodin, Ph.D., Jennifer Wortman, M.S., Scott Devine, Ph.D., and Owen White, Ph.D., internationally recognized experts in microbial genomics, now working with Dr. Shuldiner and others in the area of the gut microbiome in obesity and metabolic syndrome and the effects of nutritional and other perturbations.

Leveraging of Other Resources That Can Be Attributed to the Center

The Mid-Atlantic NORC continues to have significant synergism with the Claude D. Pepper Older Americans Independence Center that is directed by Dr. Andrew Goldberg. For example, the Muscle Biology Core of the Pepper Center provides Mid-Atlantic NORC clinical investigators with novel methods not available within our own Cores. The Diabetes Research and Training Center (DRTC) (Dr. Wondisford, Director; Dr. Shuldiner, Associate Director) is a joint venture of Johns Hopkins University and the University of Maryland School of Medicine. By design, the Core facilities provided by the DRTC complement those provided by the Mid-Atlantic NORC, particularly in the area of islet cell biology, small animal phenotyping, imaging, stem-cell biology, and transgenic technologies that are crucial for enhancing our capabilities in basic obesity and T2D research. Additionally, the DRTC adds substantial resources in the area of epidemiology and intervention (core translational component to the clinical research efforts supported by our Mid-Atlantic NORC).

We have been approached by many investigators from outside the Mid-Atlantic NORC institutions for access to Mid-Atlantic NORC resources and services. We created a new designation of membership, Affiliate Members, to accommodate these requests. We now have more than 10 Affiliate Members who have used Mid-Atlantic NORC services or who have benefited in some way from Mid-Atlantic NORC resources. For genetic studies, the MGN Core and CRT Core have contributed to the development of the Mid-Atlantic NORC biobank of thousands of DNA, plasma, and urine samples and genome-wide SNP data from well-phenotyped Amish subjects. This unique resource has been sought by large GWAS meta-analysis consortia, including CHARGE (Christopher O'Donnell, NIH), MAGIC (Richard Watanabe, University of Southern California), CDKgen (Caroline Fox, NIH), GlobalBPGen (Christopher Newton-Cheh, Harvard), and GOLD (Caroline Fox, NIH), for primary analyses and replication studies. Mid-Atlantic NORC resources have supported work of the International Chromosome 1q T2D Consortium, led by Dr. Mark McCarthy (Oxford), to identify T2D

susceptibility genes on chromosome 1q, and genetic studies in the Diabetes Prevention Program Genetics Group, led by David Altshuler and Jose Florez (Harvard/Broad), to dissect the genetic determinants of response to lifestyle and metformin interventions on diabetes prevention. Dr. Francesco Celi (NIH), in collaboration with Drs. Horenstein and Shuldiner, utilize CTR, MGN, and ABBM Core services for a bench-to-bedside project to study dietary plant sterols in Amish subjects. The Mid-Atlantic NORC continues to provide adipose tissue and assays and viral vector constructs through the ABBM and CTR Cores to Dr. Susan K. Fried (now at Boston University). The ABBM Core measures endothelial progenitor cell (EPC) counts for investigators at the Windber Institute to study the effect of nutritional interventions on CVD. Other outside benefactors of Mid-Atlantic NORC activities include Clifton Bogardus and Leslie Baier (NIDDK, Phoenix), Rima Kaddurah-Daouk (Duke University), Nir Barzilai (Albert Einstein College of Medicine), and Marc Blackman (Washington, DC, Veterans Administration Medical Center). Mid-Atlantic NORC contributions to these national and international efforts have led to publications in several high-profile journals, as well as new grant funding to Affiliate Investigators (e.g., Metabolomics Network for Drug Response Phenotype (RC2GM092729 to Kaddurah-Daouk), and an NIH Bench-to-Bedside grant (to Celi, Shuldiner, and Horenstein).