Future research should investigate the impact that unequal access to economic resources and distribution of health care resources has on women and men across age groups in Colombia.

CROSS-NATIONAL COMPARISONS OF STRESS AND WELL-BEING IN THE INTERNATIONAL FAMILY OF HEALTH AND RETIREMENT STUDIES

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Strong evidence demonstrates the long-term influence of stress and well-being on psychological, social, and physical health outcomes across the lifespan. Because of this, stress and well-being measures have been added to nearly all of the International Family of Health and Retirement Studies. However, this newly available data has not been compared cross-nationally or within-country to unpack how culture influences these important predictors of healthy aging. Using the Gateway to Global Aging Data, which provides harmonized data from the Health and Retirement Study and its sibling nationally representative studies, levels of self-reported stress (e.g. job stress, discrimination, loneliness) and well-being (e.g. quality of life, life satisfaction) are compared across 30 countries. Data come from the following studies: HRS, ELSA, SHARE, TILDA, CHARLS, KLoSA, MHAS, and JSTAR. We used data from the latest study wave for which the relevant survey was implemented. Average age of participants across studies is 67 and 55% are women. Initial analyses show stressor specific findings such as participants in Korea reported greater work stress than participants in Japan, England, the United States, and across Europe, and the United States reported higher loneliness than China and England, but not higher than Ireland. Reporting cross-national and within-country variation in these measures will be generative in pointing to new research directions for understanding how culture influences health and aging trajectories.

YOUNGER AND OLDER ADULTS PERCEPTIONS OF STRESSORS AFTER A FLOOD

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In August of 2016, historic flooding in Baton Rouge, Louisiana resulted in catastrophic damages and claimed 13 lives. This study is part of a larger research program on post-flood health and well-being across the adult lifespan. Participants (n=223, age range: 18-88 years) were tested during the immediate impact phase (Wave 1) and most participated in a follow-up assessment 9 (+/- 3) months later (Wave 2). In this study, we compared participants' narrative responses to an open-ended question at Wave 2 concerning the most stressful aspect of the 2016 flood. We hypothesized that older flood survivors would report stressors related to rebuilding and financial loss more often than younger survivors based on the Conservation of Resources theory (Hobfoll, 1989). Three groups were compared: non-flooded (controls), single disaster (flooded in 2016) and double disaster (flooded in 2005 and again in 2016). To create younger and older comparison groups, age was split at the median with sample sizes that ranged from 28 to 34 younger and older participants within each flood exposure group. Content analyses of responses by independent coders blind to the purpose of the study revealed that older flood victims reported greater stressors related to rebuilding flood-damaged homes and financial stressors than did their younger counterparts. In contrast, younger flood victims were more likely to report childcare issues and being displaced from their homes as stressors compared to the older victims. Implications of these data for understanding age-related vulnerabilities after severe weather events are discussed.

SESSION 6840 (POSTER)

INTERVENTIONS (BS)

UROLITHIN A: GUT-BRAIN DIETARY INTERVENTION IN PARKINSON'S DISEASE

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Gastrointestinal dysfunction is amongst the most common prodromal symptoms of Parkinson's disease (PD). Pathological alpha-synuclein has been detected in the intestines prior to disease onset, and a leaky gut is also implicated in its etiology. Thus, we hypothesized that modulation of the gut microbiome and intestinal immune milieu via early dietary intervention may act to mitigate PD pathogenesis. Urolithin A (UA) is a gut metabolite shown to ameliorate geriatric diseases by increasing mitophagy and dampening inflammation. The aim of our study is to elucidate its mechanism of action and therapeutic efficacy in PD, which to date is unclear. Preliminary flow cytometric data demonstrates that administration of a UA-diet significantly increased the proportion of colonic gamma-delta (γδ) T cells in nine-month-old Thy-1 α-syn mice, which are downregulated relative to non-transgenics on a non-UA control diet. PD patients have been reported to have higher levels of γδ T cells in their cerebrospinal fluid and, while little is known about colonic γδ Ts in the context of PD, these cells are anti-inflammatory and responsible for intestinal repair in several colitis models. Our data suggests a retention of lymphocytes involved in the targeted migration from the gut to the brain, which may contribute to gut epithelial integrity. Proportion of induced regulatory T cells in peripheral blood, which are critical for immune tolerance, also increased significantly with a UA-diet. In addition, UA-fed mice showed a slight improvement in novel object recognition. Additional analyses are underway to comprehensively evaluate the impact of UA on PD pathology.

COMBINING SCLEROSTIN AND DKK1 INHIBITORS TO IMPROVE BONE PROPERTIES IN THE AGED SKELETON

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Targeting the secreted Wnt inhibitor sclerostin has been an attractive strategy to improve skeletal health. Sclerostin

antibody (romosozumab-aqqg; Evenity) was recently approved by the FDA to treat patients at increased risk of fracture. However, an increased risk of cardiovascular events was reported, resulting in issue a 'black box warning' requirement for romosozumab. One potential solution to lower the risk of adverse events is to reduce the medication dose. Previously, we found that dual inhibition of sclerostin and Dkk1 produced extremely potent synergistic bone anabolic effects, in both genetic and pharmacological models. While Dkk1 inhibition alone has no consistent bone-building effects, combining antibodies that target sclerostin (Scl-mAb) and Dkk1 (Dkk1-mAb) at 3:1 ratio resulted in 2-3X more bone gain as Scl-mAb alone. Further, much lower total doses of dual antibody treatment, given at optimized proportions, generated equivalent bone anabolic effects as Scl-mAb alone (at much higher doses), suggesting that a combinational strategy has obvious translational benefits. Finally, we tested whether low-dose combination therapy can maintain the same osteogenic effect as Scl-mAb in adult (6 month) and aged (20 month) mice. Outcome measures derived from radiographic, biomechanical, and histomorphometric assays revealed that a 3:1 ratio of Scl-mAb:Dkk1-mAb at 12.5mg/kg was as efficacious as 25mg/kg of Scl-mAb alone, in both age groups. Moreover, cortical porosity—a significant factor contributing to skeletal fragility in the aged skeleton—was significantly reduced by both Scl-mAb and low-dose combination treatment. In conclusion, our findings suggest that optimized low-dose combinational therapy is viable strategy for improving skeletal fragility.

ORALLY ACTIVE, CLINICALLY TRANSLATABLE SENOLYTICS RESTORE A-KLOTHO IN MICE AND HUMANS

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Decreased α-Klotho, a geroprotective factor, and increased senescent cell burden are both associated with early onset of physical disability, cognitive impairment, and premature all-cause mortality. It has been demonstrated that eliminating senescent cells can enhance physical function, cognition, and survival in mice, as does overexpressing α-Klotho. Mice with low α-Klotho exhibit accelerated senescent cell accumulation, recombinant α-Klotho decreases senescent cell burden and restores lifespan in these mice, and senescent epidermal cells are reduced in mice overexpressing α-Klotho. Here, we tested the hypothesis that senescent cells cause decreased α-Klotho and hence that reducing senescent cells can increase α-Klotho. Senescent cell conditioned medium (CM) reduced α-Klotho in cultured non-senescent human umbilical vein endothelial cells (HUVECs), renal tubular endothelial cells, and astrocytes. These effects of senescent CM were partially attenuated by neutralizing antibodies against the senescence-associated secretory phenotype (SASP) factors, activin A and IL-1α. Transplanting senescent cells into younger mice caused decreased urine and brain α-Klotho. Genetically reducing highly p16Ink4a-expressing cells in old INK-ATTAC mice or administering the senolytics, Dasatinib plus Quercetin (D+Q) or Fisetin (F), to young mice transplanted with senescent cells, young diet-induced obese (DIO) mice, or naturally-aged mice increased urine, kidney, and/or brain α-Klotho. Treating patients with idiopathic pulmonary fibrosis (IPF), a cellular senescence-related disease, with D+Q led to increased urinary α-Klotho. Thus, targeting senescent cells causes increases in the geroprotective factor α-Klotho, potentially amplifying the beneficial effects of senolytic drugs.

OXR1 STABILIZES THE RETROMER TO EXTEND LIFESPAN AND NEURONAL HEALTH BY DIETARY RESTRICTION

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Dietary restriction (DR) delays aging and neurodegeneration, but the mechanisms behind this remain unclear. We reared over 150 fully sequenced fly strains from the Drosophila Genetic Reference Panel under ad libitum feeding or diet-restricted conditions and measured lifespan as well as healthspan to identify new targets for DR-mediated longevity. Through genome-wide association study, we identified genetic variants associated with influencing these traits under each dietary condition. A variant in mustard (mtd, called Oxidation resistance 1, OXR1, in humans), significantly associated with DR-specific lifespan. We demonstrate that mtd/OXR1 in neurons is necessary for DR-mediated lifespan extension. Neuronal knockdown of mtd also accelerates sensory decline, arguing for a specific role of mtd/OXR1 in neuroprotection. We show that mtd is essential for stabilizing the retromer complex, which is necessary for trafficking transmembrane proteins and lipids for reuse. As a result of OXR1 deficiency, the retromer destabilizes and lysosomes become overused. Overexpression of retromer proteins or supplementation with chaperone compound R55 rescues the lifespan defects and neurodegeneration seen in mtd-deficient flies, and R55 is capable of rescuing lysosomal aggregation and OXR1-retromer co-localization in cells from humans with OXR1 deficiency. We further show through multi-omic analyses in flies and humans that mtd/OXR1 associates with accelerated transcriptomic aging and proteins involved in neurodegenerative diseases, including Alzheimer's disease (AD). Overexpression of OXR1 and retromer proteins rescued AD-associated phenotypes in a fly model of AD. Thus, mtd/OXR1 enhances protein recycling in response to DR through the retromer, improving neuronal health and lifespan through mechanisms conserved across species.

EXTENDING A HEALTHY LIFESPAN WITH 3-HYDROXYANTHRANILIC ACID

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Metabolism of tryptophan by the kynurenine pathway is increasingly linked to aging. Kynurenine pathway enzymes