exercise program; gender, age, race/ethnicity, family income, and current smoking. Data analysis was performed using SAS 9.4. Of 7827 NHANES 1999–2002 participants with telomere assay data, 440 contained sufficient nutritional and medical history data to be included in our study (mean age 53 +/- 20; 42% male; 62% white). Our data demonstrated a statistically-significant positive trend for the association of Mediterranean diet score with leukocyte telomere T/S ratio (ß=0.02, p=0.05). This is the first study to examine the association between Mediterranean diet pattern adherence and leukocyte telomere length in a representative sample of the US population. Our findings indicate that Mediterranean diet pattern adherence is positively associated with LTL, suggesting a potential role in successful aging.

FUNCTION AND LEAN MASS RESPONSES TO OBESITY INTERVENTION IN WOMEN: EFFECT OF AGE AND PROTEIN INTAKE

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Women have higher rates of obesity than men and experience greater physical impairment as a result. Seeking an effective intervention for geriatric obesity, we randomized 80 obese (mean BMI=37.8 kg/m^2) women aged 45 to 78 years to a Control-Weight Loss (protein 0.8g/kg body wt; C-WL) or a High Protein-Weight Loss (protein 1.2 g/kg body wt; HP-WL) study arm. Compared to baseline, body weights were lower (p<0.001) by 5.7 and 5.2% at 4 months and 6.4 and 6.2% at 6 months for C-WL and HP-WL, respectively (no group difference). Age tended (p=0.058) to be positively associated with weight loss and affected the time course, such that being older was associated with more weight loss at 6 than at 4 months (F(1,48)=4.71, p=0.03). Several measures of function improved in both study arms. Distance walked in 6 minutes increased (p<0.01) at 4 months in HP-WL and at 6 months in both arms (p=0.001). Short Physical Performance Battery (p<0.001) and 8-foot up and go scores (p<0.01) also improved at 4 and 6 months in both groups. As expected, reductions in lean mass, fat mass, and waist circumference occurred at 4 (p<0.01) and 6 months (p<0.01) in both arms. In summary, both C-WL and HP-WL lost weight and robustly improved their function. Weight loss tended to be higher in older women, with a pattern of more weight loss at 6 than 4 months. These findings support the feasibility and the strong potential functional benefits of obesity interventions for older women.

SESSION 465 (POSTER)

PHYSIOLOGY, IMMUNITY AND AGING

ACETAMINOPHEN HEPATOTOXICITY IN MICE: EFFECT OF AGE, FRAILTY AND EXPOSURE TYPE

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Acetaminophen is a commonly used analgesic that can cause severe hepatotoxicity in overdose. Despite old age and frailty being associated with extensive and longterm utilization of acetaminophen and a high prevalence of adverse drug reactions, there is limited information on the risks of toxicity from acetaminophen in old age and frailty. This study aimed to assess changes in the risk and mechanisms of hepatotoxicity from acute, chronic and sub-acute acetaminophen exposure with old age and frailty in mice. Young and old male C57BL/6 mice were exposed to either acute (300mg/kg via oral gavage), chronic (100mg/kg/day in diet for six weeks) or sub-acute (250mg/kg, t.i.d, for three days) acetaminophen, or saline control. Pre-dosing mice were scored for the mouse clinical frailty index, and after dosing serum and liver tissue were collected for assessment of toxicity and mechanisms. There were no differences with old age or frailty in the degree of hepatotoxicity induced by acute, chronic or subacute acetaminophen exposure as assessed by serum liver enzymes and histology. Age-related changes in the acetaminophen toxicity pathways included increased liver GSH concentrations, increased NQO1 activity and an increased pro- and anti-inflammatory response to acetaminophen in old age. Frailty-related changes included a negative correlation between frailty index and serum protein, albumin and ALP concentrations for some mouse groups. In conclusion, although there were changes in some pathways that would be expected to influence susceptibility to acetaminophen toxicity, there was no overall increase in acetaminophen hepatotoxicity with old age or frailty in mice.

PHYSIOLOGICAL DYSREGULATION AS PROMISING MEASURE OF ROBUSTNESS AND RESILIENCE IN AGING STUDIES

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Longitudinal human studies have collected numerous repeated measurements of biomarkers allowing analyzing their dynamics in relation to mortality and various aging and health-related outcomes. We recently suggested novel implementation of the statistical distance measure (DM) for measuring the level of physiological dysregulation (PD) in aging body based on multiple biomarker profiles (Mech. Ageing Dev. 134: 110–117, 2013) in the framework of the stochastic process model of aging (Front. Public Health 4:3, 2016). The DM allows reducing the high-dimensional biomarker space into a single measure, which summarizes information about the PD. In this study, we constructed the DM using data on biomarkers available in two longitudinal human studies (Framingham Cohorts, Cardiovascular Health Study) and implemented different approaches to analyzing the relation of the DM to onset of "unhealthy life" (proxy for robustness), survival following disease onset (proxy for resilience), and total mortality. Application of the DM in the framework of the stochastic process model allowed for investigation of relationships between the PD and other aging-related

characteristics, not directly observable in data (such as declines in stress resistance and adaptive capacity), in the context of proxies for resilience/robustness and total mortality. We found that the PD differentially affects those outcomes, suggesting that robustness and resilience may have overlapping as well as distinct biological mechanisms, which warrants further exploring the genetic background of the PD and its relevance to longevity and disease-related pathways in our next step research using these and additional sets of longitudinal human data.

RELATIONSHIPS AMONG AGING HEALTH AND LONGEVITY IN HRS: CAUSAL ANALYSES USING MENDELIAN RANDOMIZATION

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Analyses of data from longitudinal studies of aging, health, and longevity allow for detecting associations between exposure variables (e.g., variables describing limitations physical functions, behavior and life style variables, other biomarkers) and health and longevity related traits. These associations are not always causal: confounders, inverse causation, and other factors can contribute to detected connections. Identification of modifiable causes of exceptional health and longevity has important implications for population health, but requires additional efforts. In this paper the Mendelian randomization is used to test causal influence of a number of exposure variables measured in Health and Retirement Study (HRS) on healthy lifespan and lifespan. For this purpose we first evaluated associations of selected variables with health and longevity related traits and selected those that showed significant associations for further analyses. Then we performed GWAS of lifespan and healthy lifespan and identified 100 SNPs whose variants showed most significant associations with these traits. Then analyses based on Mendelian randomization have been performed. These analyses were repeated for males and females and for black and whites separately. The list of such characteristics includes variables characterizing physical functions limitations, chronic morbidity and lifestyle. The analyses confirmed causal relationship of physical activity, smoking, physical functions limitations with healthy lifespan and lifespan. It was also found that type II diabetes, stroke, memory related disease, heart problems, depression, and lung disease have causal effects on lifespan. The results of these analyses can be used for targeting preventive strategies to improve healthy lifespan and increase longevity.

ELIE METCHNIKOFF REDISCOVERED: COMEBACK OF A FOUNDING FATHER OF GERONTOLOGY

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The year 2016 marks the centenary of the death of Elie Metchnikoff. In 1903, the Russian biologist, working at the Pasteur Institute in Paris, coined the term "gerontology," calling for a systematic study of aging. He launched such studies in his lab within the framework of his own theory of longevity: that intestinal microbes release toxins leading to premature aging and death. He believed that people could reach the age of 150 years and suggested that they repopulate the intestines with beneficial bacteria, for example, by eating yogurt. In effect, he invented the field later to be known as probiotics. His studies of intestinal microbes explored topics that today are at the forefront of modern research into the microbiome. For example, he strived to establish whether the gut microbes are essential to life, how they change throughout a person's life and how they can be manipulated to enhance health and prolong human lives. In addition to describing Metchnikoff's pioneering research, the talk will discuss the historic context of his work and dwell on his personality, including his obsession with avoiding germs. Metchnikoff's studies of intestinal flora, as he called it, were largely ridiculed by other scientists during his lifetime. But now that the link between aging and the microbiome has become one of the hottest topics in biomedical research, his ideas emerge as unusually prescient. Not only was he one of the founding fathers of gerontology, but he was ahead of the field by a hundred years.

SYSTEMS BIOLOGY OF HUMAN AGING - NETWORK MODEL 2016

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This network diagram is presented to aid in conceptualizing the many processes of aging, the causal chains of events, and the interactions among them. Contemplation of this network suggests promising intervention points for therapy development. This diagram is maintained on the Web as a reference for researchers and students. Content is updated as new information comes to light.

[www.LegendaryPharma.com/chartbg.html]

At first glance the network looks like a complicated web. However, as a conceptual summary, in one view, we can see how most biogerontological processes relate to each other. Importantly, examination of these relationships allows us to pick out reasonably plausible causal chains of events. Within these chains, we can see age-related changes or accumulations that appear to be promising targets for future therapy development. The many observable signs of human senescence have been hypothesized by various researchers to result from several primary causes. Inspection of the biochemical and physiological pathways associated with age-related changes and with the hypothesized causes reveals several parallel cascades of events that involve several important interactions and feedback loops. This network model includes both intracellular and extracellular processes. It ranges in scale from the molecular to the whole-body level. Effects due to externalities, lifestyle, environment, and proposed interventions are highlighted around the margins of the network.

EFFECT OF AGE AND CALORIE RESTRICTION ON VOLUNTARY MOVEMENT DURING ADULTHOOD OF RHESUS MONKEYS

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Various aspects of anatomy, physiology and behavior of age-matched groups of male (n=46) and female (n=30) rhesus monkeys undergoing moderate calorie restriction beginning in adulthood (R, n=38) or eating ad libitum during the day (C, n=38) have been measured regularly for more than 25 years. Calorie restriction has been shown to increase both healthspan and lifespan in this cohort of monkeys and in other species. Movement was initially monitored by