

cognitive data, ancillary studies focused on caregiver and heart disease outcomes, and provide examples of national and international mentoring that has leveraged REGARDS data. Finally, we will describe opportunities for additional data sharing and new ancillary studies.

#### DESIGN OF REGARDS: A NATIONAL COHORT OF BLACK AND WHITE ADULTS TO STUDY DISPARITIES IN STROKE AND COGNITIVE FUNCTION

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The REGARDS study enrolled 30,239 whites and blacks aged >45 from 2003 – 2007, with oversampling of blacks and residents of the Stroke Belt. Potential participants were mailed a letter/brochure followed by telephone call. After verbal consent, telephone interview assessed cardiovascular health and cognitive function. In a home visit, measurements of risk factors, biological samples, EKG, written consent were obtained; during the in-home visit, self-administrated questionnaires were left to be completed and returned. Participants are followed for hospitalizations via telephone at 6-month intervals. Annually and biennially, brief and more comprehensive assessments of global cognitive function are conducted. Medical records for suspected strokes are collected with adjudication by stroke experts. A 2nd in-home and telephone assessment was conducted 2013-2016, approximately 10 years after baseline. This presentation will describe the methodological details of REGARDS, progress on the specific aims of the current grant, and establish the context for the remaining presentations.

#### REGARDS COGNITIVE ASSESSMENT AND APPROACHES TO DEFINING COGNITIVE IMPAIRMENT AND CHANGE IN COGNITIVE FUNCTION

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Since 2003, REGARDS participants have taken part in telephone-based cognitive assessments. Global cognitive status is assessed annually with the Six-item Screener. Between 2006 and 2009, measures of learning and memory (CERAD Word List) and language/executive function (Animal and Letter Fluency) were implemented, and are administered biennially. A Brain Health Substudy, conducting in-home clinical examinations of neuropsychological, neurological, and functional status among 1000 participants, is underway to validate telephone assessments and estimate prevalence of VCID in REGARDS. Approaches to defining incident cognitive impairment and cognitive change, including definitions employed for case/cohort studies using stored blood samples, will be described. We will discuss psychometric and

methodological considerations for characterization of risks for cognitive impairment across race and region, as well as longitudinal trajectories of cognitive function.

#### USING REGARDS TO STUDY FAMILY CAREGIVER WELL-BEING, HEALTH, AND MORTALITY

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The REGARDS study has provided a unique opportunity to study both disease-specific (stroke) and broader samples of family caregivers, and to examine the effect of transitions to caregiving over time. Using REGARDS has afforded many advantages over conventional caregiving research, including the availability of biomarker and mortality data, a large sample of non-caregiving controls who can be carefully matched to caregivers, and ability to track onset of caregiving over time. Our findings illustrate the complex nature of caregiving-related effects. While caregiving leads to worse psychological well-being, we have found minimal physical health decreases and reduced mortality rates compared to matched non-caregiving samples. These findings have policy implications and have challenged the conventional beliefs about caregiving based on previous studies of convenience samples. Diverse students and junior faculty members from multiple universities have also gained experience and contributed to high impact papers from this work.

#### ADDING HEART DISEASE OUTCOMES TO REGARDS: THE REGARDS MYOCARDIAL INFARCTION ANCILLARY STUDY

Raegan Durant,<sup>1</sup> Emily Levitan,<sup>2</sup> Paul Muntner,<sup>2</sup> Todd Brown,<sup>2</sup> and Monika M Safford,<sup>3</sup>, 1. *University of Alabama at Birmingham, BIRMINGHAM, Alabama, United States*, 2. *University of Alabama at Birmingham, Birmingham, Alabama, United States*, 3. *Weill Cornell Medical College, New York, New York, United States*

The REGARDS-MI ancillary study provided new outcomes of heart disease events and adjudicated cause of death. A primary focus has been disparities in and risk factors for coronary artery disease. We demonstrated that compared to White men, Black men have a higher risk of fatal coronary heart disease (CHD) but a lower risk of non-fatal CHD. Ongoing work is investigating potential reasons for this. We have investigated the role of CHD in aging including the relationship between heart failure and cognitive function and the association of MI with functional status. The REGARDS-MI study has served as a platform for mentoring trainees and early stage investigators, many from underrepresented groups, and provided data to a large number of investigators to pursue research in CHD. To date, REGARDS-MI has contributed to nearly 200 publications and spawned additional ancillary studies. This presentation will highlight some of these publications and other research in progress.

#### OPPORTUNITIES FOR MORE AGING AND DISPARITIES RESEARCH, MENTORING, AND DATA SHARING WITH REGARDS

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One of the benefits of this large, national cohort study with black and white participants is the opportunity to involve a breadth of researchers in the science. REGARDS actively solicits and engages early career and minority investigators to lead or participate in manuscripts as well as ancillary studies. REGARDS has provided opportunities for >175 ancillary studies, including those that enrich existing outcomes, provide new outcomes, assess new exposures, link with other national data, support extended analyses, and assess genetic associations. Over 70% of the 500+ publications to date have a lead author who was not a funded REGARDS investigator. In this presentation, we will discuss some of the innovative ancillary studies and high-impact manuscripts that have grown out of REGARDS, the processes for developing an ancillary study/manuscript, and the procedures for obtaining REGARDS data. We will describe opportunities for mentored research for junior investigators, as well as independent research projects.

## SESSION 7715 (SYMPOSIUM)

### REVERSING COGNITIVE DECLINE IN AGING: REVERSIBLE MECHANISTIC DEFECTS AND A NOVEL NUTRITIONAL INTERVENTION

Chair: Rajagopal Sekhar

Co-Chair: George Taffet

Aging is the biggest risk factor for cognitive-decline and Alzheimer's disease (AD), but underlying mechanisms are not well-understood and interventions are lacking. Cognitive-decline in AD has been associated with deficiency of glutathione, (the most abundant, intracellular, antioxidant protein), elevated oxidative-stress, insulin-resistance and increased inflammation. We identified and reported that glutathione-deficiency and oxidative-stress in older-adults occur due to decreased availability of precursor amino-acids glycine and cysteine, and can be corrected with GlyNAC (a combination of glycine and the cysteine precursor N-acetylcysteine). We hypothesized that cognitive decline in older-adults is linked to glutathione-deficiency, mitochondrial-dysfunction, oxidative-stress, insulin-resistance, and inflammation. The first abstract discusses the rationale and findings of an open-label clinical trial: compared to young-humans, older-adults had cognitive-decline, glutathione-deficiency, mitochondrial-dysfunction, abnormal glucose-metabolism and insulin-resistance, oxidative-stress, endothelial-dysfunction and inflammation. These defects were improved/reversed by supplementing GlyNAC for 24-weeks, but benefits receded on stopping GlyNAC for 12-weeks. The second abstract presents a study in 8 young (20-weeks old) and 16 aged (90-weeks old) wild-type male C57BL/6J mice where we found that aged-mice had naturally-occurring cognitive-impairment, and brain defects in glutathione-deficiency, oxidative-stress, glucose-transport, mitochondrial glucose-oxidation, insulin-resistance, endoplasmic-reticulum stress, autophagy, mitophagy, inflammation, senescence, genomic and telomere damage. Aged-mice received either GlyNAC

or isonitrogenous-placebo supplementation for 8-weeks, and only GlyNAC-fed mice improved cognition and brain defects. Collectively these data highlights the discovery of novel and reversible mechanistic defects in older-adults and aged-mice with naturally-occurring cognitive-decline, and identifies that supplementing GlyNAC can improve brain-health and cognition. These findings could have important implications for reversing cognitive-decline in older-adults, and AD.

### REVERSING COGNITIVE-DECLINE IN OLDER ADULTS IN AN OPEN-LABEL CLINICAL TRIAL: NOVEL MECHANISMS AND THE ROLE OF GLYNAC

Chun Liu, Rajagopal Sekhar, Premranjan Kumar, Charles Minard, and Shaji Chacko, *Baylor College of Medicine, Houston, Texas, United States*

Age-associated cognitive-decline is an important risk factor for Alzheimer's disease, but interventions are lacking. We conducted an open-label trial to test our hypotheses on whether: (1) compared to 8 healthy young adults (25y), 8 'healthy' older adults (74y) have cognitive decline, decreased glucose availability for the brain due to mitochondrial dysfunction, elevated insulin-resistance, oxidative-stress and elevated inflammation; (2) supplementing glycine and N-acetylcysteine (GlyNAC) for 24-weeks corrects deficiency of the endogenous-antioxidant Glutathione and improves these defects, and thereby cognition; (3) stopping GlyNAC supplementation for 12-weeks results in a decline in accrued benefits. Outcome measures included cognitive testing (Montreal cognitive assessment; trail-making tests; verbal-fluency tests; digital-symbol substitution-test), mitochondrial fuel-oxidation, RBC-Glutathione concentrations, plasma oxidative-stress, insulin-resistance and inflammation, and tracer-studies to measure glucose metabolism. Results validated our hypotheses and showed that GlyNAC-supplementation corrected these defects and improved cognition. This trial suggests that supplementing GlyNAC may be important for improving/preventing age-associated cognitive-decline in older adults.

### REVERSING MITOCHONDRIAL, METABOLIC AND MOLECULAR DEFECTS IN THE BRAIN IMPROVES COGNITION IN AGED MICE

Rajagopal Sekhar, and Premranjan Kumar, *Baylor College of Medicine, Houston, Texas, United States*

Age-associated cognitive-decline is a risk factor for Alzheimer's disease (AD), but mechanisms are not well understood, and interventions are lacking. Rodent studies on AD have not led to therapeutic breakthroughs for cognitively-impaired humans. In an open-label trial in older-adults we found that supplementing GlyNAC (glutathione precursors glycine and N-acetylcysteine) improved cognitive-decline, defects in whole-body mitochondrial-function, and systemic insulin-resistance, oxidative-stress, and inflammation. We hypothesized that aged-mice will have similar defects in the brain, and studied male C57BL/6J mice as follows: young-mice (20w) were compared to two-groups of aged-mice (90-weeks) receiving either GlyNAC or isonitrogenous-placebo diets for 8-weeks. GlyNAC-supplementation improved cognition, and the following measures in the brain: glutathione-concentrations, glucose-transporters in blood-brain-barrier and neurons, mitochondrial glucose-oxidation, oxidative-stress, endoplasmic-reticulum stress, autophagy, mitophagy,