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## Symposia

**S1- SARCOPENIA: NO CONSENSUS, NO DIAGNOSTIC CRITERIA, AND NO APPROVED INDICATION HOW DID WE GET HERE?** Bruno Vellas *(IHU HealthAge, Toulouse, France)*

In addition to the role of skeletal muscle in movement and locomotion, muscle plays a critical role in a broad array of metabolic processes that can contribute to improved health or risk of disease. The age-associated loss of muscle has been termed sarcopenia. Muscle is the primary site of insulin-stimulated glucose disposal and the largest component of basal metabolic rate, directly and indirectly affects bone density, produces myokines with pleiotropic effect on muscle and other tissues including the brain, stores essential amino acids essential for the maintenance of protein synthesis during periods of reduced food intake and stress. As such, not surprisingly deterioration of skeletal muscle health, typically operationalized as decline of muscle mass and muscle strength is both a powerful risk factor and main consequence of chronic diseases, disability, and loss of independence, and it is one of the strongest risk factors for mortality. However, skeletal muscle remains one of the most plastic of all tissues, with rapid changes in rates of protein synthesis and degradation in response to physical activity and inactivity, inflammation, nutritional and hormonal status. This has made the development of pharmacological therapies to increase muscle mass (or prevent loss) an important goal for decades. However, while remarkable advances in the understanding of molecular and cellular regulation of muscle protein metabolism have occurred recently, there are no approved drugs for the treatment of sarcopenia, the loss of skeletal muscle affecting millions of older people. The goal of this symposium is to describe the possible reasons for the lack of new and effective pharmacotherapies to treat one of the most important risk factors for age-associated disease and loss of independence.

**Communication 1:** *Muscle mass not lean mass is associated with health-related outcomes: implications for defining sarcopenia,* Peggy Cawthon (California Pacific Medical Center USA)

**Communication 2:** *Geroscience of skeletal muscle and sarcopenia,* Luigi Ferrucci (National Institute on Aging, Baltimore, MD, USA)

**Communication 3:** *Sarcopenia: How we got here and the path toward a unified definition,* William Evans (University of California, Berkeley, CA, USA)

**S2- CHARACTERIZING RESILIENCIES TO PHYSICAL STRESSORS IN OLDER ADULTS: PHENOTYPE DEVELOPMENT AND VALIDATION.** Qian-Li Xue *(Department of Medicine Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA*)

**Communication 1:** *Unveiling Patterns of Physical Resilience After Knee Replacement: Insights from the RESilience in TOtal knee Replacement (RESTORE) Study,* Thomas Laskow[1], Mallak K Alzahrani[1,2], Qian-Li Xue[1,2], Ravi Varadhan[4,2], Karen Bandeen-Roche[3,2], Julius Oni[5], Frederick Sieber[6] ((1) Department of Medicine Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, Baltimore, MD, USA; (2) Center on Aging and Health, Johns Hopkins Medical Institutions, Baltimore, MD, USA; (3) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; (4) Department of Oncology Division of Quantitative Sciences, the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD, USA; (5) Department of Orthopedic Surgery, School of Medicine, Johns Hopkins University, Baltimore, MD, USA; (6) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA)

**Background:** Physical resilience describes an individual's ability to endure clinical stressors and rapidly return to, or exceed, baseline function. We hypothesize resilience manifests in two primary phenotypes: short-term stress response, and longer-term post-stressor recovery. **Objectives:** (I) Develop physical resilience phenotypes following elective total knee replacement (TKR) surgery; (II) Evaluate relationships of these phenotypes to clinical endpoints and patient-reported outcomes. **Methods:** Our study included 112 individuals aged >=60 who underwent TKR for osteoarthritis. We measured resilience phenotypes using Short Physical Performance Battery (SPPB), Pittsburgh Fatigability Scale (PFS), KOOS Quality of Life (QOL), and SF36-Physical Component Score (PCS) at baseline, 1-month, and 6-months post-surgery. Resilience outcomes (KOOS ADL function and pain subscales, physical activity via accelerometry) were assessed at 12-months. Resilience phenotypes consist of both short-term stress response and post-stressor recovery, determined by comparing 1-month and 6-month post-surgery measures to baseline, respectively. Linear

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regression was used to examine associations between resilience outcomes and resilience phenotypes, adjusting for age, race, education, sex, BMI, stressor magnitude by anesthesia dose, and baseline function. **Results:** Participant average age was 70 (SD=6.9), with 66% females and racial distribution 59% white and 42% black. Average BMI was 32 (SD=5.7), and average education was 14 years (SD=2.8). Analysis revealed better post-stressor recovery at six-months, as indicated by improvements in PFS, KOOS-QOL, and PCS, was significantly associated with greater enhancements in KOOS' ADL function ($p<0.01$ for all) and pain subscales ($p=0.019$, $<0.01$, $<0.01$, respectively) at 12-months, adjusting for covariates. These associations were independent of baseline levels of resilience measures and outcomes. In contrast, post-stressor response at one-month did not show any significant association with resilience outcomes. Changes in physical activity or SPPB scores were not linked to any resilience measure. **Conclusion:** Within a population of community-dwelling older adults undergoing TKR, resilience phenotypes at 6-months were associated with 12-month patient-reported outcomes concerning pain and function. Further work should evaluate association of trajectories with additional clinical end-points, including falls, and consider alternative corrections for baseline of resilience measures.

**Communication 2:** *Developing a Multivariate Profile of Physical Resilience through Latent Variable Modeling,*
Qian-Li Xue[1,2], Thomas Laskow[1,2], Mallak K Alzahrani[1,2], Karen Bandeen-Roche[3], Ravi Varadhan[4,2], Jeremy D. Walston[1,2], Frederick Sieber[5] ((1) Department of Medicine Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, Baltimore, MD, USA; (2) Center on Aging and Health, Johns Hopkins Medical Institutions, Baltimore, MD, USA; (3) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; (4) Department of Oncology Division of Quantitative Sciences, the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD, USA; (5) Department of Anesthesiology and Critical Care Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD, USA)

**Background:** As individuals age, they often face a variety of health challenges. Physical resilience indicates how well a person can physically cope with and recover from these challenges, which is crucial for maintaining independence and quality of life in older age. **Objectives:** (I) To develop phenotypes for physical resilience in response to a clinical stressor; (II) To assess convergent validity of these resilience phenotypes through the use of pre-stressor indicators of resilience measured at baseline. **Methods:** Using longitudinal data from 112 individuals aged 60 and above who had elective total knee replacement for degenerative joint disease, we identified resilience trajectories through four functional measures: objective performance tests (Short Physical Performance Battery, SPPB) and self-reports (Pittsburgh Fatigability Scale, PFS; KOOS Quality of Life, QOL; SF36-Physical Component Score, PCS). Our two-stage analytical method first applied latent profile analysis (LPA) to each measure using baseline, 1-month, and 6-month postoperative data, then employed latent class analysis (LCA) on these measure-specific profiles. The final resilience phenotype was determined based on this LCA classification and validated against resilience markers including frailty, self-reported health, and the Charlson Comorbidity Index (CCI). **Results:** The LPA revealed distinct resilience profiles across four measures: 4 for SPPB, 3 each for PFS, QOL, and PCS, showing varied baseline levels and/or change rates over 12 months. Subsequently, the LCA categorized the sample into two classes: 58% as non-resilient and 42% as resilient. The non-resilient group showed a higher prevalence of frailty (27.7% vs. 6.4%, $p<0.01$), poor or fair self-reported health (29.2% vs. 6.4%, $p<0.01$), and a moderate/severe comorbidity burden (CCI>2; 21.5% vs. 10.6%, $p=0.25$). **Conclusion:** This study demonstrated a robust correlation between the identified resilience phenotypes and theoretically associated measures. Future research into its contributing factors has the potential to revolutionize healthcare for older adults, shifting the focus towards promoting recovery and overall well-being, rather than merely managing health conditions.

**Communication 3:** *Physical Resilience in Older Adults Undergoing Hematopoietic Stem Cell Transplantation,*
Nicholas Schmedding[1], Ravi Varadhan[2], Marianna Zahurak[2], Jeremy Walston[1], Karen Bandeen-Roche[3], Andrew Artz[4], Richard Jones[5], Philip Imus[5] ((1) Department of Medicine Division of Geriatric Medicine and Gerontology, School of Medicine, Johns Hopkins University, Baltimore, MD, USA; (2) Department of Oncology Division of Quantitative Sciences, the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD, USA; (3) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; (4) Division of Leukemia, Department of Hematology & Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; (5) Department of Oncology Division of Hematologic Malignancy, Johns Hopkins Hospital / Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA)

**Background:** Physical resilience is the ability to maintain or regain physical function after a clinical stressor. Characterization of physical resilience in older adults undergoing hematopoietic stem cell transplantation (HCT) is important for optimizing outcomes and should include both disease-specific outcomes and measures of functional status. **Objectives:** (I) Define and measure physical resilience in older adults undergoing HCT; (II) Evaluate whether resilience metric predicts long-term survival. **Methods:** Analyzing 107 participants in the REBOUND trial aged ≥60, we defined a resilient outcome at 6 months post-transplant as being alive, not relapsed, and without aggregate adverse change versus baseline on sub-domains of short physical performance battery scores, grip strength, Pittsburgh fatigability scale scores, and weight. Each sub-domain was scored –1 for adverse change, 0 for no change, and +1 for favorable change. Relapse was

assigned a value of –5. We then summed the sub-domain scores to create a combined resilience score. Participants with a combined score ≥0 at 6 months were considered resilient and those with negative scores non-resilient. Multiple imputation was employed to approximate missing sub-domain scores using available baseline, 1-month, 6-month, and demographic data. 6-month landmark analyses were performed on imputed data sets to assess the association between resilience and subsequent survival. **Results:** 21/107 (19.6%) of participants were deceased at 6 months. After multiple imputation to address missing data, the proportion of resilient participants in the entire sample was estimated to be 43.0% (CI 32.6%, 53.4%). Utilizing imputed data, landmark analysis revealed lower subsequent mortality in resilient patients (HR 0.54 (0.21, 1.38), p=0.198). When treating resilience score as a continuous variable potentially vulnerable to outlier effects, HR was 0.79 (0.65, 0.97) and p=0.026. **Conclusion:** More than 40% of patients aged 60 and above enrolled in the REBOUND trial had a resilient response to HCT. A resilient response may be associated with better long-term survival in older patients.

## S3- GENE EXPRESSION PROFILING IN MUSCLE IDENTIFIES PATHWAY ASSOCIATIONS WITH MITOCHONDRIAL RESPIRATION, PHYSICAL PERFORMANCE, AND MUSCLE MASS IN OLDER INDIVIDUALS FROM THE STUDY OF MUSCLE, MOBILITY AND AGING (SOMMA).

Steven R. Cummings, *(San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, California. Department of Epidemiology and Biostatistics, University of California, San Francisco, California, CA, USA)*

**Communication 1:** *Expression of mitochondrial oxidative stress response genes in muscle is associated with mitochondrial respiration, physical performance, and muscle mass in older individuals,* Gregory J Tranah[1,2], Haley N Barnes[1], Peggy M Cawthon[1,2], Paul M Coen[3], Karyn A Esser[4], Russell T Hepple[4], Zhiguang Huo[4], Philip A Kramer[5], Daniel S Evans[1,2], Steven R Cummings[1,2] ((1) California Pacific Medical Center Research Institute, San Francisco, California, USA; (2) University of California San Francisco, San Francisco, California, USA; (3) Advent Health, Translational Research Institute, Orlando, Florida, USA; (4) University of Florida, Gainesville, Florida, USA; (5) Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA)

**Background:** Gene expression in skeletal muscle of older individuals may reflect compensatory adaptations in response to damage that preserve tissue integrity and maintain function. A first line of defense to prevent cellular damage is the oxidative stress response to reactive oxygen species. Identifying associations between oxidative stress response gene expression patterns and mitochondrial function, physical performance, and muscle mass in older individuals would further our knowledge of mechanisms related to managing molecular damage to preserve physical resilience. **Methods:** To characterize expression patterns of genes responsible for the oxidative stress response, RNA was extracted and sequenced from skeletal muscle biopsies collected from 575 participants (≥70 years old) from the Study of Muscle, Mobility and Aging (SOMMA). Expression levels of twenty-one protein coding RNAs related to the oxidative stress response were analyzed in relation to six measures, including: mitochondrial respiration from muscle biopsies (P1-Max OXPHOS), physical performance (VO2 peak, 400m walking speed, and leg strength), and muscle mass (thigh muscle volume and whole-body D3Cr muscle mass). **Results:** The mRNA level of the oxidative stress response genes most consistently associated across outcomes are expressed within the mitochondria. Higher expression of mRNAs that encode mitochondria located proteins SOD2, TRX2, PRX3, PRX5, and GRX2 were associated with higher levels of mitochondrial respiration and VO2 peak. In addition, greater SOD2, PRX3, and GRX2 expression was associated higher physical performance and muscle mass measures. **Conclusion:** Our study demonstrates that expression of oxidative stress response genes expressed within the mitochondria are positively associated with mitochondrial function, physical performance, and muscle mass in older persons. Identifying specific mechanisms associated with high functioning across multiple performance and physical domains may lead to interventions with greater impacts on mobility and independence. **Key words:** mobility, aging, mitochondria, gene expression, cohort study. **Disclosures:** Steven R. Cummings is a consultant to Bioage Labs. Peggy M Cawthon is a consultant to and owns stock in MyoCorps. All other authors declare no conflict of interest.

**Communication 2:** *Expression of Neuromuscular Junction pathway genes predict muscle mass and performance traits in the Study of Muscle, Mobility and Aging (SOMMA),* Cole Lukasiewicz[1], Haley N Barnes[2], Daniel S Evans[2,3], Paul M Coen[4], Zhiguang Huo[1], Steven Kritchevsky[5], Anne B. Newman[6], Karyn A Esser[1], Steven R Cummings[2,3], Gregory J Tranah[2,3], Peggy M Cawthon[2,3], Russell T Hepple[1] ((1) University of Florida, Gainesville, Florida, USA; (2) California Pacific Medical Center Research Institute, San Francisco, California, USA; (3) University of California San Francisco, San Francisco, California, USA; (4) Advent Health, Translational Research Institute, Orlando, Florida, USA; (5) Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA; (6) University of Pittsburgh, Pittsburg, Pennsylvania, USA)

**Background:** With aging skeletal muscle fibers undergo repeating cycles of denervation that are usually followed by successful reinnervation. However, in approximately the 8th decade of life the rate of reinnervation does not keep pace with denervation, resulting in the accumulation of muscle fibers that lack connection to a motor neuron, causing an acceleration of muscle atrophy and contractile dysfunction. The significance of denervation in precipitating important clinical outcomes with aging, including impaired mobility, has not been well-studied. **Methods:** The Study of Muscle, Mobility and Aging is a large cohort study with the primary objective to assess how

features of aging muscle biology relate to walking speed and other clinically relevant traits. Using transcriptomics data from vastus lateralis muscle biopsies in 575 participants we have selected 49 denervation-responsive genes (based on publicly available data) to provide insights to the burden of denervation in SOMMA participants. We performed sensitivity analyses to test the hypothesis that expression levels of denervation-responsive genes are associated with walking speed, fitness (VO2peak), maximal mitochondrial respiration (state 3), muscle mass/volume, and muscle strength/power. **Results:** We found that increased expression of 20 of the denervation-responsive genes was negatively associated with various functional and muscle mass/volume indices. For example, 400m walking speed was negatively associated with increased expression of acetylcholine receptor subunits (Chrna1, Chrnd), denervation atrophy genes (Gadd45a, Myog), and RUNX1. Similarly, maximal mitochondrial respiration was negatively associated with increased expression of sodium channels (SCN4a, SCN5a), regulators of acetylcholine receptor clustering (MuSK, RAPSN), acetylcholine receptor subunits (Chrna1, Chrnd), a glycoprotein that promotes reinnervation (NCAM1), denervation atrophy (Gadd45a), and RUNX1. **Conclusions:** We conclude that the burden denervation estimated from the abundance of denervation-responsive gene transcripts is a significant determinant of important clinical outcomes in aging humans, supporting the imperative to identify new treatment strategies to restore innervation in advanced age. **Key words:** transcriptomics, skeletal muscle, neuromuscular junction, denervation. **Disclosures:** Steven R. Cummings is a consultant to Bioage Labs. Peggy M Cawthon is a consultant to and owns stock in MyoCorps. All other authors declare no conflict of interest.

**Communication 3:** *Expression of autophagy genes in muscle is associated with physical performance, muscle mass and mitochondrial function in older individuals,* Paul M. Coen[3], Zhiguang Huo[4], Gregory J Tranah[1,2], Haley N Barnes[1], Peggy M Cawthon[1,2], Russell T Hepple[4], Daniel S Evans[1,2], Olaya Santiago Fernandez[5], Ana Maria Cuervo[5], Steven R Cummings[1,2], Karyn A Esser[4] ((1) California Pacific Medical Center Research Institute, San Francisco, CA, USA; (2) University of California San Francisco, San Francisco, CA, USA; (3) Advent Health, Orlando, Florida, USA; (4) University of Florida, Gainesville, Florida, USA; (5) Albert Einstein College of Medicine, New York, NY, USA)

**Background:** Decreasing autophagy has been identified as a key pathay of aging. Identifying associations between autophagy gene expression patterns in skeletal muscle and outcomes including physical performance, muscle mass and mitochondrial function in older individuals would further our knowledge of mechanisms related proteostasis and aging. **Methods:** Skeletal muscle biopsies collected from 575 women and men (≥70 years old) from the Study of Muscle, Mobility and Aging (SOMMA). RNA was extracted and sequenced and expression of 283 genes related to mTOR (135), autophagy regulation (68), and mitophagy (80) were determined. Associations between gene expression and mitochondrial respiration in permeabilized muscle fiber bundles from biopsies (MAX OXPHOS), physical performance measures (VO2 peak, 400m walking speed, and leg power), and muscle mass (thigh muscle volume) were determined using negative binomial regression models. **Results:** The top 20 genes associated with phenotypes were examined. For mTOR pathway genes, expression of WDR59 and WDR24, both subunits of GATOR2 complex (an inhibitor of mTORC1) and PRKAG3, which is a regulatory subunit of AMPK, were negatively correlated with multiple outcomes. In contrast, MAPKAP1, which is a subunit of mTORC2 was positively associated with outcomes. For autophagy, key transcriptional regulators including TFE3 and NFKB related genes (RELA, RELB, NFKB1) were negatively correlated with outcomes. On the contrary, regulators of oxidative metabolism that also promote autophagy and mitophagy (PPARGC1A, PPARA, EPAS1) were positively associated with multiple outcomes. In line with this, several mitophagy, fusion and fission related genes (NIPSNAP2, DNM1L, OPA1) were also positively associated with outcomes. **Conclusions:** Our study identifies gene expression patterns of autophagy and mitophagy regulation in human skeletal muscle related to with physical performance, muscle mass and mitochondrial function in older persons. Identifying specific mechanisms associated with high functioning across multiple performance and physical domains may lead to interventions to preserve mobility and independence. **Key words:** mobility, aging, autophagy, mitochondria, gene expression, cohort study **Disclosures:** Steven R. Cummings is a consultant to Bioage Labs. Peggy M Cawthon is a consultant to and owns stock in MyoCorps. All other authors declare no conflict of interest.

**S4- RESISTANCE EXERCISE AND NUTRACEUTICAL STRATEGIES IN SARCOPENIA: THE "GOLD" STANDARD?** Stuart Phillips[1], James McKendry[1], Beth Phillips[2], Philip Atherton[2] *((1) McMaster University, Canade; (2) University of Nottingham, UK)*

Sarcopenia is currently poorly defined and, as such, is difficult to treat. However, resistance exercise is the primary therapy for mitigating the effects of sarcopenia. In this talk, the presenter will highlight recent consensus statements on the effects of resistance exercise and its application in older and even frail individuals. The data will also show the many 'side effects' of resistance exercise beyond the musculoskeletal system, including reduced depression, dementia risk (or slowing of dementia progression), improved sleep duration and latency, and metabolic benefits. The clear point is that resistance exercise and its profound effects set the bar against which any therapeutic should be measured in terms of its effectiveness. In addition, resistance exercise as a treatment modality can be done in many ways, and in many 'hard-to-reach' populations through using online technologies. So, resistance exercise implementation is no longer the exclusive domain of a local gym. The most recent iterations and trials in this area will be discussed, and their implication for mitigating sarcopenia and frailty will also be addressed. English and Paddon-Jones

originally coined the catabolic crisis as an event triggered by overt sickness, inflammation, and hospitalization. However, numerous situations common to advancing age can result in inactivity and muscle disuse. For example, individuals who require orthopedic and other surgeries, hospitalization due to illness, or who experience falls will undergo transient muscle disuse and often marked reductions in muscle mass, strength, and mobility. Bed rest and limb immobilization studies have confirmed that in addition to accelerated losses of strength and muscle mass during these periods of muscle disuse, metabolic health (particularly regulation of blood glucose) is also negatively affected. Recently, studies of reduced ambulation (i.e., reduced daily steps) have shown effects on muscle strength, muscle mass and glycemic regulation. Reducing daily step count may appear to be a relatively benign event compared to bed rest or immobilization. However, the negative impact that step-reduction has on overall muscle health represents, it is proposed, a milder version of what happens in complete disuse models. Acute periods of step-reduction likely occur with far greater frequency in older persons than overt bed rest and muscle immobilization. Thus, step reduction is a salient situation in which moderate muscle disuse can affect older adults. The aim of this presentation is to summarize the current state of the science of disuse and inactivity in older persons. Despite sarcopenia's complex and multifaceted nature, resistance training (performed with a high degree of effort) and other forms of exercise offer the most potent non-pharmacological strategy to ameliorate the progression of sarcopenia and muscle disuse. Importantly, the influence of resistance training on skeletal muscle in older adults can be augmented by incorporating rational, evidence-based nutritional support strategies. In our view, there exists sufficient evidence for specific dietary components (i.e., daily protein intake ~1.6. g/kg/day), feeding strategies (i.e., protein distribution, a per-meal dose of protein ~0.4 g/kg/meal), and specific nutritional supplements (e.g., leucine, omega-3 polyunsaturated fatty acids and creatine) to support resistance exercise-induced adaptations. Consuming sufficient high-quality (i.e., leucine-rich) protein with resistance exercise appears to be the most well-supported determinant to improve or maintain skeletal muscle mass and function with advancing age. Despite the importance of leucine content in triggering and sustaining an optimal muscle protein synthetic response, leucine supplementation alone is unlikely to confer a significant benefit for skeletal muscle—excluding its capacity to rescue deficits in MPS from lower-quality protein sources. Other established (i.e., creatine) and nascent (i.e., n3-PUFAs) nutrition-based strategies provide valuable tools to overcome anabolic resistance, augment RE-induced adaptations, and ultimately thwart sarcopenia progression. Finally, further exploration of the efficacy of supplements combined with exercise before, during, and after disuse in older persons would yield valuable insights. This symposium will appeal to basic scientists and clinicians as it will move from basic mechanisms of muscle anabolism to practical applications in older persons. This bench-to-action framework will be contextualized, and the barriers to implementing resistance exercise will also be addressed.

**Communication 1:** *Disuse as a common component of the catabolic crisis: a watershed moment in aging,* James McKendry (McMaster University, Hamilton, ON, Canada)

English and Paddon-Jones originally coined the catabolic crisis as an event triggered by overt sickness, inflammation and hospitalization. However, numerous situations common to advancing age can result in inactivity and muscle disuse. For example, individuals who require orthopedic and other surgeries, hospitalization due to illness, or who experience falls will undergo transient muscle disuse and often marked reductions in muscle mass, strength, and mobility. Bed rest and limb immobilization studies have confirmed that in addition to accelerated losses of strength and muscle mass during these periods of muscle disuse, metabolic health (particularly regulation of blood glucose) is also negatively affected. Recently, studies of reduced ambulation (i.e., reduced daily steps) have shown effects on muscle strength, muscle mass and glycemic regulation. Reducing daily step count may appear to be a relatively benign event compared to bed rest or immobilization. However, the negative impact that step-reduction has on overall muscle health represents, it is proposed, a milder version of what happens in complete disuse models. Acute periods of step-reduction likely occur with far greater frequency in older persons than overt bed rest and muscle immobilization. Thus, step reduction is a salient situation in which moderate muscle disuse can affect older adults. The aim of this presentation is to summarize the current state of the science of disuse and inactivity in older persons.

**Communication 2:** *What can't resistance training do for older person's health?* Stuart Phillips (McMaster University, Hamilton, ON, Canada)

Sarcopenia is currently poorly defined and, as such, is difficult to treat. However, resistance exercise is the primary therapy for mitigating the effects of sarcopenia. In this talk, the presenter will highlight recent consensus statements on the effects of resistance exercise and its application in older and even frail individuals. The data will also show the many 'side effects' of resistance exercise beyond the musculoskeletal system, including reduced depression, dementia risk (or slowing of dementia progression), improved sleep duration and latency, and metabolic benefits. The clear point is that resistance exercise and its profound effects set the bar against which any therapeutic should be measured in terms of its effectiveness. In addition, resistance exercise as a treatment modality can be done in many ways, and in many 'hard-to-reach' populations through using online technologies. So, resistance exercise implementation is no longer the exclusive domain of a local gym. The most recent iterations and trials in this area will be discussed, and their implication for mitigating sarcopenia and frailty will also be addressed.

**Communication 3:** *Therapies to mitigate disuse and counteract the negative effects,* Beth Phillips (University of Nottingham, UK)

Despite sarcopenia's complex and multifaceted nature, resistance training (performed with a high degree of effort) and other forms of exercise offer the most potent non-pharmacological strategy to ameliorate the progression of sarcopenia and muscle disuse. Importantly, the influence of resistance training on skeletal muscle in older adults can be augmented by incorporating rational, evidence-based nutritional support strategies. In our view, there exists sufficient evidence for specific dietary components (i.e., daily protein intake ~1.6. g/kg/day), feeding strategies (i.e., protein distribution, a per-meal dose of protein ~0.4 g/kg/meal), and specific nutritional supplements (e.g., leucine, omega-3 polyunsaturated fatty acids and creatine) to support resistance exercise-induced adaptations. Consuming sufficient high-quality (i.e., leucine-rich) protein with resistance exercise appears to be the most well-supported determinant to improve or maintain skeletal muscle mass and function with advancing age. Despite the importance of leucine content in triggering and sustaining an optimal muscle protein synthetic response, leucine supplementation alone is unlikely to confer a significant benefit for skeletal muscle—excluding its capacity to rescue deficits in MPS from lower-quality protein sources. Other established (i.e., creatine) and nascent (i.e., n3-PUFAs) nutrition-based strategies provide valuable tools to overcome anabolic resistance, augment RE-induced adaptations, and ultimately thwart sarcopenia progression. Finally, further exploration of the efficacy of supplements combined with exercise before, during, and after disuse in older persons would yield valuable insights.

## S5- IMPACT OF AGING AND PHYSICAL ACTIVITY ON HUMAN NEUROMUSCULAR & MUSCLE FUNCTION: NEW INSIGHTS FROM THE MONTREAL NEUROMUSCULAR STUDY (MNMS).

Mylène Aubertin-Leheudre *(UQAM, Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, QC, Canada)*

**Communication 1:** *Skin advanced glycation end products (S-AGEs): A non-invasive biomarker to assess muscle function in older adults?* Mylène Aubertin-Leheudre (UQAM, Canada; Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, QC, Canada)

**Background:** It has been shown that a high level of blood advanced glycation end products (AGEs) is associated with a decline in muscle function (MF) and may play a role in sarcopenia. In addition, being physically active (PA) seems to reduce the accumulation of blood AGEs. Interestingly, skin-AGEs (S-AGEs) appear as a non-invasive surrogate of blood AGEs. However, the relationship between S-AGEs, MF and functional capacity (FC) remains poorly understood, as well as the impact of age and PA level on this relationship. **Objective:** we aim to: 1) investigate the relationship between S-AGEs, MF and FC; 2) compare S-AGEs concentrations in different age and/or PA level groups; 3) assess the relationship between S-AGEs, MF and FC based on age and/or PA level. **Methods:** MF [absolute and relative handgrip strength, lower limb muscle strength and muscle power], FC [SPPB (x/12); gait parameters (TUG; sec), unipodal balance (x/60sec), 30-sec chair tests (nb)] and skin AGEs level (AGE-Reader©) were assessed cross-sectionally in healthy men. Skin AGEs levels were compared according to age [Young adult (20-44y:n=45) vs. Adult (45-65y:n=38) vs. Older adult (>66y:n=34)] or PA level [inactive (<150min/week and <10000steps/day and <1.6METs: n=32) vs. active (>=150min/week or >=10000steps/day or >=1.6METs: n=85))]. Spearman/Pearson correlations between S-AGEs, MF and FC were performed according to age and/or PA level. **Results:** S-AGEs levels are correlated with age (r=0.78), PA parameters (r=(-0.27;-0.37)) and all MF (r=(-0.34;-0.54)) or FC (r=(-0.20;-0.53)) parameters. However, S-AGEs differed significantly between age groups ($p<0.001$) but not between PA status groups (p=0.68). Finally, MF parameters (r=(-0.34;-0.60)) correlated with S-AGEs levels in the older adult group. No correlation was observed in the young or adult groups. **Conclusion:** S-AGEs could be a useful clinical biomarker of MF with age. To be used as a non-invasive biomarker, cut points to help clinicians identify people at risk as well as further research using longitudinal design or investigating other populations (e.g. women or obese population) are needed. **Key words:** exercise; sarcopenia; biomarkers; geroscience. **Disclosure:** No conflict of interest. Funding: CIHR grant #417022 & FRQS salary award or scholarship.

**Communication 2:** *Neuromuscular and neurophysiological changes with age and activity levels in men: New insights from the Montreal NeuroMuscular Study (MNMS),* Marc Bélanger (UQAM, Montréal, QC, Canada)

**Rationale:** Age-associated progressive muscle mass and strength declines have been linked to deleterious consequences including reduced mobility, falls and even mortality. Numerous studies have suggested neurogenic and muscular alterations to explain these age-related declines. However, most studies provided information mainly on young and old individuals, without much evidence on the in-between age groups. Moreover, the physical activity (PA) levels of the various populations have not been considered. **Objective:** To evaluate the impact of aging on neurogenic factors and strength in active and inactive men. **Methods:** 139 generally healthy (BMI = 18-35 kg/m$^2$) men (20-93 y.o.) were recruited. PA levels, lower limb muscle power, maximal isometric knee extensor strength (Fmax), rate of force development (RFD), electromechanical delay (EMD) during Fmax, fatigue time to reach 50% of Fmax (FT50%), central activation ratio (CAR), spinal cord excitability (Hmax/Mmax) were assessed. Linear regressions were used to determine the changes with age. Significance level ≡ $p<0.05$. **Results:** PA had no effects on age-related changes; thus, data were pooled for the age factor. Muscle power, Fmax and RFD declined at rates of 2.5W/yr, 2.5 N/yr and 1.5%Fmax/s/yr, respectively. Contrarily, EMD

increased at a rate of 0.25ms/yr. The FT50% and the CAR were unaffected by age. In contrast, Hmax/Mmax decreased by 0.72%/yr and it was positively correlated with Fmax (R=0.30). Finally, there was no BMI age difference, but Fmax increased at 5.4N/kg/m² irrespective of age. **Conclusion:** PA level did not alter age-related changes as muscle mechanics (Power, Fmax, RFD) still declined with age. Because our participants were all very functional, there may be a need to better define PA levels and examine the effects of the long-term PA profiles. It may be relevant to monitor muscular reflex changes (Hmax/Mmax) with age as it is well correlated with strength and power. In contrast, central activation ratio may be impertinent to explain strength and power changes as it was constant with age. **Key words:** Sarcopenia, Physical activity level, Central activation ratio, Spinal excitability. **Disclosure:** no conflict of interest. Study supported by CIHR grant #417022.

**Communication 3:** *The involvement of mitochondrial dysfunction in human skeletal muscle aging: New insights from the Montreal NeuroMuscular Study (MNMS),* Gilles Gouspillou (UQAM, Montréal, QC, Canada)

**Background:** Aging-related muscle atrophy and weakness are major risk factors for various adverse health outcomes, including falls or institutionalization. Accumulation of mitochondrial dysfunctions, namely reduced mitochondrial bioenergetics, increased reactive oxygen species (ROS) production, and altered calcium handling, are widely considered as key contributing mechanisms to muscle aging. Physical activity (PA) or inactivity can greatly affect all aspects of mitochondrial function. However, few studies have investigated the impact of aging on human muscle mitochondrial function while account for the potential confounding effects of PA. **Objective:** To assess the impact of aging and PA on mitochondrial respiration, ROS production and calcium retention capacity (mCRC) in active and inactive participants. **Methods:** 139 men (20-93 y) were recruited. PA levels, thigh lean mass and cross-sectional area (CSA), functional capacities (step test and six-minute walking test), maximal knee extension isometric strength (KEIS) and knee extension power (KEP) were measured. Mitochondrial respiration, ROS production and mCRC were assessed in permeabilized myofibers prepared from vastus lateralis biopsy samples. **Results:** Thigh lean mass, thigh CSA, functional capacities, KEIS and KEP declined with age ($p<0.001$). PA prevented the decline in functional capacities ($p<0.001$) without preventing the decline in thigh lean mass, thigh CSA, KEIS or KEP ($p>0.05$). Age had no impact on maximal mitochondrial respiration or ROS production ($p>0.05$). Active participants displayed higher respiration and ROS production ($p<0.05$) across all age groups. mCRC was reduced with aging ($p=0.006$), an effect that was not protected by PA ($p=0.429$). mCRC was correlated with thigh lean mass ($p=0.037$), KEIS ($p=0.045$), and functional capacities ($p<0.05$). **Conclusion:** Our data indicate that aging per se is not associated with reduced mitochondrial respiration or increased ROS production in the vastus lateralis. However, they indicate that PA is a powerful stimulus to improve mitochondrial energetics across the lifespan. Importantly, this study indicates that mitochondrial calcium handling is altered with aging and highlights positive associations between mCRC and muscle mass, strength, and functional capacities. **Key words:** Mitochondria, Skeletal muscle, Sarcopenia. **Disclosure:** No conflict of interest. Funding: CIHR #417022.

**S6- THE SURGICAL PAUSE: ORIGIN, EVIDENCE AND IMPLEMENTATION.** Jason Johanning *(University of Nebraska Medical Center, Omaha, NE, USA)*

**Communication 1:** *The Surgical Pause: Origin and Dissemination,* Daniel E Hall (University of Pittsburgh, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA)

**Background:** The Surgical Pause is 2-step program that (1) systematically screens and identifies frailty among patients considering elective surgical treatment, so that (2) perioperative decision making and care pathways can be optimized for high risk, frail patients. Initially developed at the Veterans Affairs Medical Center (VAMC) in Omaha, Nebraska by the symposium chair, it has been refined, validated and replicated by the presenters across more than 50 medical centers in both the VA and private sector. In 2023 the Surgical Pause was formally adopted as a national quality program by the National Surgery Office of the Veterans Health Administration (VHA). **Methods:** After the symposium chair describes the origin of the Surgical Pause, the first presenter will summarize a narrative review of the more than 40 peer reviewed publications describing the validation of the Risk Analysis Index and implementation of the Surgical Pause. He will also describe the process through which the program was adopted for use across the entire Veterans Health Administration. **Results:** Frailty is repeatedly shown to be a powerful determinant of surgical outcomes and the recalibrated RAI has emerged as among the most thoroughly validated measures of surgical frailty, and the only tool proven feasible at scale to screen predominantly robust populations without disrupting clinic workflows. With excellent calibration and discrimination on par with other frailty tools (c= 0.815, 95% CI: 0.788 – 0.842) (1) the RAI takes a median 30 seconds to administer at the bedside with more than 750,000 assessments in VHA and private hospitals to date. Interventions tailored to frail patients include (a) interdisciplinary review and optimization of treatment plans including postoperative rescue, (b) supervised exercise to build strength, endurance and coordination, and (c) structured goal clarification to ensure treatment plans align with patients' goals and values. Outcomes replicated in multiple settings include significantly reduced rates of postoperative complications and mortality (Odds Ratio 0.82; 95% CI, 0.72-0.92) (2). **Conclusion:** The Surgical Pause is feasible at scale and proven to improve outcomes in multiple settings across hospitals in both the private sector and VHA. **Key words:** Frailty, Prehabilitation, Surgery, Perioperative, Shared Decision Making. **Disclosures:** Dr. Hall reports an unpaid consulting relationship with FutureAssure, LLC and grant funding from the National Institutes of Health and the Veterans Health Administration Office of Research

and Development. **Reference:** 1. https://www.ncbi.nlm.nih.gov/pubmed/32118596; 2. https://doi.org/10.1001/jamasurg.2022.8341

**Communication 2:** *The Surgical Pause: Update and Lessons Learned from a Randomized Trial,* Shipra Arya, (Stanford University, VA Palo Alto Healthcare System, Stanford, CA, USA)

**Background:** We designed a hybrid effectiveness implementation step-wedge cluster randomized trial called the Patient-Centered mUltidiSciplinary care for vEterans undergoing surgery (PAUSE) trial to test the frailty screening and referral to a multidisciplinary member board to guide optimization of the surgical patient prior to surgery. **Methods:** The PAUSE trial includes Veterans scheduled for elective surgery at 3 large tertiary care VAMCs (Palo Alto, Houston and Nashville) and 7 specialty groups in each center: general, vascular, orthopedics, cardio-thoracic, urology, neurosurgery and plastics/ ENT). The intervention is referral to a "multidisciplinary PAUSE board" (e.g., surgery, anesthesia, geriatrics, palliative care, case management, rehabilitation and nutrition) for recommendations after frailty screening. Each 'step' has been a randomly chosen specialty group transitioning from usual care to the PAUSE intervention. The trial is ongoing and data collection will continue into early 2025. Outcomes include 30-day and 180-day mortality, non-home discharge, re-hospitalizations and home-time. The Consolidated Framework for Implementation Research (CFIR) has been used to guide the mixed methods Formative Evaluation (FE) and analysis of factors that influence implementation. Through rapid content analysis of pre-implementation and intervention focused FE we have gathered some important insights into implementation of the intervention. We validated findings through triangulation, member-checking, and search for disconfirming evidence. **Results:** Key stakeholders identified champions, potential barriers and facilitators, and possible intervention adaptations. They indicated limited time, staff shortage, and the concern that the PAUSE board may delay surgery as the main barriers to implementation. Importantly nurses were identified as partners in intervention execution consistent with quality improvement efforts in other settings. Surgical and nursing leadership engagement was indicated as crucial to adopting any new healthcare model in the studied facilities. We also learned that existing inter-site and inter-specialty variations might influence the implementation process. **Conclusion:** Formative evaluation using rapid content analysis methods embedded in the CFIR framework delivers timely and actionable findings to inform the intervention and identify implementation modifications to optimize opportunities for success. Multistakeholder involvement and accounting for variation between clusters and sites is important for successful implementation. **Key words:** frailty, optimization, hybrid effectiveness-implementation trial, implementation science, mixed-methods. **Disclosures:** Dr. Arya reports grant funding from VA HSR&D, Stanford Cardiovascular Institute, National Institutes of Health and consulting/ speaker bureau membership for Gore Medical. **Reference:** https://clinicaltrials.gov/study/NCT05037292

**Communication 3:** *The Surgical Pause: How We Do It across 7 Florida VA Medical Centers,* Bradley Schmit, (University of Florida, VA Gainesville, FL, USA)

**Background:** As discussed by previous presenters, Frailty is associated with markedly adverse surgical outcomes and Identifying frailty preoperatively has been shown to improve these outcomes. We hypothesized that developing a multidisciplinary pre-operative clinic for high risk patients would improve post-surgical outcomes. **Methods:** I will discuss our efforts across the Sunshine Network VA hospital System (VISN 8) with the implementation of frailty screening utilizing the RAI, and development of a nurse practitioner led, standardized multidisciplinary high risk surgical prehabilitation clinic across the 7 medical centers in our region. This clinic involves multidisciplinary review, a physical therapist directed exercise program, nutritional optimization and goals of care clarification in addition to medical optimization prior to surgery for high-risk patients. **Results:** Since Sept of 2022, 37,134 surgical patients have been screened for frailty using the Risk Analysis Index across the 7 Veterans Administration medical centers in the Sunshine Network region (VISN8). Of these patients 20.3% (7,533) were identified as being "frail" with an RAI≥37. 978 patients have been referred to our surgical frailty programs. After multidisciplinary evaluation and shared decision making 57% (560) went on to proceed with surgery while 24.5% (245) opted for non-operative management and 16.5% (173) are still awaiting disposition. There have been 7 30-day post-operative mortalities in patients referred to the program for a rate of 0.7%. A majority of patient deaths amongst those referred to the program have been in the non-operative group 69.8% (60). At our highest volume center implementation of this program corresponded to improvement in the Observed: Expected (O:E) post-operative mortality from 1.91 during the quarter prior to initiation to 0.9 in the most recent quarter. **Conclusion:** In conclusion, initiation of a prehabilitation program and multidisciplinary high risk pre-surgical clinic for patients identified as frail during preoperative assessment is feasible on a large scale and has successfully selected for patients appropriate for surgical care, resulting in operative mortality similar to non-frail patients in those who do undergo surgery. **Key words:** Frailty, Surgery, Prehabilitation. **Disclosures:** Dr. Schmit reports no disclosures

## S7- SKELETAL MUSCLE MITOCHONDRIAL ENERGETICS IN THE STUDY OF MUSCLE, MOBILITY AND AGING (SOMMA).

Russell T Hepple *(University of Florida, Gainesville, FL, USA)*

**Communication 1:** *Skeletal muscle mitochondrial energetics are generally unrelated to overall muscle size the SOMMA study,* Peggy M. Cawthon (California Pacific Medical Center Research Institute, University of California, San Francisco, CA, USA)

**Background:** Skeletal muscle mitochondrial energetics, D3Cr muscle mass, and magnetic resonance (MR) total thigh muscle volume are each associated with strength and functional outcomes, but the degree to which muscle size is related to muscle energetics is unclear. We hypothesized that larger muscle size would be associated with higher muscle energetics. **Methods:** The Study of Muscle, Mobility and Aging (SOMMA) assessed muscle energetics in older adults (N=879, mean age=76.3 years, 59.2% women). Maximal production of adenosine triphosphate (ATPmax) was measured in vivo using 31Phosporous MR spectroscopy. Maximal oxygen consumption of permeabilized muscle fibers from the vastus lateralis was measured ex vivo using high-resolution supported by fatty acids and complex I- and II-linked carbohydrates (e.g., Max OXPHOSCI+CII). D3Cr muscle mass was assessed by the d3-creatine dilution protocol, and total thigh muscle volume by MR imaging. We tested whether mean values of muscle energetic measures varied across sex-specific tertiles of D3Cr muscle mass or total thigh muscle volume, with and without adjustment for potential confounders. **Results:** In unadjusted models, we found that skeletal muscle energetics varied across tertiles of D3Cr muscle mass and total thigh muscle volume, with greatest differences found in women. However, these associations were inconsistent across the various measures of muscle energetics. Adjustment for covariates attenuated the differences in muscle energetics across tertiles of muscle size, with body weight explaining much of the associations. **Conclusion:** We found, contrary to our initial hypothesis, that skeletal muscle mitochondrial energetics measured in vivo or ex vivo were largely unrelated to overall muscle size. Our results support the separate consideration of muscle size and muscle energetics when understanding reasons for functional decline. However, larger muscles may still have a greater total capacity to generate energy than smaller muscles, simply because they are bigger. Future analyses will explore whether calculations to determine whole muscle energetic potential (i.e., muscle size X muscle energetics) relate to fitness, strength, and physical performance outcomes. **Key words:** Muslce Mass, D3Cr, mitochondria, Strength. **Disclosures:** Peggy M. Cawthon is a consultant to Bioage Labs.

**Communication 2:** *Energetics and Other Predictors of the Time Required to Walk 400 Meters,* Steven R. Cummings (California Pacific Medical Center Research Institute, San Francisco, CA, USA)

**Background:** Walking 400 meters (m) is essential to independent living and takes longer with advancing age. This often progresses to mobility disability. **Methods:** SOMMA examined 879 participants ≥70 years old who had a usual 6m gait speed ≥ 0.6 m/sec and could complete a 400m walk within 15 minutes. The endpoint was the time required to walk 400m. We measured maximal oxidative capacity (MaxOXPHOS) by respirometry on biopsies from the vastus lateralis muscle. A cardiopulmonary exercise test assessed maximum oxygen consumption (VO2peak), and energy cost-capacity ratio of oxygen consumption, VO2, at a slow speed (0.67 m/s) to the capacity, VO2peak. We assessed many other potential determinants of 400m walk time. Stepwise regression identified a multivariable model of independent predictors of walk time. **Results:** On average, participants took 6.6 minutes to walk 400m. Each standard deviation lower MaxOXPHOS was associated with 22.1s (17.5-26.8s) longer walk time. The association between lower MaxOXPHOS and longer 400m walk time was mediated by a higher energy cost-capacity ratio, lower VO2peak, weaker leg power, and heavier body weight. Conditions that would reduce oxygen supply to muscle (anemia, peripheral arterial disease) were also associated with longer 400m walk time (29.1s, 16.7-41.5s; and 34.3s, 19.7-48.9s; respectively). From a multivariate model arising from analyses of over 50 potential determinants, factors associated with longer 400m walk time included several other factors including lower extremity joint stiffness and less time habitually spent in moderate-to-vigorous activity. **Conclusion:** Mitochondrial respiration is an important determinant of time to walk 400m and its effects are mediated by walking energetics and leg power. Limited oxygen supply to muscle mitochondria may play an important role in increasing the time some older people require to walk 400m. Interventions that improve mitochondrial energetics may reduce the time required to walk 400m and, perhaps, reduce the risk of mobility disability. **Key words:** Walking Speed, Mitochondria, Mobility Disability, Aging. **Disclosures:** Steven R. Cummings is a consultant to Bioage Labs.

**Communication 3:** *Race differences in walk speed, cardiorespiratory fitness and skeletal muscle mitochondrial energetics in the study of muscle, mobility and aging (SOMMA),* Paul M. Coen (Translational Research Institute, AdventHealth, Orlando, FL, USA)

**Background:** Slower walking speed predicts mobility disability in older adults and is related to lower cardiorespiratory fitness and skeletal muscle mitochondrial energetics. In the US, older adults who self-identify as Black have a disproportionately higher incidence of mobility disability. However, race and socioeconomic status (SES) are highly correlated which complicates efforts to determine whether race and SES operate independently to produce disparities in functional status. Whether older adults who are Black also have lower fitness and mitochondrial energetics compared to those who are White has not been investigated. **Methods:** The study of muscle, mobility and aging (SOMMA) examined 879 participants, including 116 who self-identified as Black, aged ≥70 years old who had a usual 6m gait speed ≥0.6 m/sec and could complete a 400m walk within 15 minutes. Mitochondrial respiration was measured in permeabilized fibers from biopsies of the vastus lateralis. A cardiopulmonary exercise test assessed maximum oxygen consumption (VO2peak). SES variables, race, sex and age were determined by self-report. We used a propensity score matching approach to match Blacks with Whites with a 1:1 ratio. **Results:** Black (n=90) and White (n=90) groups were well matched for age, sex, BMI, muscle mass, physical activity, marital

status, education, financial status, and comorbidity index (all p >0.05). Despite being well matched for these variables, Blacks had a slower 400m walking speed (1.03 vs 0.97 m/s, p=0.014), lower mitochondrial respiration (MAXOXPHOS 60.9 vs 50.8 (pmol/(s*mg)), p=0.0002), and lower cardiorespiratory fitness (1566 vs 1391 ml/min, p=0.007), when compared to Whites. **Conclusion:** Despite matching for key variables, older adults who are Black have slower walking speed, concomitant with lower fitness and muscle mitochondrial energetics which may underly disproportionately higher incidence of mobility disability. **Key words:** Aging, Race, Mitochondria, Cardiorespiratory fitness. **Disclosures:** None.

**S8- RECENT ADVANCES IN AGING FROM SIMPLE MODEL ORGANISMS.** Mark A. McCormick *(University of New Mexico Health Sciences Center, Albuquerque, NM, USA)*

**Communication 1:** *Epigenetic Gambling and Aging,* Alexander Mendenhal (University of Washington, Seattle, WA, USA)

Aging has a strong nongenetic, nonenvironmental component. Monozygotic twins live for different amounts of time. Hundreds of isogenic C. elegans aging in the same swirling flask of liquid will have an order of magnitude between their first and last deaths. Epigenetic gambling systems proposed to exist by George Martin do in fact exist, affecting development, chronic disease and aging. Probabalistic silencing of individual alleles ensures each organism expresses the same genome uniquely. These systems have been difficult to study because they are not heritable, and intrinsically variable. Evidence for how monoallelic expression manifests is inferred from sequencing and medical case data. We have developed C. elegans as a developmentally, genetically tractable model in which we can directly observe monoallelic expression manifest using fluorescent protein alleles. We have generated mutants that regulate monoallelic expression to define a developmental, genetic pathway controlling this epigenetic gambling. The components of this pathway also cooperatively regulate virus and transposon silencing, but regulate monoallelic expression in new antagonistic roles. Ultimately we want to develop the technologies to assess the expression states of individuals' genomes in individual organs, and tune each genome for prolongevity expression, while reinforcing virus and transposon silencing.

**Communication 2:** *Longevity and health benefits of the tryptophan metabolite 3-hydroxyanthrnailic acid,* George Sutphin (University of Arizona, Tucson, AZ, USA)

Tryptophan metabolism by the kynurenine pathway is increasingly linked to aging and ageassociated disease. Kynurenine pathway enzymes and metabolites influence a range of molecular processes critical to healthy aging, including regulation of inflammatory and immune responses, cellular redox homeostasis, and energy production. Aberrant kynurenine metabolism is observed during normal aging and has been implicated in a range of ageassociated pathologies, including chronic inflammation, atherosclerosis, neurodegeneration, and cancer. We discovered that knockdown of haao-1, a kynurenine pathway gene encoding the enzyme 3-hydroxyanthranilic acid dioxygenase (HAAO), extends lifespan by ~30% and delays age-associated decline in health in Caenorhabditis elegans. This lifespan extension is mediated by increased physiological levels of the HAAO substrate 3-hydroxyanthranilic acid (3HAA). In mice, knocking out Haao, the mammalian ortholog of haao-1, or feeding mice a diet supplemented with 3HAA similarly extends lifespan and improves several metrics of health. The mechanism of action linking 3HAA to aging is complex and partially overlaps with multiple pathways previously implicated in aging. Among these pathways, activation of the Nrf2/SKN-1 oxidative stress response and alterations to iron homeostasis are key players in the benefits 3HAA. This works provides a foundation for detailed examination of the molecular mechanisms underlying the benefits of 3HAA, and how these mechanisms interact with other interventions both within and beyond the kynurenine pathway. In ongoing work, we are exploring the role of 3HAA in modulating the response of C. elegans to environmental stress and bacterial pathogens, the role of kynurenine metabolism in kidney and liver cancer, and the interaction between 3HAA and iron homeostasis. We anticipate that these findings will bolster growing interest in developing pharmacological strategies to target tryptophan metabolism to improve health aging. This work was supported by NIH P30AG038070 and NIH R35GM133588.

**Communication 3:** *Greatly Increased Lifespan by tRNA Synthetase Inhibitors is Linked to Enhanced Protein Turnover,* Mark A. McCormick (University of New Mexico Health Sciences Center, Albuquerque, NM, USA)

Aging is a key driver of many important diseases in humans. Defects in proteostasis are linked to important neurodegenerative diseases of aging such as Huntington's, Parkinson's, and Alzheimer's diseases. We have identified multiple compounds that greatly increase longevity in the budding yeast S. cerevisiae and the nematode C. elegans, by inhibiting conserved tRNA synthetase enzymes. These compounds lead to accumulation of uncharged tRNA, leading via the conserved sensor kinase GCN2 to translational upregulation of the transcription factor ATF4. Here we describe work showing that multiple tRNA synthetase inhibitors can greatly upregulate ATF4 in mammalian cells, at otherwise safe doses. We also present RNASeq analysis showing that changed transcripts related to the regulation of proteostasis are highly overrepresented in these treated cells, in an ATF4-dependent manner, and show directly that these same compounds can greatly enhance proteostasis in mammalian cells via multiple mechanisms. Longlived mice have elevated ATF4 levels, suggesting the connection between ATF4 and longevity may be conserved in mammals. These findings of increased protein turnover and increased longevity by the same treatments suggest that tRNA synthetase inhibitors could potentially be used to treat or prevent multiple diseases of aging linked to defects in cellular proteostasis.

**S9- EXERCISE AND NUTRITIONAL INTERVENTIONS FOR OSTEOSARCOPENIA.** Darren Candow *(University of Regina, Regina, SK, Canada)*

**Communication 1:** *Emergence of creatine supplementation as a potential treatment for osteosarcopenia,* Darren Candow (University of Regina, Regina, SK, Canada)

Musculoskeletal aging is typically characterised by the progressive reduction in muscle (sarcopenia) and bone tissue (osteoporosis) which over time leads to the onset of osteosarcopenia, the identifiable "modern-day geriatric giant'. Osteosarcopenia inevitably increases the risk of falls, fractures and premature mortality in aging adults. While the etiology and mechanisms explaining osteosarcopenia remain to be determined, one contributing factor is fat infiltration into and around these tissues. Muscle and bone loss and increased fat mass are accelerated by periods of inactivity/disuse (e.g., during illness and hospitalization) that occur more frequently and are more difficult to recover from with advanced aging. Treatments for osteosarcopenia have been primarily limited to non-pharmacological interventions, specifically resistance training, which is anabolic to muscle (by enhancing the rates of muscle protein synthesis and balance) and osteogenic to bone (by reducing bone breakdown and increasing bone formation). In addition to resistance training, there is emerging research showing that creatine supplementation has beneficial effects on various indices of muscle and bone biology in aging adults. Specifically, the combination of creatine supplementation and resistance training has been shown to increase bone area, mineral and strength and reduce bone mineral density loss and bone resorption over time. Further, creatine supplementation increases measures of muscle density and hypertrophy which may help explain the apparent small reduction in body fat % from creatine. To date, creatine supplementation appears to have no effect on falls or fracture reduction. The safety profile of creatine supplementation for aging adults is excellent with clinical trials (up to 2 years) showing no greater adverse effects compared to placebo. This presentation will present an up-to-date evidence-based overview discussing the potential of creatine supplementation as a potential treatment for osteosarcopenia.

**Communication 2:** *Resistance training to prevent and treat osteosarcopenia,* Debra Waters (University of New Mexico, Albuquerque, NM, USA, and University of Otago, New Zealand)

Loading of both skeletal muscle and bone is critical for achieving peak and maintaining lean and bone mass. The relationship between skeletal muscle mass and bone mass is a mechanostatic model where deformations of the bone in response to loads are sensed by osteocytes, which in turn signal osteoblasts and osteoclasts to begin modifying bone architecture and mass to maintain bone homeostasis. This is achieved through complex signalling pathways involving cross-talk between skeletal muscle and bone. The age-related loss of skeletal muscle involves both the atrophy of fast-twitch muscle fibers (type IIa and IIx) and total number of myofibers. The physiological response to resistance training in older adults' results is myofiber type redistribution and myofiber hypertrophy across fiber types, preferential to type II fibers. However, the loss of myofiber number is not reversed by resistance training. Although skeletal muscle and bone require different interventions to stimulate muscle hypertrophy and osteogenesis, respectively, it has been recommended that a combination of resistance exercise with weight-bearing aerobic exercise (e.g., running, skipping, jumping, or high-impact aerobics) may provide adequate muscular loading while weight-bearing aerobic exercise provides additional mechanical loading to bone above gravity alone. This approach has been reported to increase lumbar spine and femoral neck bone mineral density, and to increase muscle mass, and strength, in older women and men. Rest periods both within and between training sessions is an important, often overlooked, element of resistance training that requires more research, particularly in older adults. Repetitive skeletal loading can desensitize the osteocytes and shorter bouts with rest intervals is reported to be more beneficial than the same number of loads performed all at once. Other training elements such as the role of protein supplement intake and timing to optimize lean mass, and the timing of training sessions to optimize circadian rhythms requires more research. This presentation will present an up-to-date evidence-based overview of resistance training as a potential treatment for osteosarcopenia.

**Communication 3:** *Sedentarism and malnutrition: the perfect storm in osteosarcopenia,* Gustavo Duque (McGill University, Montréal, QC, Canada)

Osteosarcopenia is a condition characterized by the simultaneous loss of bone mass and quality (osteopenia/osteoporosis) and muscle mass, strength and function (sarcopenia). It is commonly associated with aging but can also be influenced by other factors, such as poor nutrition and lack of exercise. Nutritional deficits, such as insufficient protein and micronutrient intake, can significantly exacerbate osteoporosis and sarcopenia, making it necessary to address nutritional factors in managing this condition. Deficiency in essential proteins, vitamins and minerals induces the formation of a weak muscle and bone matrix, affecting growth and predisposing to early degenerative changes and loss of mass and function. Sedentarism, or a lack of physical activity, can also exacerbate osteosarcopenia, leading to muscle atrophy, reduced muscle strength, and accelerated muscle loss. In addition, weight-bearing and resistance exercises are essential for maintaining and improving bone density. A sedentary lifestyle, devoid of weight-bearing activities, can contribute to the loss of bone density, making osteoporosis worse. In addition, lack of physical activity can lead to reduced mobility, making it challenging for individuals with osteosarcopenia to engage in daily activities and leading to a vicious cycle of further muscle and bone loss. Finally, sedentary behavior is associated with metabolic changes, including insulin resistance and inflammation, which can negatively impact bone and muscle health. In this session, the biological impact of poor nutrition and sedentaris.

## S10- MUSCLE MASS IS NOT EQUAL TO MUSCLE CELL MASS: IMPORTANCE OF MEASUREMENT MUSCLE COMPOSITION AND QUALITY.

Gustavo Duque *(McGill University, Montréal, QC, Canada)*

**Communication 1:** *Bioimpedance phase angle reflects the contractile to non-contractile tissue ratio in skeletal muscle mass,* Yosuke Yamada[1], Rozalyn Anderson[2], Tsukasa Yoshida[1], Steven Heymsfield[3] ((1) National Institutes of Biomedical Innovation, Health and Nutrition, Osaka, Japan; (2) University of Wisconsin-Madison, WI, USA; (3) Pennington Biomedical Research Center, Louisiana State University, LA, USA)

**Background:** Phase angle (PhA) obtained from bioelectrical impedance analysis (BIA) is recently used as a possible biomarker of muscle composition and aging, but only few studies have proven its validity. Skeletal muscle is a chemically heterogeneous tissue that contains contractile and non-contractile components. We hypothesized that PhA is proportionally related to muscle contractile to non-contractile tissue ratio. **Methods:** We assessed body cell mass (BCM) by whole body 40K counting and fat-free mass (FFM) by dual energy X-ray absorptiometry (DXA) and calculated the ratio of BCM to FFM (%) in 223 people aged 18 to 84 years (118 women and 105 men). We measured skeletal muscle mass by whole-body MRI and PhA by BIA. **Results:** PhA at 50 kHz is strongly correlated with the ratio of the muscle contractile to non-contractile mass ($r = 0.821$, $P<0.001$). The intercept of the regression analysis is not significantly different from zero ($P>0.05$). **Conclusion:** This result is consistent with the following theoretical model: Human body can be considered as a parallel-series resistors-capacitors equivalent circuit, PhA would be zero if contractile tissue surrounded by a phospholipid bilayer were not present in skeletal muscle, and PhA increases linearly as muscle cell mass increases. **Key words:** muscle composition, phase angle, contractile tissue. **Disclosures:** The authors declared no competing interests.

**Communication 2:** *Phase angle for muscle quality assessment: comparison with muscle mass in relation to physical function,* Sho Hatanaka[1], Kiyoji Tanaka[2], Hiroyuki Sasai[1] ((1) Research Team for Promoting Independence and Mental Health, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan; (2) Faculty of Health and Sport Sciences, University of Tsukuba, Ibaraki, Japan)

**Background:** The bioelectrical impedance analysis method is widely used in clinical and community settings as a non-invasive morphometric tool. Phase angle is one of the raw data obtained from the BIA method and has been attracting attention as a muscle quality indicator. In this presentation, we will theoretically interpret what aspects of muscle quality phase angle observes and then compare it to muscle mass in terms of its association with physical function from the observational study (Hatanaka et al., 2023). **Methods:** Data from the Itabashi Longitudinal Study on Aging, a community-based cohort study was used. A sex-stratified multivariate logistic regression analysis was conducted using appendicular skeletal muscle mass index (SMI) and phase angle in whole and local body part as exposures, and low physical function defined from short physical performance battery as the outcome. Discrimination of low physical function was compared using the receiver operating characteristic curve. **Results:** This study included 1,464 participants (age 76 [73–80] years; 757 women), with 58 men (8.2%) and 66 women (8.7%) exhibiting low physical function. The multivariate odds ratio [95% confidence interval] for low physical function among the highest quartile, compared with the lowest quartile were significant in phase angle in multiple sites (e.g., 0.09 [0.03, 0.32] for men, 0.12 [0.04, 0.33] for women in the left leg) but not in SMI (0.51 [0.19–1.34] for men, 0.56 [0.21–1.47] for women). Legs and whole body phase angle outperformed the SMI in discriminating low physical function ($P <0.001$). **Conclusion:** Phase angle reflected physical function better than SMI. Evaluation of phase angle should be interpreted carefully, considering the characteristics and status of the subject at the time of measurement. **Key words:** Muscle quality, bioelectrical impedance analysis, phase angle **Disclosures:** The authors have no conflicts of interest. **References:** Hatanaka S et al. Nutrition. 2023;119:112289. doi.org/10.1016/j.nut.2023.112289.

**Communication 3:** *Muscle quality assessment via BIA and BIS: Associations with physical function and physical Activity,* Yujiro Asano[2], Yosuke Yamada[2], Koki Nagata[3], Kyohei Shibuya[4], Tomohiro Okura[3,4] ((1) Health and Sports Science, University of Tsukuba, Ibaraki, Japan; (2) National Institutes of Biomedical Innovation, Health and Nutrition; (3) Faculty of Health and Sport Sciences, University of Tsukuba, Ibaraki, Japan; (4) R&D Center for Tailor-Made QOL, University of Tsukuba, Ibaraki, Japan)

**Background:** To achieve successful aging, it is important to consider not only muscle mass but also muscle quality. This study focuses the extra- to intra-cellular (resistance) ratio (ECW/ICW) which represents the ratio of water content inside and outside the cells, and Phase Angle (PhA). The objective is to examine the relationship between these indicators of muscle quality and 1) physical functions and 2) physical activities based on intensities. **Methods:** Data from two cohorts (Kasama Study and NIHN Study; n=988 and 297, respectively) were used in this study. The associations between PhA and ECW/ICW and physical function (chair stand, timed up and go (TUG), gait speed, handgrip, single leg balance) were analyzed. Multiple linear regression analysis was conducted to examine the relationship between physical function and ECW/ICW and PhA while adjusting for sex, age, body mass index (BMI), and muscle mass. Time spent in light-intensity PA (LPA), moderate- to vigorous-intensity PA (MVPA), sedentary behavior (SB), and sleep duration were assessed by tri-axial accelerometers. Compositional iso-temporal substitution was performed to examine the associations of 24-hour movement behaviors with PhA and hypothetical time reallocation in movement behaviors with ECW/ICW and PhA, regarding

sex and age. **Results:** ECW/ICW and PhA were significantly positively correlated with physical functions after adjusting for sex, age, body mass index, and muscle mass. Even after adjusting for potential confounders, relative to other behaviors more time spent in MVPA was significantly associated with higher ECW/ICW and PhA. Time reallocation from the other behaviors (SB, LPA, and sleep) to MVPA was predicted higher ECW/ICW and PhA. **Conclusion:** ECW/ICW and PhA are useful for identifying older adults with poor physical function. The ECW/ICW and PhA allow for easy and timely screening of older adults with worse physical function in clinical settings. Our results suggest that increasing or maintaining the daily time spent in MVPA is important for managing ECW/ICW and PhA in older adults, regardless of the other behaviors time consumed instead. **Key words:** extracellular water, intracellular water, compositional iso-temporal substitution analysis, physical activity. **Disclosures:** The authors have no conflicts of interest.

# Oral Communications

## OC1- EFFECT OF ANAMORELIN, A GHRELIN RECEPTOR AGONIST, ON MUSCLE AND BONE IN ADULTS WITH OSTEOSARCOPENIA.

Bess Dawson-Hughes[1], Kathryn Barger[1], Elise Reitshamer[1], Roger Fielding[1], William Evans[2], Lisa Ceglia[1,3] *((1) Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA; (2) University of California, Berkeley, CA; (3) Tufts Medical Center, Boston MA, USA)*

**Background:** Anamorelin, a ghrelin receptor agonist known to stimulate the pulsatile release of growth hormone (GH) from the pituitary, has the potential to improve musculoskeletal health in adults with osteosarcopenia. This study was done to determine the effect of anamorelin treatment for one year on muscle mass and strength and on biochemical markers of bone turnover in adults with osteosarcopenia (OS). **Methods:** We conducted a randomized, placebo-controlled, 1-year anamorelin intervention trial in 26 men and women, age 50 years and older, with OS. The primary endpoint was muscle mass by D3-creatine dilution; other endpoints were lean body mass (LBM) by dual-energy X-ray absorptiometry, muscle strength, and the bone turnover markers, serum procollagen 1 intact N-terminal (P1NP) and C-terminal telopeptide (CTX). **Results:** Anamorelin did not have a significant effect on muscle mass or LBM. It significantly increased knee flexion torque at 240°/s by 20% (P = 0.013) and had a similar but non-statistically significant effect on knee extension. Anamorelin increased bone formation (P1NP) by 75% (P = 0.006), and had no significant effect on bone resorption (CTX). Serum IGF-1 increased by 50% in the anamorelin group and did not change in the placebo group (P = 0.0001 for group difference). **Conclusion:** In this pilot study, anamorelin had no effect on muscle mass or LBM; however, it may potentially improve lower extremity muscle strength and increase bone formation in adults with osteosarcopenia. **Key words:** ghrelin receptor agonist, IGF-1, bone formation, muscle strength. **Disclosures:** BD-H, KB, and LC – none; WJE is a paid consultant for BioAge Labs, 23 and Me, and Pliant Therapeutics and is the Chief Executive Officer of MyoCorps, a company that has exclusive license to the granted patents for the D3Creatine dilution method. WJE receives support from grants from the National Institutes of Health, Muscular Dystrophy Association, Duchenne United Kingdom, and Parent Project Muscular Dystrophy. RAF reports grants, personal fees, and other from Axcella Health, other from Juvicell, other from Inside Tracker, grants and personal fees from Biophytis, personal fees from Amazentis, personal fees from Nestle, personal fees from Pfizer, outside the submitted work. **Clinical Trial Registry:** NCT 04021706. **Data Deposition:** Some or all datasets are not publically available but are available from the corresponding author on reasonable request.

## OC2- LONG-TERM EFFECTS OF RANDOMIZATION TO CALORIC RESTRICTION ON BODY COMPOSITION AND PHYSICAL PERFORMANCE IN OLDER ADULTS.

Denise K Houston[1], Rebecca H Neiberg[1], Michael E Miller[1], Dalane W Kitzman[1], W Jack Rejesk[1,2], Stephen P Messier[2], Mary F Lyles[1], Stephen B Kritchevsky[1], Barbara J Nicklas[1] *((1) Wake Forest University School of Medicine, Winston Salem, NC, USA; (2) Wake Forest University, Winston Salem, NC, USA)*

**Background:** Weight loss improves physical performance in older adults with obesity in short-term randomized controlled trials (RCTs); however, weight regain is common and may lead to sarcopenic obesity over the long-term. We assessed the long-term effects of randomization to caloric restriction (CR) on body composition and physical performance among older adults who completed a weight loss RCT ~9 years prior. **Methods:** We invited 966 older adults who had been randomized to CR or no CR (NoCR) from 5 weight loss RCTs to return for a follow-up (FU) visit. Change in body composition (DXA), SPPB, 4-m gait speed, and grip strength were assessed. Mixed effects models adjusted for sex, race, baseline value, exercise assignment (equally distributed across CR and noCR: 75.4 vs. 76.2%, p=0.76), time and study (as a random effect). **Results:** Among 831 participants still alive at follow-up (mean, 9.2 years [range, 5.6-14.7] after RCT completion), 426 (51%) completed a follow-up visit (mean±SD age and BMI at randomization, 67.3±4.5 years and 33.8±4.7 kg/m2; 70% female). Weight change during the RCTs was -8.9±6.8% in CR (n=217) vs. -1.1±4.5% in noCR (n=183; p<0.0001). Following the RCTs, CR regained weight while noCR lost weight such that weight change from baseline to ~9 year FU was similar (-5.1±9.2% vs. -4.6±8.3%, respectively; p=0.62). Although CR lost more lean mass (LS means [95% CI]: -2.6 kg [-3.4, -1.8]) during the RCTs than noCR (-0.8 kg [-1.5, -0.0], p<0.0001), change in lean mass from baseline to ~9 year FU was not different between groups (-4.8 [-5.7, -3.9] vs. -5.0 [-5.9, -4.1], respectively, p=0.66). Improvements in SPPB (0.19 [0.01-0.36], p=0.04) and 4-m gait speed (0.02 m/sec [0.003-0.05], p=0.03), but not grip strength, were greater in CR than noCR during the RCTs. Although physical performance declined with aging, 4-m gait speed and grip strength declined less in CR than noCR from

baseline to ~9 year FU (0.05 m/sec [0.01-0.08], p=0.02, and 1.74 kg [0.09-3.40], p=0.04). **Conclusion:** Despite significant weight regain in older adults randomized to CR, changes in body composition from baseline did not differ and physical performance was better in CR at ~9 year follow-up compared to noCR. **Key words:** caloric restriction, body composition, physical performance **Disclosures:** The work contained in this abstract was supported by grants from the National Institutes of Health (R01 AG056418, R01 HL093713, R01 AG020583, R37 AG018915, R01 AR052528, R01 HL076441) and the Wake Forest Pepper Center (P30 AG021332). The authors declare no competing interests.

## OC3- THE IMPACT OF ORAL INGESTION OF THE LEUCINE METABOLITE, BETA-HYDROXY-BETA-METHYLBUTYRATE (HMB), UPON THE TRANSCRIPTOME OF HUMAN SKELETAL MUSCLE.

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**Background:** Ageing and chronic diseases result in loss of skeletal muscle mass (sarcopenia/cachexia) and function, which are associated with all cause morbidity and mortality, frailty and poorer clinical outcomes (i.e., in infection/surgery). Research into novel interventions to mitigate these phenomena is a hot-bed of reaearch given the paucity of safe pharmacueticals. HMB, an endogenous metabolite of leucine, has anabolic properties within muscle - acutely stimulating muscle protein synthesis and reducing protein breakdown. While the role of HMB on muscle protein turnover is established, its transcriptomic molecular effects are unknown. **Objective:** To determine the effects of oral HMB in muscle using RNA Sequencing (RNA-Seq). **Methods:** Total RNA was extracted from vastus lateralis muscle biopsies of young males (n=14) before and ~2.5h after oral consumption of ~3.4 g HMB (1, 2). Global changes in the muscle transcriptome were assessed using RNA-Seq. Following alignment, filtering, normalisation and annotation, differential expression of i.e., up and down-regulated genes, between fasted and 'fed' (HMB) conditions, was performed in R using the edgeR package with FDR correction. **Results:** Of 15,982 genes detected, 468 were significantly upregulated with HMB, with 326 being signficantly downregulated. To determine the functional biology of these differentially expressed genes, geneset enrichment and active subnetwork-orientated enrichment analyses was performed using the pathfindR package. These genes were found to be associated with key molecular pathways regulating muscle growth (e.g., mTOR), and homeostasis i.e., immune function/inflammation (cytokines/chemokines) and the extracellular matrix (e.g., ADAMTS4). Amino acid (AA) transporter gene expression from global RNA-Seq (e.g., SLC36A1) and targeted data extraction of all AA transporters detected, revealed broad systematic regulation. **Conclusion:** HMB triggers molecular events important in the homeostasis of muscle, outlining it as a regulator of gene expression, in concert to its established role in proteostasis. That HMB upregulates AA transporters, may indicate synergy with protein intake. Future work should define HMB's transcriptomic effects in ageing/disease, and its synergy with protein nutrition. **Disclosures:** Disclosures: SLP and RR are employees of Abbott. Abbott funded the RNA Seq analysis. **References:** Wilkinson DJ et al., J Physiol. 2013 Jun 1;591(11):2911-23; Wilkinson DJ et al., Clin Nutr. 2018 Dec;37(6 Pt A):2068-2075.

## OC4- MAPPING FRAILTY: UNDERLYING CLINICAL AND PHYSIOLOGICAL DOMAINS IN OLDER ACUTELY ADMITTED PATIENTS.

Hanne Nygaard[1,2,3], Rikke S Kamper[2,3], Rasmus Gregersen[1], Anette Ekmann[2,3], Pernille Hansen[2,3], Sofie K Hansen[2,3], Martin Schultz[2,4], Eckart Pressel[2,3], Charlotte Suetta[2,3] *((1) Department of Emergency Department, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark; (2) CopenAge, Copenhagen Center for Clinical Age Research, University of Copenhagen, Denmark; (3) Department of Geriatric & Palliative Medicine, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark; (4) Geriatric Research Unit, Department of Medicine, Copenhagen University Hospital, Herlev and Gentofte, Herlev, Denmark)*

**Background:** Interventions to prevent or potentially reverse frailty should be targeted against the underlying causes of frailty. These underlying causes, specifying disabilities, health related problems and cognitive problems, are important in defining different frailty domains and allow for individualized interventions. We aimed to investigate the occurrence of five underlying frailty domains (cognition, malnutrition, multimorbidity, low muscle strength, inflammation) in older, acutely admitted patients and to explore the domain's association with the degree of frailty. **Methods:** Analyses were based on 632 acutely admitted medical patients (aged ≥65 years) enrolled in the Copenhagen PROTECT Study. Frailty was evaluated by the Clinical Frailty Scale (CFS): a score of 0-3 defining non-frail (reference group), a score of 4-5 defining frail, and a score ≥6 defining severely frail. The domains were measured by the following assessments within 24H of the index admission: cognition by "Orientation-Memory-Concentration test", malnutrition by "Short Nutritional Assessment Questionnaire", multimorbidity by "Charlson Comorbidity Index", low muscle strength by hand grip strength, and inflammation by C-Reactive protein. Relative risks (RR) were analyzed to investigate the association between the domains and the degree of frailty. **Results:** The prevalence of frailty and severe frailty was 50.9% and 19.9%, respectively. When compared to non-frail, patients with frailty had a significantly higher proportion of low muscle strength, cognitive impairment, multimorbidity, and malnutrition at RR

(95% CI) 2.4 (1.8-3.2) 2.0 (1.4-3.0), 1.8 (1.4-2.3), and 1.5 (1.2-2.1), respectively. Correspondingly, the same domains had RR of 2.7 (2.1-3.6), 2.4 (1.7-3.4), 1.7 (1.4-2.1), and 1.7 (1.4-2.2) respectively, when comparing patients with severe frailty to the non-frail. **Conclusion:** Abnormal assessments in the majority of our defined domains was significantly more frequent among frail and severely frail compared to the non-frail. The underlying domains of frailty occurred with different impact across the levels of frailty. Muscle strength marked the largest difference, followed by cognitive impairment, multimorbidity, and malnutrition in both comparisons. This underlines the importance of assessing these different domains across the spectrum of frail patients to offer individualized and targeted treatment and care. **Key words:** Frailty, intrinsic capacity, acute geriatric patients, clinical assessments. **Clinical Trial Registry:** Clinicaltrials.gov ID: NCT04151108. **Disclosures:** The Copenhagen PROTECT Study is funded by the Novo Nordisk Foundation. All authors declare no conflict of interest.

**OC5- COMPARISON OF PROTEIN INTAKE ASSESSED FROM WEIGHED PROTEIN POWDERS, FOOD DIARIES AND 24-HOUR URINE SAMPLES IN COMMUNITY-DWELLING ADULTS WITH SARCOPENIA: RESULTS FROM THE ENHANCE STUDY.** Nadjia Amini[1], Anouk Devriendt[2], Laurence Lapauw[1], Jolan Dupont[1], Laura Vercauteren[1], Kristin Verbeke[3], Sabine Verschueren[4], Jos Tournoy[1], Evelien Gielen[1] *((1) Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium; (2) Faculty of Medicine, KU Leuven, Leuven, Belgium; (3) Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium; (4) Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium)*

**Background:** Adequate protein intake and protein supplementation has a beneficial role in the treatment of sarcopenia. Till date, studies used subjective methods to determine protein intake in sarcopenic older adults. Objective data on the achieved protein intake of sarcopenic older adults receiving protein supplementation is lacking. **Objectives:** 1. To determine protein intake by nitrogen-excretion in 24-hour urine samples (objective method). 2. To validate protein intake estimated from a combination of 4-day food diaries (dietary protein) and weighed protein powders (supplemental protein)(subjective method) against protein intake estimated from 24-hour urine samples (dietary + supplemental protein). **Methods:** Longitudinal data of the ongoing Exercise and Nutrition for Healthy AgeiNg (ENHANce) study (NCT03649698) were used for an exploratory analysis. ENHANce is a 5-armed triple blinded RCT, in older adults(≥65 years) with sarcopenia defined according to the criteria of the European Working Group of Sarcopenia in Older People. This RCT aims to assess the effect of combined anabolic interventions (protein supplement, omega-3 supplement and physical exercise) on physical performance (12-week intervention). Total protein intake in participants was determined by nitrogen-excretion in 24-hour urine samples and by a combination of weighed protein powders and 4-day food diaries. Mean differences and correlation coefficients were used to assess agreement between the two methods. **Results:** A total of 50 participants were included in the analyses. Nitrogen analysis showed that the mean protein intake was 1.30 g/kg BW in the protein powder group(n=34) and 0.85 g/kg/BW in the placebo group(n=16). Mean protein intake according to the combination of food diaries and weighed powders was overestimated by 7.7 g/day compared to the method using 24-hour urine samples (79.3 g/day versus 87.0 g/day). Correlation between protein intake derived from the combined method and 24-hour urine samples were in the order of 0.480-0.785 at different measurement moments in the intervention period. **Conclusion:** Protein powder supplementation could increase protein intake, allowing participants to meet the daily recommended amount of protein intake for older adults(1.0-1.2 g/kg BW), but not that for sarcopenic older adults(1.5 g/kg BW). Also, protein intake in sarcopenic older adults can be fairly to moderately estimated by the combination of food diaries and weighed powders. **Disclosures:** All authors have no conflict of interest to declare. **References:** Tieland M et al. Eur J Nutr. 2012;51(2):173-9. DOI: 10.1007/s00394-011-0203-6; • Dedeyne L et al. BMC Geriatr. 2020;20(1):532. DOI: 10.1186/s12877-020-01900-5. Bingham SA. J Nutr. 2003;133 Suppl 3(3):921s-4s. DOI: 10.1093/jn/133.3.921S. **Key words:** Protein intake, sarcopenia, older adults, 24-hour urine samples, food diaries, weighed protein powders, protein supplementation, RCT.

**OC6- DEGREE OF FRAILTY IMPACTS TREATMENT AND OUTCOMES OF BREAST CANCER.** Olivia Turner[1,2], Maria-Cruiz Villa-Uriol[1,3], Tamara Tchkonia[5], James L. Kirkland[5], Jon Griffin[1,6], Ilaria Bellantuono[1,2], Lynda Wyld[1,2] *((1) Healthy Lifespan Institute, University of Sheffield, Sheffield, UK; (2) Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK; (3) Department of Computer Science, University of Sheffield, Sheffield, UK; (4) Department of Sociological Studies, University of Sheffield, Sheffield, UK; (5) Department of Physiology and Biomedical Engineering, The Mayo Clinic USA; (6) Department of Histopathology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK)*

**Background:** Frailty affects 25-50% of those aged ≥ 85 and is defined as an impaired ability to respond to adverse events, including surgery. Recovery is also impaired with capacity remaining lower than baseline following a stressor event. An essential sign of frailty is reduced ability to perform daily activities (APDA). **Objectives:** The objective of this study was to calculate a Rockwood Frailty Index (FI) and correlate degree of frailty against breast cancer treatment decision making and outcomes. **Methods:** This unplanned secondary analysis of 3460 women over age 70 with early breast cancer uses a validated FI derived for each patient using data from a baseline comprehensive geriatric assessment. A multivariate Cox's proportional hazards model was developed to determine risk factors for overall and non-breast cancer specific mortality, including frailty. The role of frailty as a predictor of treatment

allocation and the recovery from surgery was also assessed. **Results:** The median age of the cohort was 77 (range 70-102). Frailty was identified in 1176/3275 (37%) of patients, prefrailty in 1668/3275 (50%) and 431/3275 (13%) were robust, aligning with reported literature. The FI correlated with age (univariate) (R = 0.29, 95%CI 0.26-0.32). A multivariate Cox's proportional hazards model identified frailty as an independent predictor of overall (HR=2.71, 95%CI 1.60-4.62, P<0.001) and non-breast cancer specific survival (HR=4.37, 95%CI 2.00-9.53, P<0.001). Robust patients were significantly more likely to receive surgery (HR 1.33, 95%CI 1.275-1.393) than frail patients. Of the patients who received major surgery (mastectomy/axillary clearance) between baseline and 6 weeks, 42/129 (35%) of robust patients, 247/447 (55%) of prefrail, and 213/268 (79%) frail experienced limitations at the 6 week follow up. By 12 months post-surgery, majority of robust patients had made a full recovery, with only 17/101 (17%) having limitations, while 172/394 (44%) of prefrail and 153/189 (81%) of frail patients still had limitations. **Conclusion:** These data suggest that the degree of frailty impacts the choice of treatment for early breast cancer and also impacts on treatment outcomes and resilience. As cellular senescence is a driver of frailty, work is ongoing to determine whether levels of tissue senescence correlate with frailty and the development of post-surgical limitations. **Disclosures:** Patents on senolytic drugs and their uses are held by Mayo Clinic. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies.

## OC7- CENTILES CURVES FOR INTRINSIC CAPACITY THROUGHOUT ADULTHOOD: FROM THE INSPIRE-T COHORT TO IMPLEMENTATION.

Philipe de Souto Barreto, Wan-Hsuan Lu, Sophie Guyonnet, Yves Rolland, Bruno Vellas *(IHU HealthAge, Toulouse, France)*

**Background:** Intrinsic capacity (IC) is a function-centered construct, often measured through six capacities: locomotion, cognition, vitality/nutrition, psychology, hearing, and vision. Developing nomograms of IC would be informative for guiding primary care providers and older adult themselves to keep optimal function during aging. **Objective:** To develop centile curves of IC and discuss how these curves can be implemented in a large scale to inform clinicians and older people to keep their functions during aging. **Methods:** We developed a method to establish age-and sex-specific centiles for IC using data of almost 1,000 people from the INSPIRE-T cohort, southwest France. **Results:** IC was the lowest among older people (compared to young and middle-aged adults) and higher in men than in women. Low IC levels operationalized as IC≤10th percentile tended to have concomitant clinical conditions. **Conclusion:** Establishing IC curves can help to monitoring IC levels through a life course perspective. How these curves can be implemented and help people to situate their IC levels in comparison to same age- and sex-peers will be discussed. How such curves can be simplified without losing its clinical meaningfulness will also be discussed.

## OC8- NORMATIVE VALUES FOR GRIP STRENGTH IN OLDER PEOPLE IN LATIN AMERICA. AN ANALYSIS BASED ON POPULATION SURVEY DATA.

Luis Miguel Gutiérrez-Robledo[1], Roberto Alves Lourenço[2], Desirée López-González[3], Patricia Clark[3], Rosa Estela García-Chanes[1], Brenda Amelia Casasola-Espinosa[1], Ashuin Kammar-García[1] *((1) Dirección de Investigación, Instituto Nacional de Geriatría (Research Directorate, National Institute of Geriatric), Mexico City, Mexico; (2) Laboratório de Pesquisa em Envelhecimento Humano, Universidade do Estado do Rio de Janeiro (Human Aging Research Laboratory, University of the State of Rio de Janeiro), Rio de Janeiro, Brazil; (3) Unidad de Epidemiología Clínica, Hospital Infantil de México Federico Gómez (Clinical Epidemiological Unit, Children's Hospital of Mexico Federico Gómez), Mexico City, Mexico)*

**Background:** Decreased muscle strength and physical function are associated with disability and mortality in older adults. Normative values for the muscle strength test are not usually available for older people and much less for the population of Latin America, but they are necessary for its clinical application and as an indicator of health conditions. **Objective:** Develop normative values for grip strength tests in population samples in Latin America of people aged 60 years and older, considering functional status and the differences between having or not having comorbidities. **Methods:** Five population studies on aging were used (CRELES (2009), SABE-Colombia (2015), SABE-Ecuador (2010), ELSI (2015-3016), MHAS (2012)). They were used to estimate age- and sex-specific normative values for grip strength in people 60 years and older. Participants were without disability or cognitive impairment. **Results:** Of a total of 24,764 people aged 60 years and over without disability or cognitive impairment, 47% (n= 11,648) people have the grip strength test. Curves were estimated considering the differences with and without comorbidities. Sex-specific 5th, 10th, 20th, 50th, 80th, 90th and 95th percentile values for this performance-based test were estimated. **Conclusion:** The normative values developed can be used in clinic and research to identify relatively underperforming persons of the same age, sex, and with or without comorbidities in Latin America. The proposal to include comorbidities in the estimation is an important factor that should be included for further assessment. **References:** Albrecht BM, Stalling I, Bammann K. Sex- and age-specific normative values for handgrip strength and components of the Senior Fitness Test in community-dwelling older adults aged 65-75 years in Germany: results from the OUTDOOR ACTIVE study. BMC Geriatr. 2021 Apr 26;21(1):273. doi: 10.1186/s12877-021-02188-9. PMID: 33902490; PMCID: PMC8074447. Bindawas SM, Vennu V, Al-Orf SM, Alshammari SA, Al-Amoud MM, Calder PC, Al-Muammar MN, Alhamdan AA. Normative Data for Handgrip Strength in Saudi Older Adults Visiting Primary Health Care Centers. Medicina (Kaunas). 2019 Jun 6;55(6):251. doi: 10.3390/medicina55060251. PMID: 31174395; PMCID: PMC6631678. Bohannon RW. Muscle strength: clinical

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**OC10- CHAIR STAND OR SPPB: WHICH ONE IS BETTER FOR PREDICTING DISABILITY?**

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**Background:** Despite the Short Physical Performance Battery has been used to identify risk of disability in older persons, clinicians still have doubts about using the SPBB or just the chair stand test to identify risk of disability in previously nondisabled older persons. So, this study aimed to compare SPPB and chair stand test and verify which is more effective to detect incident disability in previously nondisabled older persons. **Methods:** We used longitudinal data from the English Longitudinal Study of Aging (ELSA), including 5,857 older persons aged ≥ 60 with gait speed > 0.8 m/s and without disability at baseline. Participants performed chair-stand alone and a three-item of the Short Physical Performance Battery – SPPB (standing balance, a 2.4-meter walk, and five repetitive chair stands). A chair-stand test time longer than 15 s and the SPPB score less than or equal to 8 indicates poor performance. Basic activities of daily living (BADL) were evaluated using the modified Katz index (bathing, feeding, walking, transferring, dressing, and toileting). Instrumental activities of daily living (IADL) were evaluated using the adapted Lawton scale (housekeeping, doing laundry, preparing meals, using transportation, shopping, using the telephone, handling finances, and managing medications). The incidence of difficulties on IADL and BADL in the 8-year follow-up period was analysed, and scores ranged from 0 to 7 and 0 to 6, respectively. Generalized linear mixed models were used to estimate the trajectories of IADL and BADL disability incidence, controlling for sociodemographic, behavioural, and clinical characteristics. **Results:** Chair stand > 15 s (IADL: 0.02; 95% CI: 0.02 – 0.02 and BADL: 0.02; 95% CI: 0.01 – 0.02) and SPPB ≤ 8 (IADL: 0.02; 95% CI: 0.01 – 0.02 and BADL: 0.02; 95% CI: 0.01 – 0.02) were almost identical in predicting incident disability after 8 years. In sensitivity analysis, the chair stand can distinguish BADL disability incidence (0.02; 95% CI: 0.01 – 0.02) between 60 and 69 years old, while the SPPB cannot (0.01; 95% CI: 0.00 – 0.02). **Conclusion:** The chair stand test is sufficient to predict incident disability in previously nondisabled older persons over 8 years, and appears to be better than SPPB, especially among younger people. **Key words:** chair stand test, SPPB, physical performance, disability, IADL, BADL. **Disclosures:** The author declared no competing interests.

**OC11- HORMONE REPLACEMENT THERAPY AND MUSCLE LOSS IN POST-MENOPAUSAL WOMEN: ANALYSIS FROM THE BALTIMORE LONGITUDINAL STUDY OF AGING USING REPEATED DUAL-ENERGY X-RAY ABSORPTIOMETRY.**

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**Background:** In 2050, older adults are expected to comprise 22% of the global population (1). While women generally outlive men, they commonly experience a decline physical function and an increase in age-related muscle decline (2, 3). It has been theorized that post-menopausal hormonal changes could be a cause of muscle loss and body composition alterations (4–6). Divergent findings exist in the literature (4, 6, 7), with some studies reporting a favorable impact of estrogen with/without progesterone-based hormone replacement therapy (HRT) on body composition (8, 9), while others fail to observe such effects (10–13). **Objectives:** We aimed to determine the relationship between post-menopausal HRT and longitudinal body composition changes (i.e. muscle and fat-mass) in the Baltimore Longitudinal Study of Aging (BLSA), (14), a large, community based cohort of aging adults. **Methods:** We applied propensity score matching(ratio 1:3) to pair women who received HRT with those who did not, based on baseline characteristics. Linear mixed-effects models (LMEM) accounting for between-participant variability were used to estimate cross-sectional and longitudinal relationships between

HRT and repeated measurements of muscle (grams) and fat-mass (grams) using Dual-Energy-X-ray Absorptiometry. **Results:** We identified 192 menopausal women, comprising 48 HRT-treated and 144 non-treated participants, with a total of 873 eligible study visits from 2003 to 2020 (mean of 2 visits per HRT-treated and 5 visits per non-treated participant). The cohort was 70% White, with a median age of 68 and a median of BMI 25.7 at the index visit. In cross-sectional analysis, HRT displayed a positive association with total-body lean-mass (beta: 969.9;95% CI: 518.9;1420.05;p<0.001) and a negative association with total-body fat-mass (beta: -1397.7;95% CI:-2248.22, -547.61;p: 0.001). Upon introducing time-interaction into the models, the association between HRT and total-body lean-mass became non-significant (beta: 212.5; 95% CI: -268.78, 693.84,p:0.38), while the negative association with fat-mass remained significant (beta: -1722.67; 95% CI: -2682.69, -762.39; p< 0.001). **Conclusion:** Among post-menopausal women in the BLSA, fat-mass was lower and muscle-mass higher in those on HRT compared to matched controls, an association which persisted over-time for fat-mass. However, HRT was not associated with the longitudinal preservation of muscle-mass. Thus, the ability of HRT to prevent frailty and related functional declines may be limited. **Disclosures:** None. **References:** 1. World Health Organization, National Institute of Health, https://www.nia.nih.gov/sites/default/files/2017-06/global_health_aging.pdf, Accessed October 11, 2023. 2. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006;61(10):1059-1064. doi:10.1093/GERONA/61.10.1059. 3. Austad SN. Why women live longer than men: sex differences in longevity. Gend Med. 2006;3(2):79-92. doi:10.1016/S1550-8579(06)80198-1. 4. Javed AA, Mayhew AJ, Shea AK, Raina P. Association Between Hormone Therapy and Muscle Mass in Postmenopausal Women: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(8):e1910154-e1910154. doi:10.1001/JAMANETWORKOPEN.2019.10154. 5. Experts Agree About Hormone Therapy, Menopause Relief | The North American Menopause Society, NAMS. Accessed October 10, 2023. https://www.menopause.org/for-women/menopauseflashes/menopause-symptoms-and-treatments/the-experts-do-agree-about-hormone-therapy. 6. Taaffe DR, Newman AB, Haggerty CL, et al. Estrogen replacement, muscle composition, and physical function: The Health ABC Study. Med Sci Sports Exerc. 2005;37(10):1741-1747. doi:10.1249/01.MSS.0000181678.28092.31. 7. Changes in muscle strength in women following the menopause: a longitudinal assessment of the efficacy of hormone replacement therapy - PubMed. Accessed October 10, 2023. https://pubmed.ncbi.nlm.nih.gov/10369797/#. 8. Dobs AS, Nguyen T, Pace C, Roberts CP. Differential effects of oral estrogen versus oral estrogen-androgen replacement therapy on body composition in postmenopausal women. J Clin Endocrinol Metab. 2002;87(4):1509-1516. doi:10.1210/JCEM.87.4.8362. 9. Sørensen MB, Rosenfalck AM, Højgaard L, Ottesen B. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res. 2001;9(10):622-626. doi:10.1038/OBY.2001.81. 10. Tankó LB, Movsesyan L, Svendsen OL, Christiansen C. The effect of hormone replacement therapy on appendicular lean tissue mass in early postmenopausal women. Menopause. 2002;9(2):117-121. doi:10.1097/00042192-200203000-00006. 11. Dayal M, Sammel MD, Zhao J, Hummel AC, Vandenbourne K, Barnhart KT. Supplementation with DHEA: effect on muscle size, strength, quality of life, and lipids. J Womens Health (Larchmt). 2005;14(5):391-400. doi:10.1089/JWH.2005.14.391. 12. Thorneycroft IH, Lindsay R, Pickar JH. Body composition during treatment with conjugated estrogens with and without medroxyprogesterone acetate: analysis of the women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial. Am J Obstet Gynecol. 2007;197(2):137.e1-137.e7. doi:10.1016/J.AJOG.2007.05.042. 13. Bea JW, Zhao Q, Cauley JA, et al. Effect of hormone therapy on lean body mass, falls, and fractures: Six-year results from the Women's Health Initiative Hormone Trials. Menopause. 2011;18(1):44. doi:10.1097/GME.0B013E3181E3AAB1. 14. Shock NW, Others A. Normal Human Aging: The Baltimore Longitudinal Study of Aging. Published online November 1984.

## OC12- EXERCISE PROGRAMS TO PREVENT FUNCTION AND MOBILITY LOSS IN OLDER ADULTS DISCHARGED FROM EMERGENCY DEPARTMENTS WITH MINOR INJURIES: THE CEDECOMS CLINICAL TRIAL.

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**Background:** Yearly in Canada, over 420,000 seniors sustain injuries and around 65% seek care to emergency departments (EDs). While 75% of such seniors are discharged home, nearly one in five experience functional losses that persist over 6 months after the consultation. ED services do not meet the specific needs of these seniors. On the other hand, there is convincing evidence of the functional benefits of physical exercises in community-dwelling older adults, but

such intervention is not commonly recommended to injured seniors at discharge from the EDs. **Objective:** To compare the effects of exercise programs (intervention), to usual practice at discharge from EDs (control) on functional decline and physical abilities within 6 months of consultation for minor injuries in seniors at moderate and high-risk of decline. **Design and settings:** Stepped-wedge pragmatic randomized trial in four Canadian EDs in 2017-20. Participants were assessed 3 times: baseline at EDs, 3- and 6-month. Intervention included multicomponent and risk-level adapted exercise programs, 2-3 times/week for 12 weeks. The primary outcome, functional decline, was defined as 2-point loss on the Older American Resource Service (OARS) scale. Basic physical abilities (leg-strength, walking speed, balance) were measured by the Short Physical Performance Battery (SPPB). Generalized linear mixed log-binomial regressions were used to examine the between-group differences in outcomes. **Results:** Among the 447 moderate-risk participants, there was half as much functional loss at 3-month in intervention vs control (13% [CI 95%: 9%-19%] vs 27% [CI 95%: 20%-38%]) and a trend for better balance overtime. Among the 345 high-risk participants, there was a trend in intervention for more improvements overtime on the SPPB-total and leg-strength scores, but wide variations in controls' outcomes did not allow for significant results. **Conclusion:** 12-week multicomponent exercises programs help early functional recovery after minor injuries in moderate-risk seniors. Longer-term exercise interventions would be needed to improve functional recovery in high-risk individuals.

**OC13- SALBUTAMOL, BUT NOT GHRELIN, CAN AMELIORATE CALORIC RESTRICTION INDUCED MUSCLE-ATROPHY.**

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**Background:** The prevalence of sarcopenia is increasing and new therapeutic treatments could be of help. Salbutamol increases muscle protein synthesis (1), but can also introduce cardiovascular side-effects (2), which are unfavorable in especially an older patient population. Ghrelin influences growth-hormone secretion and downstream IGF-1 (3), and might serve as a suitable alternative. These compounds were tested in a novel mouse model of muscle atrophy in which effects of short-term caloric restriction (CR) alone (left-leg) and combined CR + immobilization (right leg) can be assessed. Underlying mechanisms regulated in this model have been shown to overlap with mechanisms regulated in aged humans (4). **Objectives:** To test the effects of salbutamol and ghrelin treatment on muscle atrophy induced by short-term CR and immobilization. **Methods:** C57BL/6J mice were calorically restricted (-40%) and one hindleg was taped and immobilized for two weeks to induce muscle atrophy. Four groups were included, one healthy reference group, one untreated group, one group treated with salbutamol and one group treated with acetylated-ghrelin. Body weight and lean mass were measured over-time, and after the two weeks of treatment, muscles of hindlimbs were dissected and weighted. RNA-seq, western blots and myofiber typing by means of immunohistochemistry are currently being performed as well to identify the mechanisms underlying muscle atrophy and the treatment effects. **Results:** Salbutamol, but not ghrelin, ameliorated CR induced loss of body lean mass and loss of hindlimb skeletal muscle mass. Strikingly, salbutamol treatment did not ameliorate muscle atrophy in the hindlimb that was immobilized. Circulating insulin and IGF-1 levels were increased in mice exposed to salbutamol treatment, however, ghrelin treatment failed to increase the concentration of IGF-1. **Conclusion:** Salbutamol ameliorated CR induced loss of muscle, but was not effective in the hindlimb that was immobilized as well. This indicates a potential synergistic mechanism between salbutamol treatment and muscle contraction. Mice exposed to ghrelin treatment did not show any functional beneficial effects, perhaps due to downregulation of endogenous ghrelin secretion or desensitization. The ongoing measurements will disclose mechanisms underlying the beneficial effects of salbutamol, and potentially reveal effects on ghrelin supplementation on a molecular level in skeletal muscle. **Disclosure:** None. **References:** 1. Hostrup M, Reitelseder S, Jessen S, Kalsen A, Nyberg M, Egelund J, et al. (2018). Beta2-adrenoceptor agonist salbutamol increases protein turnover rates and alters signalling in skeletal muscle after resistance exercise in young men. J Physiol. 596:4121–4139. 2. Burggraaf J, Westendorp RGJ, In't Veen JCCM, Schoemaker RC, Sterk PJ, Cohen AF, et al. (2001). Cardiovascular side effects of inhaled salbutamol in hypoxic asthmatic patients. Thorax. 56:567–569. 3. Lewiński A, Karbownik-Lewińska M, Wieczorek-Szukała K, Stasiak M, Stawerska R (2021). Contribution of ghrelin to the pathogenesis of growth hormone deficiency. Int J Mol Sci. 22:1–21. 4. Jong JCBC De, Caspers MPM, Keijzer N, Worms N, Attema J, Ruiter C De, et al. (2023). Caloric Restriction Combined with Immobilization as Translational Model for Sarcopenia Expressing Key- Pathways of Human Pathology. Aging Dis. 14:937–951.

**OC14- INNOVATING LARGE ANIMAL MODELS OF FRAILTY AND EXPOSURE MEMORY: EVIDENCE THAT EARLY LIFE EVENTS CAN BUFFER THE ADVERSE IMPACT OF FRAILTY ON MORTALITY IN PET DOGS WITH EXCEPTIONAL LONGEVITY.**
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**Background:** Frailty index (FI) operationalizes frailty as the proportion of health deficits present in each individual, providing insights into the aging process and its consequences, predicting mortality and healthy life-expectancy. However, using the identical FI instrument, human cohorts have been shown to differ significantly in mortality risk associated with increasing FI. What constitutes the critical context, the particular aspects of physiology including early-life exposures that might buffer the adverse impact of increasing deficit accumulation on mortality? **Methods:** We used a novel animal model of highly-successful human aging, capitalizing on the first systematic study of the oldest-living pet dogs in North America, gathering detailed data on exceptionally long-lived dogs physiologically equivalent to human centenarians. Data from 82 female dogs of one breed (Rottweilers) are presented. Frailty index was constructed by assessing accumulation of 34 deficits using information from interviews with dog owners and validated through in-person examination by veterinarian. Logistic regression was used to determine relationship between exposure variables and FI, and between increasing FI and mortality. To probe impact of physiological context, we created age-adjusted risk models evaluating two exposure variables: hypothalamic-pituitary-gonad (HPG) axis integrity (duration of ovary exposure) and lifetime inflammation score (low,high). **Results:** Increased deficit accumulation in canine centenarians was associated with increased mortality risk. Each .01 unit increase in FI was associated with age-adjusted odds-ratio (OR) of 1.12 (95%CI,1.05-1.20) for mortality(p=0.002). Early disruption of HPG axis (ovary removal) exacerbated the adverse impact of increasing FI on mortality (OR=1.19(95%CI,1.01-1.41) (p=.04). Avoidance of HPG axis disruption during the 24-month developmental period had 65% buffering effect on mortality consequence of FI; notably, in females with intact HPG axis, increasing FI no longer had significant adverse impact on mortality (OR =1.07(95%CI,0.97-1.18) (p=.17). Extent of inflammation was not associated with deficit accumulation or its mortality consequence. **Conclusion:** This research attempts to understand how heterogeneity in the mortality consequences of FI hinges upon physiological context. We show that early life influences that retain or disrupt hypothalamic-pituitary-gonad axis integrity can exert significant impact on mortality consequences of deficit accumulation later in life. Future research using the dog model should explore early life interventions that can enhance resilience and mitigate adverse consequences of frailty. **Key words:** frailty index, dog, HPG axis, FI and mortality. **Disclosures:** The authors declare no competing interests.

**OC15- CURRENT STATE OF THE ART OF CELL-BASED THERAPY FOR AGING FRAILTY AND NEURO-COGNITIVE DISORDERS.**
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Frailty, a condition affecting healthspan in elderly individuals, lacks effective treatments. Here I will discuss the therapeutic potential of allogeneic medicinal signaling cells (MSCs; Lomecel-B) in improving the physical strength and vigor of older individuals with frailty. Lomecel-B comprises a stem cell type that acts through a variety of mechanisms, notably by promoting vascular health/angiogenesis and by exerting long-lasting anti-inflammatory effects. I will discuss the current understanding of MSCs in broad context and present findings from a recent clinical trial involving intravenous Lomecel-B treatment in elderly subjects with frailty. Briefly, we conducted a randomized, double-blind, placebo-controlled trial of Lomecel-B (single infusion) in 148 patients with mild to moderate frailty. Primary endpoints included measures of strength and vigor such as a six-minute walk test (6MWT) up to 9 months after infusion, the PROMIS physical function patient reported outcomes, and assessments of biomarkers. We found that the difference in 6MWT outcomes between the highest dose of Lomecel-B (200 million cells) and placebo was 41.3 m (95% CI: -2.4 - 84.9 M p=0.0635) at 6 months and 63.4 m (95% CI: 17.1 - 109.6 M; p=0.0077) at 9 months. Thus, infusions of Lomecel-B lead to dose-dependent mobility improvements in older individuals with frailty. I will discuss these findings in the context of the state of the art of MSC therapies, potential mechanisms of action, and summarize their potential in treating aging frailty.

**OC16- EXPLORING THE PROGNOSTIC VALIDITY OF THE AWGC CRITERIA FOR CACHEXIA IN JAPANESE PATIENTS WITH CANCER, SARCOPENIC DYSPHAGIA, AND HEART FAILURE.**
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**Background:** Cachexia, a debilitating syndrome, carries significant prognostic implications, particu-larly in various clinical contexts. The Asian Working Group for Cachexia (AWGC) has developed criteria tailored for Asian populations, yet their prognostic validity in specific patient cohorts re-mains

underexplored. This study consolidates findings from three distinct investigations to assess the prevalence and prognostic significance of cachexia defined by the AWGC criteria across diverse patient populations. **Methods:** Retrospective cohort studies were conducted involving patients with advanced cancer, sarcopenic dysphagia, and heart failure. Data were collected on cachexia status according to the AWGC criteria, including parameters such as weight loss, body mass index, grip strength, and bio-chemical markers. Survival outcomes and functional measures were assessed across patient co-horts. **Results:** Across all studies, a high prevalence of cachexia, ranging from 76% to 87.4%, was ob-served in respective patient populations. Cachexia was consistently associated with older age, lower body mass index, greater weight loss, poorer functional status, and elevated inflammatory markers. In patients with advanced cancer and sarcopenic dysphagia, cachexia significantly correlated with shorter median survival times and increased mortality risk, independent of confounding factors. Additionally, cachexia tended to be associated with reduced functional capacity, as evidenced by shorter walking distances in older patients with heart failure. **Conclusion:** These findings underscore the prognostic significance of AWGC-defined cachexia across diverse clinical settings. Cachexia emerged as a robust predictor of mortality and functional decline, warranting attention in patient care and research endeavors. Further validation studies and targeted interventions are needed to mitigate the adverse impact of cachexia on patient outcomes and quality of life.

**OC17- PATIENT-REPORTED OUTCOMES IN SARCOPENIA.** Charlotte Beaudart *(Research Institute for Life Sciences (NARILIS), Department of Biomedical Sciences, Faculty of Medicine, University of Namur, Namur, Belgium)*

**Background:** Patient-reported outcome measures (PROMs) are designed to evaluate patient experiences, including pain, quality of life, and satisfaction with healthcare. In recent years, there has been a growing emphasis on patient-centered research, recognizing patient perspectives as a vital element in assessing the effectiveness of healthcare interventions. PROMs facilitate the capture of treatment effectiveness aspects that are of paramount importance to patients. Among PROMs, health-related quality of life (HRQoL) is frequently evaluated, with measurement conducted through generic HRQoL questionnaires such as the SF-36 or EQ5D, as well as specific instruments. **Methods:** Literature review. **Results:** This presentation explores various aspects related to the use of PROMs in sarcopenia research. Firstly, we will provide an overview of interventional trials aiming to manage sarcopenia that have employed PROMs as primary or secondary evaluation criteria. Subsequently, we will assess the impact of these interventions on PROMs, focusing on their effects on quality of life. Secondly, we will delve into a theoretical exploration of the diverse psychometric properties required for the validation of PROMs. This discussion will provide valuable insights into the rigorous methodology necessary to ensure the reliability and validity of PROMs used in clinical research. Lastly, we will introduce the SarQoL questionnaire, the first validated quality of life instrument specifically designed for sarcopenia. Developed in 2015, the SarQoL questionnaire (available at http://www.sarqol.org) represents a significant advancement in capturing the unique HRQoL aspects relevant to individuals with sarcopenia. **Conclusion:** This presentation promises to shed light on the pivotal role of PROMs in sarcopenia research, providing a comprehensive view of their application in intervention assessment and the critical psychometric properties involved in their validation.

**OC18- COMMON DATA ELEMENTS AND STANDARDIZED OUTCOMES IN GEROSCIENCE RESEARCH.** John Muscedere[1,2] *((1) Canadian Frailty Network, Kingston, ON, Canada; (2) Queen's University, Kingston, ON Canada)*

**Background:** The field of geroscience is growing rapidly as researchers aim to better understand the genetic, molecular, and cellular mechanisms that make aging a risk factor for chronic diseases and common aging-related conditions. As the field of geroscience grows, it stands to benefit from the standardization of data elements and outcomes. A lack of standardization impairs one's ability to interpret, generalize, and implement research findings. A need for common data elements and standardized outcomes has been identified and addressed in other aging-related research. Most recently, our team developed common data elements and core outcomes for frailty. This has provided us with lessons to be applied in the development of common data elements and standardized outcomes in geroscience research. **Methods:** The Canadian Frailty Network (www.cfn-nce.ca; CFN), a not-for-profit pan-Canadian nationally-funded research network, identified the need for standardization in frailty research and consequently a need for a set of common data elements (CDEs) and core outcome measures (COMs). CFN chose to lead a global initiative to arrive at a frailty CDEs and COMs set, also known as FOCUS: The Frailty Outcomes Consensus Project. Lessons learned from this process can be applied to the development of common data elements and standardized outcomes in geroscience research. **Results:** Over 200 individuals from 20 different countries participated in CFN's FOCUS project. It underscored the need for representation from participants to arrive at a broadly accepted standardized set. Additionally, discussions with participants revealed the need to consider applications of the set in various settings as well as cultural contexts. Parallels can be drawn between the need for standardized frailty data elements and outcomes as well as the process by which to develop them, and that of the need for standardized geroscience data elements and outcomes. **Conclusion:** Standardized outcome sets have been successfully developed in aging-related research. Geroscience stands to benefit from the development of standardized set. Lessons learned from previous processes can be applied to the development of a geroscience set.

**OC19- HIGHER THYROID HORMONE LEVELS ARE ASSOCIATED WITH LOWER MUSCLE QUALITY: RESULTS FROM MROS.S.** Jennifer S Mammen[1], Stephanie Harrison[2], Eric S Orwoll[3], Douglas C Bauer[2], Peggy M Cawthon[2,4] *((1) Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine, Baltimore MD, USA; (2) Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA; (3) Division of Endocrinology, Diabetes and Clinical Nutrition Oregon Health Sciences University School of Medicine, Portland OR, USA; (4) San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, CA, USA)*

**Background:** Thyroid hormone is catabolic and therefore excess is a possible risk factor for sarcopenia (1). Defining the degree of risk and at what level of exposure is critical as thyroid hormone therapy is among the most common prescriptions (2) and ~20% of those on therapy are over treated (3, 4), representing a potentially significant reversible contributing factor to frailty. **Objectives:** Assess the relationship between thyroid hormone levels and pituitary hormone surrogate markers of thyroid functional status with muscle mass and muscle quality in older adults. Secondary analyses included effects on body composition and the effect of thyroid hormone prescriptions on the relationship between thyroid hormone and outcome. **Methods:** Cross-sectional analysis of the MrOS study of men age 65+ with CT-scan and thyroid function test data available. Exposures included thyrotropin (TSH) and free thyroxine (FT4). Outcomes included AI-algorithm derived CT-scan measures of skeletal muscle area and density at T12 and L3, and visceral and subcutaneous adiposity at L3. Multivariable models were adjusted for age, race, body mass index, height, smoking and use of thyroid medications. **Results:** Our cohort consisted of 731 men who were 91.2% non-Hispanic White, with a mean age of 74 years (SD 5.9). Eight percent were on thyroid hormone therapy with a mean TSH=3.01 mU/L (SD 2.66) compared to 2.53 mU/L (SD1.83, NS) among the cohort overall. Only one participant had frankly elevated FT4 levels. Thyroid hormone use was significantly more common (22.5%) in the highest quartile of FT4. Higher FT4 levels were significantly associated with lower skeletal muscle density at both T12 (beta= -1.0, SE 0.38, p=0.005) and L3 (beta=-1.2, SE 0.27, p<0.000) and higher visceral adiposity (beta=7.9, SE 2.5, p=0.002) in unadjusted and fully adjusted models (shown). TSH was not a consistent predictor of body composition. There were no significant interactions. **Conclusion:** Higher FT4 levels are associated with lower skeletal muscle density and higher visceral fat mass, a pattern that is consistent with lower quality body composition. Additional research is needed to establish the causal relationship between thyroid hormone excess and poor muscle quality. Clinicians should be cautious to avoid over treatment with thyroid hormone in frail older adults. **References:** 1. Ibad HA, Mammen JS, Simonsick EM, Kwoh CK, Guermazi A, Demehri S. Higher thyroid hormone has a negative association with lower limb lean body mass in euthyroid older adults: Analysis from the Baltimore Longitudinal study of aging. Front Aging. 2023;4:1150645. 2. Brito JP, Ross JS, El Kawkgi OM, et al. Levothyroxine Use in the United States, 2008-2018. JAMA Intern Med. 2021;181(10):1402-1405. 3. Mammen JS, McGready J, Oxman R, Chia CW, Ladenson PW, Simonsick EM. Thyroid hormone therapy and risk of thyrotoxicosis in community-resident older adults: Findings from the Baltimore Longitudinal Study of Aging. Thyroid : official journal of the American Thyroid Association. 2015;25(9):979-986. 4. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Archives of Internal Medicine. 2000;160(4):526-534.

**OC20- THE EFFECT OF BETA-HYDROXY-BETA-METHYLBUTYRATE (HMB) UPON ACUTE FED-STATE MUSCLE PROTEIN SYNTHESIS IN HEALTHY OLDER MEN AND WOMEN: A RANDOMIZED DOUBLE-BLIND CONTROLLED CLINICAL TRIAL.** K Smith[1], H Abdullah[1,2], S Rudrappa[1,2], I Idris[1,2], JJ Bass[1], H Crossland[1], DJ Wilkinson[1], SL Pereira[3], BE Phillips[1], PJ Atherton[1] *((1) MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research and Nottingham NIHR BRC, School of Medicine, University of Nottingham, Derby, UK; (2) Department of Diabetes and Endocrinology, Royal Derby Hospital, Derby, UK; (3) Abbott Nutrition, Research and Development, Columbus Ohio, USA)*

**Background:** Anabolic resistance manifests as a reduction in muscle protein synthesis (MPS) stimulation in response to feeding and is suggested to underlie the chronic age-related loss of muscle mass. Some of the suggested underlying mechanisms impacting anabolic resistance include increased amino acid splanchnic uptake and myocellular signalling deficits. HMB, a naturally occurring leucine metabolite that stimulates MPS acutely (1), has been proposed as a potential nutritional tool to overcome age-associated anabolic resistance. **Objectives:** To investigate the impact of HMB on acute MPS responses to an oral bolus of 40 grams protein in older adults. **Methods:** Twenty-four community-dwelling older adults (68.5 ± 0.6 years (average); 13 men, 11 women) were randomized in a cross-over double-blind design to 40g whey protein with or without 3g calcium-HMB. Fasted and fed state plasma HMB and aminoacidemia, rates of MPS, and muscle anabolic signalling biomarkers were assessed. **Results:** In the presence of high protein, HMB was rapidly absorbed, showing an increase in plasma levels 30 min post-feeding and across the 3-h postprandial period (p<0.001). In older men and women, both groups displayed significant increases in MPS in response to high protein feeding (fasted (0h) to 3h-postprandial change (mean ± SEM), Males: Whey, +0.032 ± 0.006%.h-1; Whey + HMB, +0.023 ± 0.004 %.h-1; Females: Whey, +0.023 ± 0.006%.h-1; Whey + HMB, +0.038 ± 0.006%.h-1, p<0.05). In older women only, the addition of HMB further enhanced the MPS response (0-3h fed change, p=0.0495) and area under the curve (0-3h fed, p=0.0364) versus protein alone. Plasma aminoacidemia increased in response to protein feeding and was not altered by HMB. In measuring anabolic

signalling, only p70S6K1Thr389 was increased by feeding in both groups ($p<0.001$) and was not altered by HMB. **Conclusion:** High-dose protein feeding increased MPS in older men and women. Although 40g protein was not enough to overcome anabolic resistance in older women, the addition of HMB enhanced this MPS feeding response. Given the relationship between low muscle mass and falls, and the higher prevalence of falls in older women, the present work provides evidence for the clinical potential of HMB along with high protein to mitigate anabolic resistance. **Key words:** Anabolic resistance, HMB, protein. **Clinical Trial Registry:** NCT02052232, https://clinicaltrials.gov/. **Disclosures:** This study was funded by Abbott. SLP is an employee of Abbott. **Reference:** 1. Wilkinson, D. J et al (2013) The Journal of physiology, 591(11), 2911-2923. https://doi.org/10.1113/jphysiol.2013.253203.

## OC21- PHYSICAL PERFORMANCE AND INCIDENCE OF NEGATIVE EVENTS IN VERY OLD ADULTS: RESULTS FROM THE ILSIRENTE STUDY.

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**Background:** Declining physical performance in old age is associated with a wide range of negative health related outcomes, including disability, poor quality of life, admission to hospital, admission to residential care, and death (1 3). However, it is unclear which physical capabilities should be prioritized to obtain prognostic information in older adults. **Methods:** ilSIRENTE was a prospective cohort study of older adults residing in the mountain community of the Sirente geographic area in Central Italy. The study was designed by the Department of Geriatrics of the Università Cattolica del Sacro Cuore (Rome, Italy) an d the teaching nursing home Opera Santa Maria della Pace (Fontecchio, L'Aquila, Italy) in partnership with local administrators and primary care physicians of the Sirente Mountain Community Municipalities. The protocol was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore. Prior to enrollment, all participants or their proxies, when appropriate, provided signed informed consent. Baseline assessments began in December 2003 and were completed in September 2004. Follow up visits took place after 24 months of baseline assessment. Information about medical history, medications, and lifestyle habits (e.g., smoking, alcohol consumption, physical activity) was collected using validated questionnaires. Physical performance was assessed usin g isometric handgrip strength , walking speed at usual and fast pace, 5 time sit to stand test , and sit to stand power measures. Absolute, relative, allometric, and specific muscle power values of lower extremities were calculated using the equations validated by Alcazar et al. (5). Appendicular skeletal muscle mass was estimated from calf circumfe rence using a validated equation (6). History of falls, incident falls, and disability status according to basic Activities of Daily Living (ADLs) were recorded over two years. Survival status was obtained from the participants' general practitioners and w as confirmed by the National Death Registry over 10 years from enrolment. Linear, binary, and Cox regressions were used to evaluate the association between physical Linear, binary, and Cox regressions were used to evaluate the association between physical performance measures and health outcomes. performance measures and health outcomes. **Results:** Mean age of the 255 participants was 84.2 ± 5.1 years, and 161 (63.1%) were women. Mean age of the 255 participants was 84.2 ± 5.1 years, and 161 (63.1%) were women. Logistic regression indicated that hanLogistic regression indicated that handdgrip strength was significantly associated with incident ADL grip strength was significantly associated with incident ADL disability, whereas specific muscle power was an independent predictor of death. No significant disability, whereas specific muscle power was an independent predictor of death. No significant associations were observed between any physical performance measure and incident falls.associations were observed between any physical performance measure and incident falls. **Conclusion:** Our findings indicate selective associations between physical performance tests and Our findings indicate selective associations between physical performance tests and the occurrence of negative events in very old adults, with poor handgrip strength predicting the occurrence of negative events in very old adults, with poor handgrip strength predicting disability and specific muscle power being longitudinally associated with deathdisability and specific muscle power being longitudinally associated with death. **Disclosures:** The authors have no conflict of interest to discloseThe authors have no conflict of interest to disclose. **References:** 1. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. 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**OC22- RESULTS OF A SAFETY AND TOLERABILITY PILOT STUDY OF A RANDOMIZED, PARALLEL GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF A NOVEL KETONE ESTER TARGETING FRAILTY VIA IMMUNOMETABOLIC GEROSCIENCE MECHANISMS.** Brianna J. Stubbs, Elizabeth Stephens, Chatura Senadheera, Sawyer Peralta, Stephanie Roa-Diaz, Laura Alexander, Wendie Silverman-Martin, Thelma Garcia, Peter Turnbaugh, James Johnson, John Newman *(Buck Institute for Research on Aging, Novato, CA, USA)*

**Background:** Ketone bodies function as an energy and a signaling metabolite and have been hypothesized to have multiple effects on geroscience pathways. Ketone esters (KE) are a nutritional tool that induce ketosis without other dietary changes but no studies have addressed their translation into an aging population. Our long-term goal is to test the effect of KE on geroscience mechanisms and clinical outcomes relevant to frailty in a multisite study of pre-frail older adults scheduled to begin in 2024. Here we will present the results of a pilot trial that will inform the design of the upcoming study. **Objectives:** The primary objective of this randomized, placebo controlled, double-blinded, parallel group, pilot clinical trial was to determine the tolerability of 12 weeks of KE ingestion in older adults. Secondary outcomes included determining KE safety and the acute blood ketone kinetics after KE consumption. Exploratory clinical outcomes were changes in physical and cognitive function, and quality of life. Exploratory geroscience biology outcomes included general and inflammatory aging biomarkers and gut microbiome. **Methods:** Older adults (> 65y) who were living in the community, independent in activities of daily living, and with no unstable acute medical conditions (n=30) were recruited. The study intervention was a KE in a flavored beverage (n=15) or a visually, calorically and taste-matched placebo (PLA) containing canola oil. Firstly, acute beta-hydroxybutyrate kinetics after 12.5 or 25g of KE consumption were assessed. Secondly, after collection of baseline measurements, participants were randomly allocated to consume KE or PLA daily for 12 weeks:12.5g for week 1, and 25g from week 2. A questionnaire was used to assess side-effects daily for 2 weeks, and then via recall at bi-weekly for the remainder. Safety assessments were repeated at week 4. Stool samples were collected throughout the study. All measures were repeated at week 12. **Results:** Enrollment for the study was completed on August 29th 2023, with data due to report in early 2024. **Conclusion:** This study will provide critical data demonstrating the feasibility, tolerance, and safety of 12 weeks of KE consumption in older adults which will facilitate the use of KE in trials designed to directly study ketone impacts on geriatric conditions via geroscience mechanisms, such as our upcoming study of pre-frail subjects. Disclosures: The principal investigator (Dr. Newman), Dr. Brianna Stubbs, and the Buck Institute hold shares in BHB Therapeutics. Drs. Newman and Stubbs are inventors on patents relating to the use of ketone bodies that are assigned to The Buck Institute. All other authors have no conflicts to declare. Individual and institutional extensive conflict management plans were developed and approved by the Buck Institute and the IRB. Actions and decisions important to subject safety and study integrity are carried out by parties with no potential financial conflict. Participant consent is obtained by licensed registered nurses who have no financial conflict. Decisions on subject enrollment, continuation, and discontinuation are made by independent medical officers unaffiliated with Buck Institute and with no financial conflict. Data analysis for the primary outcome is carried out by an independent statistician with no financial conflict. Study staff, including the principal investigator, will maintain blinding through study completion unless unblinding is required for safety concerns.

**OC23- USING DEEP LEARNING TO PREDICT PHYSICAL FUNCTION FROM ANATOMICAL MRI SCANS – RESULTS FROM THE SOMMA AND OAI DATASETS.** Bragi Sveinsson[1,2], Vijaya B. Kolachalama[3,4], Evelyn Hsieh[5,6], David Felson[3,5] *((1) Athinoula A. Martinos Center for Medical Imaging, Radiology, Massachusetts General Hospital, Boston, MA, USA; (2) Radiology, Harvard Medical School, Boston, MA, USA; (3) Medicine, Boston University, Boston, MA, USA; (4) Computer Science and Faculty of Computing & Data Sciences, Boston University, Boston, MA, USA; (5) Section of Rheumatology, Yale School of Medicine, New Haven, CT, USA; (6) Section of Rheumatology, VA Connecticut Healthcare System, West Haven, CT, USA)*

**Background:** As the aging population grows, so too will the prevalence of sarcopenia and the associated loss of muscle strength, performance, and mass. Methods to predict the presence of low muscle performance, preferably in an objective, quantitative manner without patient input, will correspondingly be increasingly important to start an appropriate treatment regimen at an early stage. Here, we describe a deep learning approach to predicting muscle performance from magnetic resonance images (MRIs) from the study of Muscle, Mobility,

and Aging (SOMMA) (1) and Osteoarthritis Initiative (OAI) (2) databases. **Objectives:** We aimed to investigate whether neural networks trained on anatomic thigh MRIs could predict physical function metrics, such as leg strength, walking speed, and the chair stand test. To test the method's generalizability, we used two different datasets. Once we trained and validated a neural network, we conducted a pilot study to predict physical function metrics from our own MRI data. **Methods:** We analyzed 15 bilateral axial MRI slices of the mid-thigh from each of 3,515 OAI participants and 835 SOMMA participants. Everyone in the datasets with such thigh MRIs was included in the study. Each cohort also collected measures of leg strength, walking speed (20 meters for OAI, 4 m and 400 m for SOMMA), and the chair stand test. We trained a ResNet18 neural network to predict whether each functional metric was above or below the median, using 90% of each dataset for training and 10% for validation. We then tested our trained network on prospectively acquired MRI data from 8 subjects, using self-reported exercise as the physical function label. **Results:** Our neural network was able to accurately classify persons as above or below median leg strength with over 70% accuracy on both SOMMA and OAI datasets. Less predictive power was achieved with other physical metrics, such as walking speed and chair stands. For the 8 prospectively acquired cases, the classification accuracy for self-reported exercise was 63%. **Conclusion:** Our study indicates that deep learning can predict muscle performance from thigh MRIs with over 70% accuracy, potentially allowing objective, quantitative prediction of lowered muscle performance at an early enough stage to start preventative treatment for sarcopenia. **References:** 1. Cummings S, et al. The Journals of Gerontology: Series A. 2023. doi: 10.1093/gerona/glad052. 2. Eckstein F, et al. Nat Rev Rheumatol. 2012 Oct;8(10):622-30. doi: 10.1038/nrrheum.2012.113.

**OC24- MIRNAS COMMONLY EXPRESSED IN BOTH SARCOPENIA AND FRAILTY: A SYSTEMATIC REVIEW.** Hyung Eun Shin[1,2,] Jae Young Jang[2], Heeeun Jung[3], Chang Won Won[4], Miji Kim[5] *((1) Department of Orthopaedics, Emory Musculoskeletal Institute, Emory University School of Medicine, Atlanta, GA, USA; (2) Department of Biomedical Science and Technology, College of Medicine, Kyung Hee University, Seoul, Republic of Korea; (3) KHU–KIST Department of Converging Science and Technology, Graduate School, Kyung Hee University, Seoul, Republic of Korea; (4) Elderly Frailty Research Center, Department of Family Medicine, College of Medicine, Kyung Hee University, Kyung Hee University Medical Center, Seoul, Republic of Korea; (5) Department of Biomedical Science and Technology, College of Medicine, East–West Medical Research Institute, Kyung Hee University, Seoul, Republic of Korea)*

**Background:** Coexistence of sarcopenia and frailty is more strongly associated with adverse health outcomes than each condition. As the importance of coexistent sarcopenia and frailty is emerging, exploring their underlying mechanisms is warranted. Noncoding ribonucleic acids (RNAs) have recently been proposed as potential biomarkers of sarcopenia and frailty. **Objectives:** This systematic review aimed to identify noncoding RNAs commonly expressed in sarcopenia and frailty, and to examine the predicted target genes and biological pathways of them. **Methods:** We systematically searched the literatures on PubMed, Embase, Cochrane Library, Web of Science, and Scopus for literature published till November, 15, 2023. Eligible studies that compared the participants aged over 18 with sarcopenia or frailty with nonsarcopenic or nonfrail participants were included. These studies define sarcopenia as low muscle mass, low muscle strength, or low physical performance as well as the criteria of Asian Working Group for Sarcopenia (AWGS) 2014, AWGS2019, European Working Group on Sarcopenia in Older People (EWGSOP) 1, EWGSOP2, Sarcopenia Definition and Outcome Consortium (SDOC), Foundation for the National Institutes of Health (FNIH), and International Working Group on Sarcopenia (IWGS). In addition, studies that define frailty as the Fried frailty phenotype, Frailty index, Clinical frailty scale, and FRAIL scale were included. A total of 7,202 literatures were initially retrieved. After de-duplication, 34 studies (26 sarcopenia-related and 8 frailty-related) were screened for full-text review, and 15 studies (11 sarcopenia-related and 4 frailty-related) were finally included. **Results:** miR-29a-3p, miR-29b-3p, and miR-328 were identified as commonly expressed in same direction in sarcopenia and frailty. These micro RNAs (miRNAs) regulate transforming growth factor-β (TGF-β) signaling via extracellular matrix (ECM) components and calcineurin/nuclear factor of activated T cells 3 (NFATc3) signaling via sarcoplasmic/endoplasmic reticulum Ca2+ ATPase 2a (SERCA2a), which are involved in regulation of skeletal muscle fibrosis and cardiac hypertrophy, respectively. miR-155-5p, miR-486, and miR-23a-3p were also commonly expressed in sarcopenia and frailty, although in different or conflicting directions. **Conclusion:** Therefore, shared miRNAs exhibiting consistent expression patterns can be potential biomarkers for detection of both sarcopenia and frailty. Further research is needed to validate whether these shared miRNAs are expressed in individuals with sarcopenia and frailty. **Disclosures:** The authors have no conflicts of interest to declare. **References:** 1. Agostini, S., Mancuso, R., Citterio, L.A., Mihali, G.A., Arosio, B., Clerici, M., 2023. Evaluation of serum miRNAs expression in frail and robust subjects undergoing multicomponent exercise protocol (VIVIFRAIL). J Transl Med 21, 67. 2. Agostini, S., Mancuso, R., Costa, A.S., Guerini, F.R., Trecate, F., Miglioli, R., Menna, E., Arosio, B., Clerici, M., 2021. Sarcopenia associates with SNAP-25 SNPs and a miRNAs profile which is modulated by structured rehabilitation treatment. J Transl Med 19, 315. 3. Carini, G., Mingardi, J., Bolzetta, F., Cester, A., Bolner, A., Nordera, G., La Via, L., Ieraci, A., Russo, I., Maggi, S., Calza, S., Popoli, M., Veronese, N., Musazzi, L., Barbon, A., 2022. miRNome Profiling Detects miR-101-3p and miR-142-5p as Putative Blood Biomarkers of Frailty Syndrome. Genes (Basel) 13. 4. Chen, Z., Bemben, M.G., Bemben, D.A., 2019. Bone and

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**OC25- LONG-TERM OBESITY AS A DRIVER OF EARLY EXPRESSION OF BIOLOGICAL AGING SIGNATURES AND REDUCED MUSCLE MASS IN YOUNG ADULTS.** M. Paulina Correa[1], Raquel Burrows[1], Cecilia Albala[1], Felipe Salech[1,2,4], Rodrigo Troncoso[1], Carlos Sepúlveda[1], Daniel Bunout[1], Christian Gonzalez-Billault[1,2,3,4] *((1) Institute of Nutrition and Food Technology, Universidad de Chile, Santiago, Chile; (2) Faculty of Medicine, Universidad de Chile, Santiago, Chile; (3) Faculty of Science, Universidad de Chile, Santiago, Chile; (4) Geroscience Center for Brain Health and Metabolism, Santiago, Chile)*

**Background:** Reduced muscle mass (RMM) can occur in individuals with sedentary lifestyles or obesity, even at a young age. It is unclear whether young people with RMM also exhibit aging signs. We investigate whether obesity since childhood or adolescence causes the expression of cell-molecular aging markers in 30-year-olds, contributing to RMM and muscle aging. **Methods:** Multiple-events case-control study in a Chilean birth cohort. In 174 participants (28.9±0.6y, 49% females). BMI was estimated periodically from birth-adulthood; three trajectories were traced (cubic polynomials): always having a healthy BMI (TG1); obesity starting in adolescence and persisting into adulthood (TG2); obesity starting in early childhood and persisting into adulthood (TG3). At 29y, we measured body fat/muscle mass (DXA); apelin, irisin, myostatin, oncostatin, osteocrin, IGF-1, IGF-2, FGF-21, GDF-15, leptin, IL-2, IL-6, IL-10 (Luminex); hs-CRP (ELISA); telomere length and DNAmAge. **Results:** In the sample, 40% fell into TG3 and 24% into TG2; no sex differences. Mean BMI was 23.1±3.6, 34.3±4.4 and 37.7±6.0 in TG1, TG2 and TG3 (ABC; P<0.001). In males and females, lean mass was significantly reduced in TG2 and TG3 compared to TG1. For males, muscle mass was 66.6%±6.2, 58.9%±5.4, and 58.6%±5.4 in TG1, TG2, and TG3 (ABB; P<0.01). For females, muscle mass was 59.4%±5.7, 50.7%±5.4, and 50.1%±6.5 in TG1, TG2, and TG3 (ABB; P<0.01). TG2 and TG3 had significantly higher IL-2, IL-6, IL-10, and hs-CRP than TG1 (ABB; P<0.01). Additionally, both had significantly higher apelin, myostatin, irisin, oncostatin, and osteocrin than TG1 (ABB; P<0.01). Moreover, TG2 and TG3 had higher FGF21 and leptin than TG1 (ABB; P<0.001). Only participants in TG3 showed significant increase in GDF15 (AAC; P<0.001). Likewise, IGF-1 and IGF2 were lowered in TG2 and TG3 than TG1 (ABB; P<0.001). Telomeres were shorter in TG2 and TG3 than TG1, whereas DNAmAge was significantly above the chronological age in TG2 and TG3, a pattern not found in TG1. **Conclusion:** Persistent obesity since childhood/adolescence in 30-year-olds leads to early expression of aging hallmarks, including epigenetic alterations, telomere attrition, chronic inflammation, impaired intercellular communication, and mitochondrial dysfunction. This phenotype coincides with RMM. Findings might help understand how obesity speeds up aging and sarcopenia onset. **Key words:** Obesity, sarcopenia, skeletal muscle, aging hallmarks, accelerated aging. **Disclosure:** This research was

supported by ANID-Chile (ACT210006, FONDECYT1210283) and Fundación MAPFRE Spain, through competitive research funding schemes. The authors declare no financial, personal, or professional interests that could influence this work or the results presented. **References:** Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. Pediatr Diabetes. 2017 Dec;18(8):895-902. doi: 10.1111/pedi.12505. Correa-Burrows P, Burrows R, Albala C, Court FA, Salech F, Sanhueza G, Gonzalez-Billault C. Multiple events case-control study in a prospective cohort to identify systemic, cellular, and molecular biomarkers of obesity-induced accelerated aging in 30-years-olds: the ObAGE study protocol. BMC Geriatr. 2022 May 2;22(1):387. doi: 10.1186/s12877-022-03032-4. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023 Jan 19;186(2):243-278. doi: 10.1016/j.cell.2022.11.001. Granic A, Suetterlin K, Shavlakadze T, Grounds MD, Sayer AA. Hallmarks of aging in human skeletal muscle and implications for understanding the pathophysiology of sarcopenia in women and men. Clin Sci (Lond). 2023 Nov 29;137(22):1721-1751. doi: 10.1042/CS20230319.

**OC26- MITOCHONDRIAL PROTEIN INTERACTOME AND FUNCTION IN FRAILTY AND SARCOPENIA.** Gavin Pharaoh[1], Nathan Kaiser[2], Anna Bakhtina[2], Jim Bruce[2], David Marcinek[1] *((1) Department of Radiology, University of Washington, Seattle, WA, USA; (2) Department of Genome Sciences, University of Washington, Seattle, WA, USA)*

**Background:** Frailty is a condition characterized by decreased resilience and increased vulnerability to adverse health outcomes and death. Importantly, sex has a major impact on frailty development with females generally experiencing higher frailty than males. Mitochondrial dysfunction is a hallmark of aging and is proposed as a cause of sarcopenia and frailty. **Objectives:** We hypothesized that disruptions in mitochondrial protein-protein interactions impair mitochondrial function and contribute to the development of sarcopenia and frailty. The goal of this study is to identify sex-specific and independent contributions of the mitochondrial protein interactome to the development of frailty and sarcopenia. **Methods:** We measured a clinical frailty index, hindlimb muscle mass, and in vivo hindlimb muscle force in male and female 7- and 27-month-old C57Bl6/J mice from the NIA aging mouse colony (n=10/age and sex). At endpoint, we measured mitochondrial respiration, membrane potential, and the protein-protein interactome in isolated gastrocnemius muscle mitochondria. Machine learning analysis of frailty index data was used to predict biological age. **Results:** Female mice had earlier onset and more severe frailty and a larger decline in muscle mass, while the loss of force was similar between sexes. ADP sensitivity of mitochondrial respiration was reduced in aged muscle mitochondria. We observed significant remodeling of the mitochondrial protein interactome with age, with greater remodeling in the aged females. Both sexes exhibited heterogeneity in the extent of frailty and sarcopenia with a correlation between the loss of muscle mass, force, and contraction speed with increased frailty. Higher age-related change in the mitochondrial protein interactome was correlated with lower muscle mass, lower muscle force, and increased frailty. Older biological age predicted using the frailty index was associated with greater global changes in the mitochondrial protein interactome. **Conclusion:** Old female mice have higher frailty, sarcopenia, and more severe changes in the muscle mitochondrial interactome. Age-related disruptions in the mitochondrial protein interactome are associated with sarcopenia and frailty. **Disclosures:** The authors declare no conflicts of interest.

**OC27- INTRINSIC CAPACITY AND FALLS IN OLDER ADULTS; A 5-YEAR FOLLOW-UP.** Lara Vlietstra[1], Clifford Qualls[2], Bruno Vellas[3], Sandrine Andrieu[4], Eduardo Caldas Costa[5], Debra L. Waters[6,7,8] *((1) School of Physical Education, Sport and Exercise Sciences, University of Otago, Dunedin, New Zealand; (2) Department of Mathematics & Statistics and School of Medicine, University of New Mexico, Albuquerque, NM, USA; (3) IHU HealthAge, Toulouse, France); (4) Department of Epidemiology and Public Health, CHU de Toulouse, UMR 1295 INSERM, University Toulouse III, Toulouse, France; (5) ExCE Research Group, Department of Physical Education, Federal University of Rio Grande do Norte, Natal, RN, Brazil; (6) School of Physiotherapy, University of Otago, Dunedin, New Zealand; (7) Department of Medicine, University of Otago, Dunedin, New Zealand; (8) Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, NM, USA)*

**Background:** Ensuring older individuals receive comprehensive and individualised care is crucial. The World Health Organization (WHO) proposed the use of the Integrated Care for Older People (ICOPE) screening tool to identify older people with declines in intrinsic capacity (IC). IC and the impact on age-related adverse outcomes, such as falls, remain underexplored. **Objectives:** To determine if IC is related to falls, and if people with poor IC have a fall earlier and have subsequently more falls, compared to people with good IC. **Methods:** Data of 401 participants over a 5-year follow-up, from the New Mexico Aging Process Study (NMAPS) were used. Intrinsic capacity was defined at baseline using the screening variables according to the ICOPE, including vision, hearing, mobility (grip strength and gait speed), nutrition (Mini Nutritional Assessment), memory (mini-mental state examination), and psychological health (Geriatric Depression Scale). Falls were assessed using bimonthly falls calendars over a 5-year follow-up period. ICOPE variables were categorized according to validated cut-scores, to create a composite ICOPE score. Poisson regression and Cox proportional hazards models were used to analyse the data. Analyses were adjusted for age. **Results:** Over the 5-year follow-up, 308 (77%) participants (mean age 74.7 (SD 7.02) and 37% male) reported at least one fall. A total of 1254 falls were reported over the 5-year follow-up. All ICOPE screening variables were independently

related to the total number of falls, irrespective of the low prevalence of cognitive impairment (6%), malnourishment (9%) and depression (6%) in the current cohort. Participants with three or four abnormal ICOPE variables had significantly higher incidence rate ratios (IRR) (IRR 0.396 and IRR 0.552, p = 0.000, respectively) for the total number of falls. Therefore, poor intrinsic capacity was defined as 3 or more abnormal ICOPE screening variables. Although not significant, people with poor intrinsic capacity had a fall slightly earlier (hazard ratio 1.06, p = 0.671) compared to people with good intrinsic capacity. Additionally, people with poor intrinsic capacity had significantly more subsequent falls (IRR 1.23, p = 0.000) compared to people with good intrinsic capacity. **Conclusion:** All ICOPE screening variables are independently related to the total number of falls. Furthermore, people with poor intrinsic capacity have significantly more falls, compared to people with good intrinsic capacity. **Disclosures:** The authors declare no competing interests.

**OC28- RELATIONSHIP OF ENDOGENOUS PLASMA CONCENTRATIONS OF B-HYDROXY B-METHYL BUTYRATE (HMB) WITH FRAILTY IN COMMUNITY DWELLING OLDER ADULTS WITH TYPE-2 DIABETES MELLITUS.** Alejandro Álvarez-Bustos[1], Jose A Carnicero[1,2], Ricardo Rueda[3], Suzette L Pereira[4], Angela Santos-Fandila[3], Jose M López-Pedrosa[3], Francisco José García-García[1,5], Leocadio Rodríguez-Mañas[1,6] *((1) Centro de Investigación Biomédica en Red sobre Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain; (2) Fundación de Investigación Biomédica Hospital Universitario de Getafe, Getafe, España; (3) Abbott Nutrition, Granada, Spain; (4) Abbott Nutrition, Columbus, OH, USA; (5) Servicio de Geriatría, Hospital Virgen del Valle, Toledo, Spain; (6) Servicio de Geriatría, Hospital Universitario de Getafe, Getafe, Spain)*

**Background:** Supplementation with β-Hydroxy β-Methyl Butyrate (HMB) appears to be effective in preventing muscle breakdown and increasing myogenesis. However, endogenously produced HMB levels and its association with phenotypic factors have been little studied, especially in in older populations or patients with chronic disease. **Objectives:** The purpose of this study is to explore whether an association exists between HMB levels and frailty status in older adults with Type-2 Diabetes Mellitus (T2DM). **Methods:** Data were taken from the Toledo Study of Healthy Ageing, a community-dwelling aged 65 years cohort. Determination of endogenous HMB concentration in the plasma samples was analyzed by Abbott Nutrition, following the protocol described by A. Santos-Fandila et al. (1). Frailty was assessed at baseline and at 2.99 median years according to the Frailty Phenotype (FP) (2) standardized to our population (3) and the Frailty Trait Scale (FTS) (4). The associations between HMB levels and frailty were assessed using three nested multivariate logistic regressions and segmented by sex. Glucose, HMB and glucose interaction, age and body composition were used as covariables. **Results:** 228 participants (mean age 75.4 years, 52.2% women) were included. HMB levels showed an inverse cross-sectional association with frailty, which was modified when the interaction term HMB*glucose was included, remaining significant only for FTS [OR(95%CI): 0.274 (0.100, 0.750)]. This association seemed to be indeed stronger in men, in whom it remained significant for both FP [OR(95%CI): 0.173 (0.037, 0.813); p-value 0.026] and FTS [OR(95%CI): 0.094 (0.019, 0.470), 0.004] after adjusting for the interaction term, age and body composition. However, there appears to be threshold points for glucose levels, above which the protective effect of HMB is lost: 138.1 and 137.33mg/dl adjusted by gender for the whole sample and 135.15 and 133.35 mg/dl for men, when frailty was assessed using FP or FTS-12 respectively. On the other hand, endogenous HMB levels at baseline was not associated with incident frailty. **Conclusion:** Endogenous HMB levels was found to be inversely associated with frailty in T2DM, and this association was found to be dependent on circulating fasted glucose levels. **References:** 1. Santos-Fandila A, Zafra-Gómez A, Barranco A, Navalón A, Rueda R, Ramírez M. Quantitative determination of β-hydroxymethylbutyrate and leucine in culture media and microdialysates from rat brain by UHPLC-tandem mass spectrometry. Anal Bioanal Chem 2014;406:2863–2872. 2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56. 3. Garcia-Garcia FJ, Gutierrez Avila G, Alfaro-Acha A, Amor Andres MS, De La Torre Lanza MDLA, Escribano Aparicio M V. et al. The prevalence of frailty syndrome in an older population from Spain. the Toledo study for healthy aging. Journal of Nutrition, Health and Aging 2011;15:852–856. 4. García-García FJ, Carcaillon L, Fernandez-Tresguerres J, Alfaro A, Larrion JL, Castillo C et al. A New Operational Definition of Frailty: The Frailty Trait Scale. J Am Med Dir Assoc 2014;15:371. e7-371.e13. **Fundings:** TSHA was funded by grants from the Spanish Ministry of Economy, Industry and Competitiveness, cofinanced by the European Regional Development Funds (RD120001/0043) and the Centro de Investigación Biomédica en Red en Fragilidad y Envejecimiento Saludable (CB16/10/00464). The research leading to these results has received support from a Collaborative Study Agreement (February 2019) grant from Abbott Laboratories S.A. **Statements and declarations:** The authors declare no competing interests. Ricardo Rueda, Suzette L Pereira, Angela Santos-Fandila, Jose M López-Pedrosa are Abbott employees. Leocadio Rodríguez-Mañas have received funds from Abbott Laboratories and Nestlé companies for scientific conferences.

**OC29- INFLUENZA INDUCES SKELETAL MUSCLE CACHEXIA IN AGED MICE.** Andreia N. Cadar[1], Spencer R. Keilich[1], Dominique E. Martin[1], Laura Haynes[1], Jenna M. Bartley[1] *((1) University of Connecticut Center on Aging and Department of Immunology, Farmington, CT, USA)*

**Background:** Declines in immune response pose a great burden on older adults, leaving them susceptible to infectious

diseases, including influenza. Influenza infection in older adults commonly results in hospitalization and catastrophic disability, leading to overall loss of independence. Previous findings demonstrate that flu infection induces muscle degradation and damage that is more severe and prolonged in aged mice. **Objective:** We aim to explore the effects of flu infection on skeletal muscle gene expression and immune cell populations to further understand mechanisms of flu-associated disability in older adults. **Methods:** Young (3-4 mo.) and aged (19-21 mo.) C57BL/6 male mice were infected with a sublethal dose of PR8 influenza. Gastrocnemius muscles were harvested for RNA sequencing, confocal microscopy, flow cytometry and cytokine/chemokine analyses. **Results:** Our findings show differential gene expression changes between young and aged mice, specifically downregulation of muscle regeneration and organization genes and upregulation of proinflammatory cytokine and migratory cell pathways in aged muscle. Pathway analysis showed that many differentially expressed pathways in the aged muscle were related to T cell activation. Confocal microcopy confirmed increased leukocytes (CD45+) and T cells (CD3+) intramuscularly following flu. Further flow cytometric analyses showed that aged mice have increased infiltrating CD8 T cells during infection compared to young mice, while young muscle has increased infiltrating regulatory T cells (Tregs) in compared to their aged counterparts. Young muscle also had significantly increased IL-33 later in infection, while aged mice had no increases. Since Tregs are crucial for muscle repair, these differences suggest that flu induces muscle injury in aged mice that is not sufficiently repaired, likely due to insufficient IL-33 levels and Treg accumulation. **Conclusion:** We observed differential immune cell infiltration into skeletal muscle during flu infection suggesting that dysregulated immune responses with aging directly impact skeletal muscle. This results in altered skeletal muscle homeostasis with prolonged inflammation and degradation. **Disclosures:** The authors declare no conflicts of interest. This work is supported by NIH/NIA R21 AG060389 awarded to LH. JMB and LH are supported by the UConn Claude D. Pepper Older Americans Independence Center (P30AG067988). ANC is supported by a NIAMS/NIH predoctoral fellowship (T32AR079114).

## OC30- ASSOCIATIONS OF MUSCLE COMPOSITION BY MAGNETIC RESONANCE IMAGING WITH STRENGTH, POWER, AND PHYSICAL PERFORMANCE IN OLDER ADULTS IN THE SOMMA STUDY.

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**Background:** Muscle composition measurements derived by magnetic resonance imaging (MRI) consisting of thigh fat-free muscle volume (FFMV), muscle fat infiltration (MFI), and a personalized sex-, height-, weight-, and BMI-invariant muscle volume z-score (MVz) have previously been linked to morbidity, mortality, hand grip strength, and self-reported mobility function (slow walking pace, no stair climbing, more than one fall in the previous year) in the UK Biobank imaging study. The aim of this study was to investigate their association with a wide range of measurements capturing strength, power, and physical performance collected according to gold standard sarcopenia assessment techniques. **Methods:** Women (N=520) and men (N=359) aged ≥70 years from the Study of Muscle, Mobility and Aging were imaged using a rapid MRI-protocol and analyzed for thigh FFMV and MFI using AMRA® Researcher (AMRA Medical, Linköping, Sweden). Data from UK Biobank was used to calculate MVz for each SOMMA participant (1). Sex-specific Spearman correlations were used to assess the association of MRI muscle composition (FFMV, MVz, MFI) with peak leg power (Watts/kg), 400m walk test (m/s), 4m walk test (m/s), 5 chair stands time (s), four square step test time (s), stair climb total time (s), and narrow walk speed (s). **Results:** The participants were mean (SD) 76.4 (5.0) years old with BMI 27.6 (5.6) kg/m2. The strongest correlations were found for MFI and MVz with peak leg power: 0.18/0.39/-0.49 (all $p<0.001$) and 0.27/0.44/-0.47 (all $p<0.001$) for FFMV/MVz/MFI in women and men respectively, and 400m walk test: 0.05 ($p=0.245$)/0.20 ($p<0.001$)/-0.40 ($p<0.001$) and 0.17 ($p=0.002$)/0.33 ($p<0.001$)/-0.40 ($p<0.001$), followed by stair climb total time, 4m walk test, narrow walk speed, 5 chair stands time, and four square step test time. All correlations were significant for MVz and MFI while the correlations of FFMV (that were weaker compared to those with MVz for all tests) were non-significant with 5 chair stands time (in both women and men) and with four square step test time (in men only). **Conclusion:** Correlations of MRI muscle composition with strength and function were similar (or somewhat stronger) in men compared to women. In general, correlations were stronger for muscle volume in the form of a sex-, height-, weight-, and BMI-invariant z-score (MVz, with unit standard deviations) than in absolute volume (FFMV, with unit liters). The strongest correlations for all tests were observed for MFI. **Key words:**

muscle volume z-score, muscle fat infiltration, myosteatosis, magnetic resonance imaging. **Disclosures:** JL, MP, and ODL are employees and shareholders of AMRA Medical AB. **References:** 1. Linge J, et al. J Cachexia Sarcopenia Muscle. 2021 Dec;12(6):1513-1526. doi: 10.1002/jcsm.12834

**OC31- DEVELOPMENT OF A NOVEL CONVERSION TO SYNCHRONIZE CT AND MR PDFF.** Rachel Fenske[1], Jevin Lortie[1], Luke Vander Kooy[1], John Garrett[2,3], Scott Reeder[2], Perry Pickhardt[2], Adam Kuchnia[1] *((1) Department of Nutritional Sciences, University of Wisconsin-Madison, Madison, WI, USA; (2) Department of Radiology, University of Wisconsin-Madison, Madison, WI, USA; (3) Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, USA)*

**Background:** Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have been instrumental in advancing the assessment of body composition, providing valuable insights into wasting disorders such as sarcopenia and cachexia. CT is widely used clinically and thus is more readily available. MR proton-density fat-fraction (PDFF) is considered a non-invasive reference measure of fat infiltration in various tissues, including muscle and fat. However, the lack of harmonization between these two imaging modalities limits routine clinical analysis of prognostic body composition measures. The objective of this study was to evaluate the relationship between CT tissue density and MR PDFF in muscle and adipose tissue. **Methods:** A retrospective analysis was conducted using a cohort of 50 heathy adults who had been referred for CT colonographic screening between February 2013 and June 2014. In addition to non-contrast CT, quantitative chemical shift–encoded MR was performed with an investigational version of a multiecho 3D spoiled gradient-echo acquisition similar to obtain confounder-corrected PDFF maps at various co-registered axial locations including the twelfth thoracic vertebrae (T12), the first lumbar vertebrae (L1), and the third lumbar vertebrae (L3). Paraspinal muscle (T12 and L1) and subcutaneous fat (L3) were analyzed using either regions of interest (ROI), cross sectional area (CSA), or both. Linear regressions were separately fitted for ROI and CSA at the respective locations. **Results:** For paraspinal muscle ROIs assessed at T12, MR PDFF exhibited a strong positive correlation with CT HU ($R2=0.645$, $P<0.0001$, $y=-0.44x+29.59$). At L1, MR PDFF from the paraspinal muscle was highly correlated with CT HU when measured as both ROI ($R2=0.726$, $P<0.0001$, $y=-0.46x+31.41$), and CSA ($R2=0.761$, $P<0.0001$, $y=-0.49x+32.74$). For subcutaneous fat ROIs assessed at L3, MR PDFF exhibited a moderate positive correlation with CT HU ($R2=0.466$, $P<0.0001$, $y=-0.27x+67.09$). **Conclusion:** MR PDFF and CT HU exhibited significant positive correlations for both subcutaneous fat and paraspinal muscle at multiple co-registered axial locations. The strongest association within muscle occurred at L1. These developments suggest that tissue fat percent may be quantifiable with routine CT scans, expanding the clinically relevant measures of body composition that can be exploited from opportunistic imaging. **Key words:** CT, MRI, body composition, PDFF. **Disclosures:** Dr. Pickhardt is an advisor to Nanox, Bracco, and GE Healthcare. Dr. Garrett holds equity in NVIDIA and RadUnity. Dr. Reeder is the founder of Calimetric, LLC, holds stock in Elucent Medidcal Inc, Reveal Pharmaceuticals, Inc, RevOps Health Inc, and HeartVista (where he also performs consulting services). All other authors have no disclosures.

**OC32- INABILITY TO PARTICIPATE IN SPORTS AND RECREATIONAL ACTIVITIES MAY BE DEVASTATINGLY IMPACTED BY THIGH FAT DISTRIBUTION IN KNEE OSTEOARTHRITIS PATIENTS.** Sarah Costa[1], Brad Gardea[1], Siwen Liu[1], Kenneth Tam[2], Eva Szabo[1], Andy Kin On Wong[1] *((1) Department of Medical Imaging, UHN, Toronto, ON, Canada; (2) Biomedical Engineering, University of California Davis, CA, USA)*

**Background:** Our knee osteoarthritis (OA) patient partners assert that inability to participate in sports and recreation maybe more damaging to quality of life than pain alone. There is evidence for physical activity's benefit to mitigate OA progression, but little attention is paid on disease risk factors' impact on ability to participate in sports and recreation. **Objective:** To evaluate how differences in thigh muscle fat distribution predict future sports and recreation participation. Methods: A total of 259 participants (254 right and 259 left thighs) from the 24-month visit (v03) of the Osteoarthritis Initiative were randomly selected among those with available thigh images. T1-weighted turbo spin echo magnetic resonance images (0.977x0.977x5.0mm voxels, 15 contiguous slices) of the thigh were corrected by reducing noise, enhancing edges, and removing blood vessels using snakes and thresholding. The iterative threshold-seeking algorithm (ITSA) was used to separate subcutaneous fat from muscle, and to segment inter- and intramuscular fat (IMF) from within thigh muscles, while accounting for partial voluming effects. A general linear model following a knee-level analysis related the Knee Osteoarthritis Outcomes Score (KOOS) sports and recreation subscale (KOOS-SR) at the 36-month visit (v05) to total IMF percentage in the thigh (v03). The model adjusted for participant ID, age, sex, and BMI. Additional models accounted for knee extension power obtained by dynamometry. **Results:** Among N=513 knees and corresponding thighs (mean age: 62.5(8.2) yrs, BMI: 28.0(5.2)kg/m2, 47.1% Kellgren-Lawrence grade 2+), general linear models showed that 10 units higher IMF% of the thigh was associated with a 6.8(3.0,10.7)% lower KOOS-SR (poorer participation). This effect remained significant after accounting for knee extension power. This shows that the lower participation in sports and recreation may not be due to any differences in the muscles' function but perhaps related to inflammation or other yet undescribed factors. **Conclusion:** Having a higher fat distribution in the thighs may be an important indicator to alert patients who place importance on participation in sports and recreation. The potential impact of losing this critical part of their quality of life may be mitigated

by future interventions examining thigh muscle fat loss even when exercise is ineffectual or infeasible.

**OC33- ASSOCIATION OF HEALTHY LIFESTYLE AND SOCIAL ENVIRONMENT WITH MORTALITY AMONG ADULTS WITH FRAILTY: FINDINGS FROM THE UK BIOBANK.** Junhan Tang[1], Yanan Ma[2], Jie Chen[3], Jirong Yue[4], Chenkai Wu[1] *((1) Duke Kunshan University, Kunshan, China; (2) China Medical University, China; (3) Zhejiang University, China; (4) West China Hospital, China)*

**Background:** Among people living with frailty, adherence to a healthy lifestyle may be a low-cost and effective strategy to decrease frailty-induced health risks across different social environments. **Objectives:** The aim of the present study was threefold. First, we examined whether adherence to a healthy lifestyle, including not smoking, no excessive alcohol consumption, adequate physical activity, and a healthy diet, was associated with a lower all-cause mortality among physically frail persons. Second, we examined the association between lifestyle factors and all-cause mortality by different social environments. Third, we evaluated the joint association of lifestyles and social environment with all-cause mortality. **Methods:** We included 15,594 frail participants at baseline from the UK Biobank study. We used four lifestyle factors to create a composite healthy lifestyle score and seventeen social factors to construct a polysocial score. We classified the lifestyle score into two levels (unhealthy and healthy) and the polysocial score into three levels (low, intermediate, and high). We used Cox regression to determine the association of each lifestyle factor and lifestyle score with all-cause mortality, respectively. We also examined the associations across polysocial score categories. We evaluated the joint association of the lifestyle score and the categorical polysocial score with all-cause mortality. **Results:** During up to 14.41 years of follow-up, we documented 3,098 deaths from all-cause death events. After multivariable adjustment, we found a significant association between not smoking and adequate physical activity with all-cause mortality across polysocial score categories, respectively. We also found a significant association between a healthy diet and all-cause mortality among frail participants living in an intermediate social environment. A healthy lifestyle was associated with a lower all-cause mortality risk across polysocial score categories, especially among those with a low polysocial score. **Conclusion:** Adherence to a healthy lifestyle, particularly not smoking, adequate physical activity, and a healthy diet, may provide a feasible solution to decreasing mortality risk among frail adults across different social environments, especially for those in the socially disadvantaged group. **Disclosures:** None.

**OC34- LONGITUDINAL ASSOCIATIONS BETWEEN FRAILTY AND EPIGENETIC AGE ACCELERATION IN THE HEALTH AND RETIREMENT STUDY.** Benjamin Seligman *(Department of Medicine, David Geffen School of Medicine at UCLA, Geriatric Research, Education, and Clinical Center, VA Greater Los Angeles Health Care System, Los Angeles, CA, USA)*

**Introduction:** Epigenetic age acceleration (eAA) and frailty both provide important tools for assessing aging physiology in older adults. Both measures are associated with adverse health outcomes and death, and are cross-sectionally associated. However, the longitudinal relationship between eAA and frailty is unclear, with prior studies reaching conflicting results over the association between eAA and change in frailty (1, 2). Understanding their association over time will help clarify how molecular changes are related to phenotypes of aging. **Methods:** Data were taken from the Health and Retirement Study (HRS). We first assessed Spearman correlations between 13 measures of eAA from the 2016 wave of HRS and both a frailty index (HRS-FI, 1996-2018) and the Fried Frailty Phenotype (FFP, 2006-18). We then used linear regression with adjustment for age, gender, BMI, and smoking status to assess the relationship between baseline eAA and subsequent change in both frailty measures and change in frailty measures with subsequent eAA. **Results:** Correlations and their time trends varied widely between eAAs and HRS-FI (r2: -0.04–0.23, β: -0.002–0.007) and FFP (r2: -0.08–0.23, β: -0.002–0.013). Two eAAs were associated with change in HRS-FI and none with change in FFP. Change in HRS-FI and FFP were each associated with change in four different eAA measures, though these associations had generally small effect sizes (HRS-FI: 0.0002–0.01, FFP: 0.007–1.24). **Conclusion:** Associations over time between measures of eAA and frailty vary widely and are weak on average. Our findings are most consistent with eAA serving as a marker of exposure to prior frailty, rather than a molecular precursor to aging phenotypes. **Disclosures:** I am a consultant for Ceresti Health. **References:** 1. Verschoor et al. Clin Epigenetics 2021;13(1):1-10. 2. Seligman et al. J Gerontol Ser A. 2022;77(9):1760-1765.

**OC35- MALNUTRITION IN COVID-19 SURVIVORS: PREVALENCE AND RISK FACTORS.** Matteo Tosato, Riccardo Calvani, Francesco Landi *(Università Cattolica del Sacro Cuore Roma, Italy)*

**Background:** Nutritional status is a critical factor throughout COVID-19 disease course. Malnutrition is associated with poor outcomes in hospitalized COVID-19 patients. **Aim:** To assess the prevalence of malnutrition and identify its risk factors in COVID-19 survivors. **Methods:** Study cohort included 1230 COVID-19 survivors aged 18-86 attending a post-COVID-19 outpatient service. Data on clinical parameters, anthropometry, acute COVID-19 symptoms, lifestyle habits were collected through a comprehensive medical assessment. Malnutrition was assessed according to Global Leadership Initiative on Malnutrition (GLIM) criteria. **Results**: The prevalence of malnutrition was 22% at 4-5 months

after acute disease. Participants who were not hospitalized during acute COVID-19 showed a higher rate of malnutrition compared to those who needed hospitalization (26% versus 19%, p<0.01). Malnutrition was diagnosed in 25% COVID-19 survivors over 65 years of age compared to 21% younger participants (p<0.01). After multivariable adjustment, the likelihood of being malnourished increased progressively and independently with advancing age (Odds ratio [OR] 1.02; 95% CI 1.01–1.03) and in male participants (OR 5.56; 95% CI 3.53–8.74). Malnutrition was associated with loss of appetite (OR 2.50; 95% CI 1.73–3.62), and dysgeusia (OR 4.05; 95% CI 2.30–7.21) during acute COVID-19. **Conclusion**: In the present investigation we showed that malnutrition was highly prevalent in a large cohort of COVID-19 survivors at 4-5 months from acute illness. Our findings highlight the need to implement comprehensive nutritional assessment and therapy as an integral part of care for COVID-19 patients. **Disclosures:** No conflict of interest. **References:** 1. James PT, Ali Z, Armitage AE, Bonell A, Cerami C, Drakesmith H, et al (2021). The Role of Nutrition in COVID-19 Susceptibility and Severity of Disease: A Systematic Review. J Nutr 151(7):1854–78. 2. di Filippo L, de Lorenzo R, D'Amico M, Sofia V, Roveri L, Mele R, et al (2021). COVID-19 is associated with clinically significant weight loss and risk of malnutrition, independent of hospitalisation: A post-hoc analysis of a prospective cohort study. Clin Nutr 40(4):2420–6. 3. Alvarez J, Bernal M, Serrano C, LLorente B, Villa P, nevado E (2021). Malnutrition, sarcopenia and disability in critical Covid 19 patients. Clin Nutr ESPEN 46:S764.

## OC36- LOW ADHERENCE TO PHYSICAL ACTIVITY IS ASSOCIATED WITH INCIDENT MOBILITY IN OLDER ADULTS WITH PHYSICAL FRAILTY AND SARCOPENIA: RESULTS FROM THE SPRINTT RANDOMIZED CLINICAL TRIAL.

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**Background:** Physical activity (PA) and nutrition are the most effective strategies to prevent mobility disability and other negative outcomes in older adults. However, considerable heterogeneity was observed in response to PA across interventional studies. This may be explained by different levels of adherence to PA interventions among participants. **Objectives:** To examine the effects of adherence to a PA intervention on the risk of developing mobility disability in older adults with Physical Frailty and Sarcopenia (PF&S). **Methods:** Participants were community-dwelling older adults (70+ years) with PF&S enrolled in the SPRINTT trial (NCT02582138). PF&S was operationalized as having a total score from 3 to 9 at the Short Physical Performance Battery (SPPB), low appendicular lean muscle mass, and the ability to complete the 400 m walk test in <15 minutes. For the present investigation, data from participants allocated to the multicomponent intervention (PA plus nutrition) were analyzed. Adherence to PA was defined based on the number of weekly sessions attended and agreement with recommendations of the American College of Sports Medicine. Adherence was categorized as low (<2 sessions/week, LA), meeting recommendations (2-3 sessions/week, MR), and high recommendations (>3 sessions/week, AR). The primary outcome was incident mobility disability, operationalized as incident inability to complete the 400-m walk test in <15 minutes at follow-up. **Results:** 689 participants (mean age 79.3 years, 72.6% women) were included. In those with SPPB 3-7, MR [OR (95%CI): 0.56 (0.34, 0.93), p-value 0.025] and AR [OR (95%CI): 0.26 (0.16, 0.42), p-value <0.001] groups had lower risk of mobility disability compared to the LA group. In participants with SPPB 8-9, AR group had a significant lower likelihood of mobility disability comparing with the LA group [OR (95%CI): 0.18 (0.06, 0.57), p-value 0.004]. No significant differences were observed between MR and AR groups. **Conclusion:** In older adults with PF&S, a high adherence to PA recommendations is associated with reduced incidence of mobility disability.

## OC37- FRAILTY AND THE RISK, CLINICAL EXPRESSION, AND OUTCOMES OF NEUROLOGICAL DISORDERS.

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The concept of frailty has been triggering growing interest in many medical areas. Nevertheless, it is quite surprising that it has so far attracted relatively limited attention in Neurology. This is particularly puzzling given that many neurological conditions are characterized by marked clinical heterogeneity and complexity. Moreover, their pathophysiology is sustained by aging-related alterations (the hallmarks of aging) that are shared with frailty. However, frailty is emerging as an independent risk factor for the most prevalent brain disorders like Alzheimer's disease, Parkinson's disease, cerebrovascular diseases, and multiple Sclerosis. Moreover, it affects the role played by genetics and lifestyle on the risk of late-life neurological illnesses. Frailty has also been shown to influence the phenotypic expression of neurological diseases and can help stratify the risk profiles among affected individuals. Overall, there is emerging evidence that measuring frailty can improve the scientific understanding and clinical approach to major neurological conditions and that reducing frailty might hold

promise for brain health optimization and the prevention of brain disorders. In parallel, there is an urgent need to gather evidence on how frailty can improve patient care, resource allocation, and health outcomes.

**OC38- THE UTILIZATION OF CONTINUOUS GLUCOSE MONITORING IN GUIDING INSULIN THERAPY IN OLDER ADULTS RESIDING IN LONG-TERM CARE FACILITIES: A RANDOMIZED CLINICAL TRIAL.** Thaer Idrees[1], Iris Castro[1], Hyungseok D. Oh[2], Monica D. Gavaller[2], Zohyra Zabala[1], Emmenlin Moreno[1], Bobak Moazzami[1], Elena Cabb[2], Theodore M Johnson 2nd[3,4,5], Limin Peng[6], Guillermo E. Umpierrez[1] *((1) Division of Endocrinology; (2) Division of Geriatrics; (3) Division of General Internal Medicine, Department of Medicine, Emory University, Atlanta, GA, USA; (4) Department of Family and Preventive Medicine, Emory University, Atlanta, GA, USA; (5) Birmingham/Atlanta VA GRECC, Decatur, GA, USA; (6) Emory University Rollins School of Public Health, Atlanta, GA, USA)*

**Background:** The prevalence of diabetes among older adults is estimated to affect one third of residents in long term care facilities (LTCF) in the US (1-4, 4-7). This population is frequently co-diagnosed with multiple comorbidities and has unpredictable oral intake and functional behaviors. Currently, the standard of care for glucose testing at LTCF is the utilization of point-of-care (POC) capillary glucose testing which frequently misses hypoglycemia events. **Objective:** to evaluate the efficacy of utilizing glucose telemetry system in managing diabetes in long term care facility. **Methods:** we conducted a randomized clinical trial at LTCF to evaluate the efficacy of guiding insulin treatment using continue glucose monitoring (CGM) to reach glycemic control. We recruited 97 participants with type 2 diabetes (T2D) who were divided into a control group wearing blinded CGM, and an intervention group who wore a real time CGM (rt-CGM). The diabetes management was directed by LTCF primary providers using POC testing for the control group and utilizing CGM 24 hrs profile for the intervention group. **Results:** Participants' mean age was 74.7±11 years, and hemoglobin A1c: 8.06±2.2% (65 mmol/mol). The percent time above range (TAR, >180 mg/dL), and below range (TBR, <54 mg/dL) were similar between the intervention and the control group (45.79± 30.74 vs 49.13± 28.11, p=0.55); and (0.23± 0.85 vs. 0.56± 2.24; P= 0.88). However, when the detection of hypo- or hyperglycemia was compared between CGM and POC testing, there were significant greater proportion of subjects with hypoglycemia <70 mg/dL (40.2 vs. 14%) and <54 mg/dL (21 vs. 1.0%); as well as hyperglycemia >250 mg/dL (77% vs. 56%), all p<0.001. **Conclusion:** This RCT indicates that guiding diabetes therapy using real time CGM resulted in a similar glycemic control to standard of care among older adults with T2D in long-term care facilities. CGM technology demonstrated superior ability in detecting hypoglycemia and hyperglycemia compared to POC testing.

**Key words:** Continuous glucose monitoring, nursing home, skilled nursing facility, diabetes mellitus. **Clinical Trial Registry:** NCT04818242. **Disclosures:** This RCT was funded by Dexcom. GEU is partly supported by research grants from National Institutes of Health (NIH/NATS UL 3UL1TR002378-05S2) from the Clinical and Translational Science Award program, and from National Institutes of Health and National Center for Research Resources (NIH/NIDDK 2P30DK111024-06). GEU has received research support (to Emory University) from Dexcom, Abbott, Bayer, Sanofi and Lilly. TI, IC, HDO, MDC, ZZ, EM, BM, PV, EC, TMJ, LP declare no conflict of interest. **References:** 1. Resnick, H.E., et al., Diabetes in U.S. nursing homes, 2004. Diabetes Care, 2008. 31(2): p. 287-8. 2. Newton, C.A., et al., Prevalence, quality of care, and complications in long term care residents with diabetes: a multicenter observational study. J Am Med Dir Assoc, 2013. 14(11): p. 842-6. 3. Dybicz, S.B., et al., Prevalence of diabetes and the burden of comorbid conditions among elderly nursing home residents. Am J Geriatr Pharmacother, 2011. 9(4): p. 212-23. 4. Mooradian, A.D., et al., Diabetes mellitus in elderly nursing home patients. A survey of clinical characteristics and management. J Am Geriatr Soc, 1988. 36(5): p. 391-6. 5. Funnell, M.M. and W.H. Herman, Diabetes care policies and practices in Michigan nursing homes, 1991. Diabetes Care, 1995. 18(6): p. 862-6. 6. Hauner, H., et al., Undiagnosed diabetes mellitus and metabolic control assessed by HbA(1c) among residents of nursing homes. Exp Clin Endocrinol Diabetes, 2001. 109(6): p. 326-9. 7. Travis, S.S., et al., Analyses of nursing home residents with diabetes at admission. J Am Med Dir Assoc, 2004. 5(5): p. 320-7.

**OC39- DECIPHERING THE MULTIFACETED AGING CODE IN OUTBRED MICE: GENDER-BASED INSIGHTS FROM NATURAL AND ACCELERATED AGING.** Yohan Santin[1], Mattia Chiesa[1], Sophie Guyonnet[3,4], Bruno Guiard[5], Bruno Vellas[3,4], Angelo Parini[1,3] *((1) Institute of Metabolic and Cardiovascular Diseases, Toulouse, France; (2) Centro Cardiologico Monzino, Milano, Italy; (3) IHU HealthAge, Toulouse, France; (4) Institute of Aging, Toulouse, France; (5) Center for Integrative Biology, Toulouse, France)*

**Background:** Aging is a major risk factor for declining health and chronic diseases. Importantly, the conventional approach of linking aging solely to chronological age falls short in capturing the intricate aspects of this multidimensional process. This variability in aging experiences highlights the need to delve deeper into the intricate mechanisms related to advancing age. This lies in the notion of biological aging, which encompasses the simultaneous decline of multiple organ systems, progressing gradually and persistently. However, consensus on defining biological age remains elusive, prompting the development of composite scoring systems that integrate a diverse array of health parameters. Furthermore, there is a dearth of well-documented information regarding the divergent aging trajectories between male and female individuals. **Methods:** In this context, we designed a large cross-sectional cohort of outbred Swiss mice (1576 male and female mice) in which spontaneous and voluntary physical

activities were monitored from 6 to 24 months of age under either normal or high fat/high sucrose diet-induced accelerated aging. At different ages (6, 12, 18, and 24 months), multiorgan functional phenotyping has been carried out to identify early signs of organ dysfunction. In addition, a large biological fluids/feces/organs biobank has been generated. **Results:** Comprehensive functional assessment of various organs/systems underlined three populations of mice in all groups and at all ages: low-, intermediate-, and high-performance mice. More interestingly, without a priori Topological Data Analysis further highlighted clusters of mice closely associated with functional status, emphasizing the biological heterogeneity of the aging process. Furthermore, we uncovered unexpected gender disparities in the age-related patterns of multi-organ function decline, with mobility data and accelerated aging-related frailty status alterations displaying particular sensitivity to these sex-based distinctions. **Conclusion:** Overall, these findings underscore the heterogeneity of the aging process and emphasize the paramount significance of incorporating both male and female subjects in preclinical investigations to gather deeper insights into the intricacies of the aging process. Importantly, multi-omics analysis will be performed on biological fluids and key organs to enhance our delineation of biological aging. This analysis will enable us to assess multiple hallmarks of aging and discern biomarkers linked to normal versus accelerated biological aging. **Key words:** INSPIRE mouse cohort, biological aging, gender differences. **Disclosures:** The authors declared no competing interests.

**OC40- MULTI-TRAIT GENOME-WIDE ASSOCIATION STUDY OF MUSCLE MASS AND STRENGTH IN THE UK BIOBANK.** Zijie Zhao[1], Ting Ye[2], Caitlin Latimer[3], Paul Yates[4,5], Paul K. Crane[6], James S. Andrews[7], Qiongshi Lu[1] *((1) Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, WI, USA; (2) Department of Biostatistics, University of Washington, Seattle, WA, USA; (3) Department of Pathology, University of Washington, Seattle, WA, USA; (4) Department of Geriatric Medicine, Austin Health, Heidelberg, Australia; (5) Department of Medicine, University of Melbourne, Melbourne, Australia; (6) Department of Medicine, University of Washington, Seattle, WA, USA; (7) Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA)*

**Background:** Sarcopenia is characterized by age-related progressive declines in skeletal muscle mass and strength. Evidence points to a substantial heritability of sarcopenia, but our understanding of its genetic underpinning remains incomplete, partly due to a lack of sufficiently powered sarcopenia phenotype data in existing genetic cohorts. The UK Biobank includes genetic data on close to 500,000 participants along with measures of hand grip strength (HGS) and appendicular lean mass (ALM) measured by bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA), providing an unprecedented opportunity to identify genetic associations for various components of sarcopenia. **Objective:** We conducted a multi-trait genome-wide association study (GWAS) on hand grip strength (N=408,144), BIA-based ALM (N=408,144), and DXA-based ALM (N=18,182) in the UK Biobank. Methods: We performed GWAS using REGENIE while controlling for sex, age, genotyping array, and genetic ancestry. We also leveraged shared genetic components across multiple muscle mass and strength phenotypes to perform a GWAS on a latent sarcopenia factor underlying all phenotypes. Post-GWAS heritability and genetic correlation analyses were performed to gain insights into the genetic architecture of multiple complex traits. **Results:** We identified 177, 393, and 3 independent genome-wide significant ($p<5e-8$) loci for HGS, ALM-BIA, and ALM-DXA, respectively. Variant rs143384 was identified as a top association for all three traits (p=4.2e-52, 1.3e-105, 1.6e-15). This variant resides in the 5' UTR region of GDF5, an important gene for skeletal and joint development which is also known to associate with osteoarthritis, dysplasia, and knee pain. On the genome level, all three traits showed substantially heritability (12.5%, 26.6%, and 28.4%). We further identified a common sarcopenia factor for these three traits through genomic structural equation modeling. The latent factor showed a larger heritability (33.5%) compared to individual traits with significant enrichment in active genomic regions for skeletal muscle (p=3.2e-13). We also found significant genetic correlations of this latent factor with a variety of health outcomes including atrial fibrillation, cholesterol levels, type-2 diabetes, and stroke. **Conclusion:** Together, our findings suggest substantial shared genetic basis across multiple muscle mass and strength traits and implicate genetic overlap between sarcopenia, skeletal development, and several important health outcomes. **Disclosures:** None.

**OC41- DISTURBANCES IN BRAIN HEALTH AND RELATED AMINO ACID KINETICS IN OLDER ADULTS AT RISK OF FRAILTY, AND THE ROLE OF CHRONIC MORBIDITIES.** Minchae C Kang, Nicolaas EP Deutz, Laura E Ruebush, Mariëlle PKJ Engelen *(Center for Translational Research in Aging & Longevity, Texas A&M University, College Station, TX, USA)*

**Background:** Frailty is associated with lower cognition and well-being. We observed in older adults with mild cognitive impairment and depression specific perturbations in brain-related amino acid kinetics using novel isotope tracers, particularly when chronic morbidities were present. We studied whether prefrailty is characterized by early signs of cognitive impairment and reduced well-being (depression/anxiety) that could be explained by metabolic perturbations of amino acids, and whether presence of age-related diseases further affects these outcomes. **Methods:** We selected 515 older adults (age>50) from the MEDIT database and stratified them into three groups based on presence of prefrailty (frailty phenotype (FP)) and chronic morbidities (Charlson comorbidity index (CCI)); Robust-healthy (n=105/134(m/f), FP=0, CCI=0), prefrail-healthy (n=34/44(m/f), FP:1-2, CCI=0), and prefrail-diseased (93/105(m/f), FP:1-2, CCI≥1). Cognitive assessment: Stroop Color Word Test (SCWT), Trail Making Test (TMT),

and Montreal Cognitive Assessment (MoCA). Depression and anxiety: Hospital Anxiety and Depression Scale (HADS). Amino acid kinetics: stable isotope tracer. Plasma amino acid enrichments: LC-MS/MS to calculate whole-body production (WBP) rates. Statistics: one-way ANOVA on decay curves (covariates sex, age, and lean mass) (metabolic markers), and ANCOVA (covariates age and sex) (cognition/mood). **Results:** We observed worse cognitive functions indicated by higher values for SCWT and TMT in prefrail-healthy and prefrail-diseased as compared to robust-healthy ($p<0.01$). MoCA score was lower in prefrail-healthy than robust-healthy and prefrail-diseased ($p<0.002$). Prefrail-diseased showed elevated self-reported depression and anxiety ($p<0.012$). No changes were found in plasma glycine while leucine, valine, tryptophan, and tyrosine concentrations were lower in prefrail-diseased ($p<0.05$). Lower WBP of glutamine, and tryptophan, and higher WBP of taurine were observed in prefrail-healthy and -diseased ($p<0.002$). WBP of valine, leucine, and tyrosine were lower in prefrail-healthy than robust-healthy ($p<0.05$). Compared with prefrail-healthy, prefrail-diseased had higher WBP of leucine, taurine, and tyrosine ($p<0.001$). We found lower glutamate but higher glycine WBP in prefrail-diseased ($p<0.02$). **Conclusion:** Older adults at risk of frailty are characterized by cognitive impairment and dysregulated metabolism of brain-related amino acids. Prefrailty with chronic diseases is associated with mood disruption, further exacerbation of executive functions, and a specific pattern of some amino acids, indicating that brain health and metabolism are already impaired at the pre-stage of frailty. **Key words:** Cognitive impairment, depression, aging, amin acid metabolism. **Clinical Trail Registry:** NCT01734473, NCT01787682, NCT01624792, NCT01890824, NCT02082418, NCT02157844, NCT02065141, NCT03159390, NCT02566434, NCT02770092, NCT02908425, NCT02780219, NCT02780206, NCT01871350, NCT03327181, NCT03796455, NCT04928872, NCT04461236, NCT04459156. **Disclosures:** None.

## OC42- SKELETAL MUSCLE AND CIRCULATING MICRORNAS ADAPTATION FOLLOWING HIGH-INTENSITY INTERVAL TRAINING WITH OR WITHOUT L-CITRULLINE IN OBESE OLDER ADULTS.

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**Background:** High Interval Intensity Training (HIIT) without or with L-citrulline supplementation (CIT) counteract muscle dysfunction by improving muscle strength and mitochondrial functions in obese older adults. These phenotypic changes might result from the microRNAs (miRNAs)-driven epigenetic regulations. **Objectives:** Investigate the impact of 12 weeks-HIIT on miRNA differential level of expression (DLE) in muscle biopsy and serum of obese older adults; the association of DLEs to clinical and biological adaptations to HIIT and provide potential biomarkers of HIIT adaptations. **Methods:** 68 participants following 12 weeks-HIIT randomized in two groups were supplemented daily with a placebo (HIIT-PLA, n=31) or with CIT (HIIT-CIT, n=37). Phenotypic variables, blood, muscle biopsies outcomes were collected pre- and postintervention. The miRNome of muscle and serum (n=13) and the miRNAs DLEs (n=68) were analyzed pre- and post-intervention by Next Generation Sequencing and TaqMan-real-time qPCR, respectively. **Results:** The level of expression (LE) of muscle-related miRNAs (miR-133a-3p, 133a-5p, -1, -206, -499, -208) was not modified following HIIT with or without CIT. HIIT modulated the LE of muscle-unrelated miRNAs in muscle (miR-504-5p, $p=0.022$) and in serum [miR-151a-3p and miR-4433b-5p ($p=0.001$), miR-483-3p ($p=0.044$), miR-744-5p $p=0.004$)]. HIIT with CIT supplementation induced moderate changes in miRNAs LE versus HIIT alone with only the muscle miR-504-5p downregulation ($p=0.022$). In HIIT-PLA, HIIT-CIT and population subgroups (based on sex, age, BMI, dynapenic status), the significant DLEs of muscle (miR-151a-3p, -106b-5p, -504-5p, -127-5p, -744-5p) and circulating (miR-151a-3p, -4433b-5p, -483-3p, -106b-5p,

-484, -744-5p) miRNAs were associated with clinico-biological parameters changes. The downregulation of muscle miR-151a-3p and circulating miR-483-3p, miR-106b-5p, miR-4433b-5p targeting insulin-like-growth-factor1 signalling improved protein anabolism, lipid and carbohydrate homeostasis. Lower LE of muscle miR-151a-3p, circulating miR-483-3p, miR-4433b-5p and higher serum miR-151a-3p were correlated with significantly lower adiposity parameters (leptin, triglyceride, cholesterol, free-fatty-acid, AT genes, BMI), ferritin, insulin level and sensitivity and to improvement of lean mass (p=0.001), BMI (p=0.05) and of 4m-walking test (p=0.05), for miR-4433b-5p. MiR-744-5p DLE was associated to glycemia (p=0.001) and BMI (p=0.05) improvements. **Conclusion:** Modulation of muscle and serum miRNAs LEs correlated with clinico-biological adaptations following a 12 weeks-HIIT with or without CIT. MiR-151a-3p, miR-483-3p, miR-4433b-5p, miR-744-5p appeared as potential biomarkers of HIIT adaptations.

**OC43- OSTEOSARCOPENIC OBESITY AND OVERLAP SYNDROMES: COMPARISON OF BODY COMPOSITION, BLOOD BIOMARKERS AND 2-YEAR OUTCOMES IN HEALTHY OLDER ADULTS.** WS Lim[1,2], A Yeo[1], CN Tan[1], JP Lim[1,2], JQ Chia[1,2], K Pek[1], N Hafizah[1,3], YY Ding[1,2], J Chew[1,2] *((1) Institute of Geriatrics and Active Ageing, Tan Tock Seng Hospital, Singapore; (2) Department of Geriatric Medicine, Tan Tock Seng Hospital, Singapore; (3) Department of Continuing and Community Care, Tan Tock Seng Hospital, Singapore)*

**Background:** Osteosarcopenic Obesity (OSO) syndrome is characterized by the co-existence of decreased bone density (O)[osteopenia/osteoporosis], muscle mass/strength (S)[sarcopenia] and increased adiposity (O)[obesity]. Although associated with poor physical performance and lower functional ability, controversy exists as to whether OSO constitutes a distinct entity, hampered by the lack of direct comparative studies with overlap syndromes (OO, OS and SO) which comprehensively examine body composition/blood biomarkers and longitudinal outcomes. **Objectives:** We aim to compare body composition, blood biomarkers and predictive ability for 2-year outcomes between OSO with overlap syndromes amongst healthy community-dwelling older adults. **Methods:** Participants (N=230; mean age:67.2±7.4 years; mean FRAIL:0.17±0.42) from GeriLABS-2 cohort study were assessed for three DXA body composition parameters: 1) Skeletal muscle index using AWGS'2019 cutoffs for sarcopenia; 2) Percentage body fat mass for obesity; and 3) Bone mineral densitometry for osteoporosis. They were classified as reference (0-1 present, 46.1%); overlap syndromes (2 present, 41.7%) or OSO (all 3 present, 12.2%). We measured blood biomarkers for insulin resistance (adiponectin/HOMA-IR), metabolism (IGF-1/myostatin), and osteokines (osteocalcin/sclerostin), and assessed 2-year outcomes for level of activities (Frenchay Activities Index; International Physical Activity Questionnaire and Life Space Assessment); muscle function (Short Physical Performance Battery; handgrip and knee-extension strength); and quality of life (EQ5D-5L). We performed regression analysis to compare the impact of OSO versus overlap syndromes on 2-year outcomes. **Results:** OSO had the lowest bone density and skeletal muscle index(P<0.001), and highest visceral adipose tissue (P<0.05), whereas overlap syndromes and OSO had higher percentage fat mass (P =.001). Compared with reference and overlap groups, OSO had significantly lower adiponectin (1.16±0.19 vs 1.29±0.14 vs 0.97±0.12, P<0.001), higher HOMA-IR (1.76±0.57 vs 1.74±0.36 vs 2.69±0.36, P<0.001), and lower sclerostin (2.63±0.56 vs 2.49±0.53 vs 2.06±0.59, P<0.001). In regression analysis for 2-year outcomes, both overlap (OR=10.13; 95%CI,1.90-54.04) and OSO (OR=16.30; 95%CI,2.14-124.06) predicted weak knee-extension, and only OSO (OR=4.12; 95%CI,1.11-15.22) predicted weak handgrip, with no difference for other outcomes. **Conclusion:** Our study provides proof-of-concept evidence that demonstrates distinct differences in body composition), insulin resistance, and increased 2-year risk of weaker muscle strength for OSO vis-à-vis overlap syndromes, highlighting the need to integrate the muscle-fat-bone interface when considering the implications of body composition in clinical practice.

**OC45- ASSESSING HAND GRIP STRENGTH VIA A NOVEL BLUETOOTH CONNECTED DEVICE AND APP AMONG OUTPATIENTS ASSISTS HEALTHCARE PROVIDERS IN IMPROVING NUTRITION CARE.** Kartik Varadarajan[1], Amy R. Sharn[2], Ganesh Kadhe[2], Irfan Shaikh[2], Suela Sulo[2], Supratik Bhattacharyya[3,4] *((1) SQUEGGTM: Smart Hand Grip Trainer, Pembroke Pines, FL, USA; (2) Abbott Nutrition, Medical Affairs and Research, Columbus, OH, USA; (3) SKN Diabetes & Endocrine Centre, Kolkata, India; (4) Apollo Sugar, Kolkata, India)*

**Background:** Hand grip strength is a key assessment of functional status and an important malnutrition criterion. Low hand grip strength (weakness) is associated with worsening activities of daily living and quality of life, decreased mobility, increased falls, and poor cognitive functioning. An innovative hand dynamometer previously validated against the Jamar dynamometer, SQUEGGTM: Smart Hand Grip Trainer (SQUEGGTM) and app, Muscle Strength Assessment Tool (MSAT), were designed to make hand grip strength assessment more accessible. **Objectives:** The study aimed to measure hand grip strength via SQUEGGTM device and MSAT, among patients receiving care in outpatient clinics within India. Healthcare professionals' (HCP) insights on utilizing the novel tools were also assessed. **Methods:** This retrospective study utilized patient data collected via SQUEGGTM and MSAT and HCP insights via short digital questionnaire. The combined SQUEGGTM and MSAT assessment can be completed in ~2 minutes. HCPs provided insights about their use of these tools, and how it impacted their clinical and nutrition decision making. The survey used either a yes/no or a 5-point Likert scale, with higher scores reporting higher levels of satisfaction/agreement. **Results:** A total of 3,393 patients were included in analyses, of which 51% were female with a mean age of 44

± 15 years. 37% of outpatients experienced handgrip strength limitations and 50% reported average hand grip strength. A total of 293/353 (83%) HCPs completed the questionnaire; top specialties included: 32% dietitian; 30% physician; 26% diabetologist. HCPs reported that SQUEGGTM and MSAT helped identify problems with hand grip strength in their patients, most commonly among aging (60%), diabetes (57%), general illness (46%), and post-hospitalization (36%) patients. 98% of HCPs recommended an oral nutrition supplement to improve patient nutrition following confirmation of handgrip strength limitations. **Conclusion:** A third of outpatients in India experience handgrip strength limitations among those sampled. SQUEGGTM and MSAT helped HCPs to identify problems with hand grip strength among patients and inform nutrition interventions to impact nutrition status. These findings highlight the importance of implementing nutrition-focused programs among outpatients receiving care post-hospitalization and/or for acute or chronic disease management to alleviate the burden of hand grip strength limitations and improve outcomes. **Key words:** functional status, hand grip strength, nutrition. **Disclosures:** ARS, SS, GK, and IS are Abbott employees. This study was financially supported by Abbott.

## OC46- A MACHINE LEARNING ALGORITHM TO RETROSPECTIVELY TRACK DAILY MEALS IN ELDERLY FRAIL INDIVIDUALS WEARING CONTINUOUS GLUCOSE MONITORING DEVICE.

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**Background:** In elderly frail individuals, an accurate and detailed dietary assessment is crucial to control and prevent the well-known risk of malnutrition. Traditional handwritten food diaries are error-prone and time-consuming, for both investigators and study participants. On the contrary, the continuous datastream passively collected from digital health technologies, such as continuous glucose monitoring (CGM) devices, in combination with machine learning (ML) algorithms, could enable the objective tracking of daily meals. **Objectives:** To develop a ML algorithm to retrospectively identify meal intakes in elderly frail individuals from CGM timeseries. **Methods:** In the Geriatric Anorexia Study (NCT04858932), 50 healthy, community-dwelling individuals (26 females, 29 frail or pre-frail, mean±SD age: 72.26±5.02 years, BMI: 24.96±3.33 kg/m2) were monitored for 2-weeks in free-living conditions with several digital devices, including a CGM and a digital food scale to record the mealtime of pre-packaged meals. CGM timeseries were partitioned in consecutive 45-min windows, labelled as 0/1 based on absence/presence of meals recorded in that window. For each window, 46 features were extracted from CGM data collected in previous and following windows, and participants' demographics. To address class imbalance, random undersampling was applied to training data (70% of subjects) and used to train 3 ML classifiers: Random Forest, LASSO, and Support Vector Machine (SVM). Model selection and feature elimination were performed in 5-fold cross validation (CV), and the resulting models were tested using the remaining 30% of subjects. **Results:** 1015 meals across 337 total days were available for analysis. In CV, the SVM with gaussian kernel showed the highest area under receiver operating characteristic curve (AUROC: 0.885±0.017). On the test set, the model showed accuracy of 0.785 and F1-score of 0.643. **Conclusion:** These preliminary results support the use of CGM, combined with ML, to objectively track meal intakes in elderly frail participants, thus reducing the burden and incompliance of traditional food logs, and in turn supporting the assessment of recommended diet protocols. Further assessment should be performed on an independent dataset. **Key words:** Digital Health Technologies, Continuous Glucose Monitoring, Machine Learning, Malnutrition, Meal tracking. **Disclosures:** The authors declare no competing interests. NC, DJP, FIK, SK, HZ, AM, MS, CD, DC are employees at Pfizer, Inc.

## OC47- ANTISENSE OLIGONUCLEOTIDE TARGETING MIR-128-3P ATTENUATES AGING-ASSOCIATED DECLINE IN MUSCLE FUNCTION AND ENDURANCE EXERCISE CAPACITY.

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**Background:** Sarcopenia is the progressive loss of muscle mass and function during aging. While this decline is associated with increased falls, obesity, and impaired recovery from illness, lifestyle changes (resistance exercise and dietary management) are the only available treatments. We have demonstrated that the microRNA miR-128-3p is a master metabolic regulator that, when suppressed, improves cardiac and skeletal muscle function in animal models of Duchenne muscular dystrophy as well as all pathological hallmarks of heart failure in myocardial infarction models. Importantly, the human miR-128-3p genetic loci are linked to poor lung function and weak grip strength in the UKBiobank. We hypothesized that therapeutic targeting of miR-128-3p might attenuate aging-related sarcopenia and frailty, and we then evaluated our state-of-the-art locked nucleic acid antisense oligonucleotide (LNA ASO) targeting miR-128-3p in an aging-related sarcopenia mouse model to test this hypothesis. **Methods:** Aged (86-week-old; n=15/group) C57BL/6J mice and young (9-week-old; n=10/group) controls were treated once-weekly with anti-miR-128 (or scramble control) LNA ASO (10 mg/kg) by subcutaneous injection. Skeletal muscle function was measured by the twolimb wire hanging test at 5, 9, and 15 weeks of treatment. Capacity for endurance exercise was measured by treadmill running until exhaustion at thirteen weeks of treatment. After twenty weeks of treatment, mice were sacrificed and tissues harvested for analysis. **Results:**

Aged mice treated with anti-miR-128 LNA ASO ran an average of 207 meters further compared with control treated animals (58% improvement; P=0.0207). Anti-miR-128 treatment increased wire hanging time by an average of 7 seconds (62 % improvement; P=0.0627), 5 seconds (48 % improvement; P=0.0615), and 6 seconds (66% improvement; P=0.0286) at 5, 9, and 15 weeks of treatment, respectively. miR-128-3p expression was robustly knocked down in the GA muscle as measured by RT-qPCR at harvest. Gene set enrichment analysis of bulk RNA sequencing from the GA revealed upregulation of oxidative phosphorylation and downregulation of inflammatory pathways. **Conclusion:** miR-128-3p LNA ASO treatment improves skeletal muscle function and endurance exercise capacity in aged mice. Preliminary data suggests this may be through improving mitochondrial oxidative function. Further analysis is needed to fully elucidate the mechanism of action. **Key words:** antisense, mitochondria, exercise tolerance, microRNA. **Disclosures:** Anders Näär is CEO of Elenae Therapeutics, Lei Xu is COO of Elenae Therapeutics.

## OC48- MUSCLE MYOSTATIN AND MITOCHONDRIAL DYSFUNCTION IN HEMIPARETIC STROKE: A RANDOMIZED CLINICAL TRIAL OF RESISTIVE EXERCISE AND PROTEIN SUPPLEMENTATION.

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**Background:** High-intensity resistive training (RT) is an effective rehabilitation strategy for stroke survivors at high risk for sarcopenia. It is unknown whether inadequacies in protein intake limit skeletal muscle growth with RT in stroke survivors or its effect on myostatin, a key negative regulator of skeletal muscle hypertrophy. **Objective:** To test the effects of 12 weeks 3x/week lower-body RT+placebo and RT+protein supplementation (RT+PRO, 1.2 g/kg/day) on strength, body composition, VO2peak, function, muscle myostatin, and mitochondrial substrate metabolism. **Methods:** Randomized controlled clinical trial in 53 older adults with chronic stroke who underwent one-repetition maximum (1-RM) tests, DXA scans, fitness and function tests, and bilateral muscle biopsies. **Results:** Forty-five older adults completed (n=23 RT+placebo, n=22 RT+PRO). There were no significant between group changes in body weight, muscle mass, VO2peak, 6-minute walk distance or gait speed. Paretic 1-RM strength is between 43% and 71% lower than non-paretic strength for the leg press and leg extension with 30-50% gains after exercise in non-paretic and paretic 1-RM leg press and leg extension strength. Muscle myostatin mRNA is higher in paretic vs. non-paretic muscle at baseline (P=0.00007) and after training (P=0.009). Reductions in myostatin are not different between groups and decreased in the total sample (P=0.00004). In RT+PRO, myostatin mRNA expression decreased in paretic leg (242.8±33.1 vs. 77.4±15.2 AU, P=0.003) and non-paretic muscle (152.6±38.8 vs. 79.3±13.5 AU, P=0.09). In the RT+placebo, myostatin expression decreased in the paretic limb (227.5±37.0 vs. 96.4±22.8 AU, P=0.007) and non-paretic limb (110.3±23.8 vs. 65.6±13.2 AU, P=0.05). Results from western blotting for protein levels of SIRT3, cytochrome c oxidase subunit II (COXII), dynamin-related protein1 (DRP1), and optic atrophy protein (OPA1) indicate 37% less OPA1 compared to DRP1 in both the paretic and non-paretic muscle at baseline and 44% less OPA1 compared to DRP1 in paretic muscle post exercise. There was no change in OPA1 levels (36% less) compared to DRP1 in non-paretic muscle post RT. **Conclusion:** Reductions in skeletal muscle myostatin and changes in mitochondrial fission occur with RT suggesting that skeletal muscle can be modified by exercise in conditions of sarcopenia due to chronic stroke. **Key words:** Skeletal muscle, resistive training, myostatin, mitochondria, aging. **Clinical Trials Registry:** NCT02347995. **Disclosures:** none. **References:** Ryan AS, Ivey FM, Serra MC, Hartstein J, Hafer-Macko CE. Sarcopenia and physical function in middle-aged and older stroke survivors. Archives of Physical Medicine and Rehabilitation, 2017; 98(3):495-499. PMID: 27530769.

## OC49- A NOVEL DRUG COMBINATION WITH THERAPEUTIC POTENTIAL FOR SARCOPENIA.

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**Background:** Aging involves the erosion of core resilience mechanisms that leads to the deterioration of cellular functions and pathology. Sarcopenia, an age-related progressive loss of muscle mass and strength, reduces mobility, diminishes quality of life, and increases risk of falls and morbidity. **Objectives:** Given that no or limited effective treatments exist for several age-related disorders, Rejuvenate Biomed aims to identify novel safe combination drugs that prevent or delay the onset of age-related diseases (first indication, sarcopenia) and promote healthy aging. **Methods:** To identify novel safe drug combinations, Rejuvenate Biomed employs two working platforms: an in-silico discovery arm (CombinAgeTM) and a C. elegans screening/validation arm (CelegAgeTM). Drug combinations successfully validated in C. elegans are further tested for efficacy in mouse models, before undergoing clinical trial investigations. RJx-01 (metformin + galantamine), was tested in a Phase 1b randomized, double-blind, placebo-controlled study with 42 healthy males aged 65 to 75 placed in a full-length cast of the dominant lower extremity for 2 weeks to induce disuse atrophy. 21 participants received RJx-01 and 21 received a placebo during the two weeks of casting and four weeks post-cast removal. In addition to safety, tolerability, and PK, the study determined muscle mass and strength using a collection of clinical endpoints, as well as systemic and muscular biomarkers relevant to the molecular mechanisms of sarcopenia. **Results:** Using the aforementioned in-house platforms, Rejuvenate Biomed identified RJx-01 as a potential

therapeutic for sarcopenia. Studies in worms revealed that RJx-01 improved lifespan, and locomotion, while in mouse, the drug improved physical performance, muscle strength, skeletal muscle ultrastructure, mitochondrial morphology, autophagy, lysosomal function, and satellite cell content (1). Phase 1b clinical trial results indicate that RJx-01 is safe and well tolerated; no severe or serious adverse events were reported. The RJx-01 proprietary formulation also exhibited high bioavailability. Results evaluating the impact of RJx-01 on exploratory pharmacodynamic parameters are currently under analysis. **Conclusion:** Preclinical studies indicate synergistic beneficial effects of RJx-01 in the treatment of sarcopenia-related phenotypes. Combined with the promising results of the Phase 1b study, Rejuvenate Biomed is preparing a Phase 2 clinical study with RJx-01 for treating chronic sarcopenia. **Disclosures:** EM, JF and SH are employees of Rejuvenate Biomed, and AB is CEO of Rejuvenate Biomed. All other authors declare that there is no conflict of interest. **References:** 1. Tezze C, et al. JCI Insight 2023; 8(15):e168787. https://doi.org/10.1172/jci.insight.168787.

## OC50- BASELINE ASSOCIATIONS BETWEEN APPENDICULAR LEAN MASS AND MUSCLE STRENGTH, POWER AND PHYSICAL PERFORMANCE IN OLDER ADULTS IN THE WHEY PROTEIN AND ALKALI SUPPLEMENTATION TRIAL.

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**Background:** To examine the baseline associations between appendicular lean mass (ALM), muscle strength, and physical performance in healthy underactive older adults enrolled in the Whey Protein and Alkali Supplementation Trial (NCT04048616). **Methods:** Dual energy x-ray absorptiometry-derived ALM adjusted for height squared (ht2), double leg press (DLP) power at 40% and 70% of the one-repetition maximum (1RM), knee extension torque at 240°/s, grip strength, 6-meter gait speed, 5-chair sit-to-stand (STS) time, and one-leg balance (categorized as completers [stand on one leg for 30s] or noncompleters) were measured at baseline. Associations between ALM/ht2 and muscle strength and performance measures were examined by Pearson correlation coefficients or T-test. **Results:** Data were analyzed for 137 randomized participants (71 males, 66 females) with baseline data. Mean±SD age was 74±6 yrs and 81% were White. Using the Sarcopenia Definitions and Outcomes Consortium criteria,1 56% of men and 47% of women met current cutoffs for sarcopenia based on either low grip strength or slow gait speed. ALM/ht2 was positively correlated with DLP 1RM force (R=0.641, p<0.001), DLP peak power at 40% and 70% of the 1RM (R=0.433 and 0.455 respectively, p<0.001), knee extension peak torque (R=0.421, p<0.001), and maximum grip strength (R=0.586, p<0.001). ALM/ht2 was not significantly correlated with STS time (R=0.011, p=0.90) or gait speed (R= -0.024, p=0.78), and the mean ALM/ht2 did not differ significantly by balance group (0.19±0.21kg/m2, p=0.36). Participants who completed the balance test had a significantly faster gait speed (1.05±0.02s) compared to those unable to complete the test (0.95±0.02s; p<0.001). STS time was inversely correlated to gait speed (R=-0.238, p=0.01) and grip strength was positively correlated to lower extremity strength (DLP 1RM) (R=0.650, p<0.001). **Conclusion:** In this trial population of older adults, higher ALM/ht2 was strongly associated with greater muscle strength and power, but not with balance or tests that include a balance component, such as gait speed and STS time. These data suggest that the ALM/ht2, an indirect measure of muscle mass, is a better determinant of muscle strength than of physical performance measures that involve balance and coordination. **Key words:** muscle strength, physical performance, lean body mass, aging. **Disclosures:** None. **References:** 1. Bhasin S, Travison TG, Manini TM, et al. Sarcopenia Definition: The Position Statements of the Sarcopenia Definition and Outcomes Consortium. J Am Geriatr Soc 2020;68:1410-8.

## OC51- BLOOD PRESSURE VARIABILITY AND FRAILTY IN PEOPLE LIVING WITH END-STAGE KIDNEY DISEASE.

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**Background:** Cardiovascular disease and frailty represent two major clinical concerns for people living with end-stage kidney disease (ESKD). Blood pressure variability (BPV) is often regarded as a predictor of cardiovascular adverse events and all-cause mortality in the context of ESKD, and as an overall marker of aging in geriatric populations. Nevertheless, the relationship between BPV and geriatric syndromes, such as frailty, in people living with ESKD is not well understood. **Objective:** To examine the association between very short-term (beat-to-beat) BPV and frailty in people living with ESKD and receiving hemodialysis. **Methods:** Sixty-nine people receiving hemodialysis (median age=62.0 years, interquartile range [IQR]=19.0; 52.2% male; median dialysis vintage=1.1 years, IQR=2.4) took part in this cross-sectional study. Systolic and diastolic BPV were recorded for 10 consecutive minutes in resting conditions in the supine position on a non-dialysis day using continuous, non-invasive blood pressure monitoring (Task Force Monitor). The normalized low and high frequency components of BPV (LFnu-BPV and HFnu-BPV), the very

low, low, and high frequency components of BPV (VLF-BPV, LF-BPV, and HF-BPV), as well as the power spectral density (PSD-BPV) and low frequency/high frequency ratio of BPV (LF/HF-BPV) were taken for the analysis. Frailty was evaluated through the Fried frailty phenotype. **Results:** Twenty-six (37.7%) and 43 (62.3%) participants were classified as frail and non-frail, respectively. Frail participants had higher median systolic (2.1, IQR=5.2 mmHg2 vs. 1.1, IQR=1.6 mmHg2, p=0.002) and diastolic HF-BPV (0.9, IQR=2.3 mmHg2 vs. 0.5, IQR=1.0 mmHg2, p=0.048) compared to their non-frail counterparts. In addition, frail participants had higher median systolic VLF-BPV (3.2, IQR=12.5 mmHg2 vs. 2.0, IQR=2.4 mmHg2, p=0.012), LF-BPV (2.0, IQR=3.8 mmHg2 vs. 1.1, IQR=2.0 mmHg2, p=0.016), and PSD-BPV (6.6, IQR=27.6 mmHg2 vs. 4.5, IQR=5.9 mmHg2, p=0.005) compared to the non-frail. In age- and sex-adjusted logistic regression analyses, only systolic VLF-BPV (odds ratio [OR]=1.13, 95% confidence interval [CI]:1.01-1.26, p=0.035), HF-BPV (OR=1.26, 95%CI:1.01-1.57, p=0.044), and PSD-BPV (OR=1.06, 95%CI:1.01-1.12, p=0.029) were associated with increased odds of being frail. **Conclusion:** Higher systolic BPV is associated with frailty in people receiving hemodialysis. Beat-to-beat assessments of BPV through continuous, non-invasive blood pressure monitoring may be useful in evaluating frailty in ESKD populations. **Key words:** Frailty, cardiovascular diseases, end-stage kidney disease, blood pressure. **Disclosures:** The authors declared no competing interests.

**OC52- EXERCISE TRAINING PROMOTES A MITOCHONDRIAL "HEALTHY AGING" SIGNATURE IN SKELETAL MUSCLE.** Esther Garcia-Dominguez[1], Julio Domenech-Fernandez[2], Cristina Garcia-Dominguez[1], Cristina Blasco-Lafarga[3], Maria Concepcion Jimenez-Gomez[4], Enrique Calvo[4], Jose Luis Cabrera-Alarcon[4], Antonio L. Serrano[5], Pura Muñoz-Canoves[5], Juan Gambini[1], Gloria Olaso-Gonzalez[1], Jose Antonio Enriquez[4], Mari Carmen Gomez-Cabrera[1] *((1) Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia, Fundación Investigación Hospital Clínico Universitario/ INCLIVA, Valencia, Spain. CIBERFES ISCIII, Madrid, Spain; (2) Department of Orthopedic Surgery, Hospital Arnau de Vilanova, Valencia, Spain; (3) Physical Education and Sports Department, University of Valencia, Valencia, Spain; (4) Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain. CIBERFES ISCIII, 28029 Madrid, Spain; (5) Altos Labs, San Diego Institute of Science, San Diego, CA, USA)*

**Background:** In the 21st century, a new type of patient has become progressively frequent. This modern patient currently consumes around 75% of health systems resources and is characterized by being old (>75 years), having high comorbidity rates, and high risk of functional decline. The decrease in skeletal muscle mitochondrial oxidative capacity with age adversely affects physical function. However, the factors that are associated with this decrease have not been well characterized. **Objectives:** To establish a mitochondrial "healthy aging" skeletal muscle signature in a human cohort and to test the role of exercise training in the promotion of this signature in old frail mice. **Methods:** A mixed-gender cohort of individuals who were either young (n=8), older adults with good physical function (n=11) (OAGF), or older adults physically impaired (n = 11) (OAPI) was characterized and muscle biopsies were obtained. In the animal study, a mixed-gender cohort of C57Bl/6J 23-month-old mice was trained for 10 weeks and compared to age-matched G6PD-Tg mice, a model of robustness. **Results:** We found signs of muscle atrophy and a significant decrease in the skeletal muscle mitochondrial content in the OAPI group that was absent in the age-matched OAGF one. These results harmonized with mitochondrial respiration analysis that was performed using substrates that supply electrons to complexes I, II, and IV. To better understand which proteins were associated with the maintenance of skeletal muscle function we performed a proteomic analysis in skeletal muscle extracts enriched in mitochondria and found downregulated ETC and OXPHOS subunits and those involved in the biosynthesis of the coenzyme Q, in the OAPI group. These proteins remained upregulated in elderly individuals which preserved their physical function. We found that mitochondrial alterations in skeletal muscle proteins associated with aging could be reversed through an exercise training protocol in old wild-type mice. As a model of "healthy aging", we used the G6PD-Tg animals, previously characterized robust mice in our research group. **Conclusion:** The maintenance of the functional status is nowadays the cornerstone of geriatric medicine and gerontology research. We have found that exercise training promotes a mitochondrial "healthy aging" signature in skeletal muscle with implications for frailty.

**OC53- FRAILTY RESILIENCE IS STRONGLY ASSOCIATED WITH NOVEL PACE-OF-AGING AND SYSTEM-SPECIFIC EPIGENETIC CLOCKS.** Jenel Fraij Armstrong[1], Sanish Sathyan[2], Joe Verghese[2,3], Albert T. Higgins-Chen[4,5], Sofiya Milman[3,6] *((1) Program in Computational Biology & Bioinformatics, Yale University, New Haven, CT, USA; (2) Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, USA; (3) Department of Medicine, Institute for Aging Research, Albert Einstein College of Medicine, Bronx, New York, USA; (4) Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; (5) Department of Pathology, Yale School of Medicine, New Haven, CT, USA; (6) Department of Genetics, Albert Einstein College of Medicine, Bronx, New York, USA)*

**Background:** Epigenetic clocks are commonly used aging biomarkers based on DNA methylation. Previous research has found that epigenetic clocks can predict age-related health outcomes, including frailty. Recently, the Frailty Resilience Score (FRS) was developed to quantify resistance to frailty in the presence of factors known to elevate frailty risk. FRS is calculated as the difference between observed frailty index (FI) and expected FI based on age, sex, and frailty

polygenic risk score (PRS). FRS has proved to be a reliable predictor of mortality, however, no studies have examined the associations between epigenetic clocks, including our novel Systems Age epigenetic clocks that quantify aging in various physiological systems, and FRS. **Objectives:** To determine whether existing and novel epigenetic clocks are associated with the Frailty Resilience Score. **Methods:** We used data from two longitudinal studies: the Health and Retirement Study (HRS; n = 1,662; Age 50+) and LonGenity (n = 307; Age 65-94). HRS contains a representative sample of Americans, while LonGenity subjects are Ashkenazi Jews, with about half having a parent who lived to 95+. Methylation was measured at two timepoints in LonGenity, and once in HRS. A modified version of FRS that omits frailty PRS was used in HRS. We calculated PCHorvath1, PCHannum, PCPhenoAge, PCGrimAge, DunedinPACE, and Systems Age scores. We used linear models to quantify the associations of each epigenetic clock with the FI and FRS scores, adjusting for age and sex. Correlations of clock scores with FI and FRS were also recorded. **Results:** All epigenetic clocks examined and the majority of Systems Age scores have significant associations with FRS and FI in both HRS and LonGenity. DunedinPACE, a novel DNA methylation biomarker of the pace of aging, showed the most significant association and the strongest correlation with FRS in LonGenity. The combined Systems Age score showed the most significant association and the strongest correlation with FRS in HRS driven mostly by the Heart system score, but also by the Musculoskeletal, Metabolic, and Inflammation scores. **Conclusion:** FRS is a novel measure of frailty resilience and there are significant associations between FRS and existing epigenetic clocks, especially the novel DunedinPACE and SystemsAge clocks.

## OC54- WOMEN AND MEN WITH INCREASED BMI AND LOW MUSCLE MASS DETERMINED BY D3-CREATINE DILUTION HAVE SLOWER GAIT SPEED AND WEAKER GRIP STRENGTH.

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**Background:** Previous studies of the sarcopenic obesity phenotype in older adults have indicated a prevalence under 10%, and an association with functional limitations, cardiovascular disease diagnoses, mortality, and arthritis. **Objectives:** We determined the association of sarcopenic obesity with physical performance. **Methods:** In a sample of 200 older men and women mean age 74±7 yrs (56% female) from the Framingham Offspring cohort, we measured total muscle mass using D3-creatine dilution, and divided the sample at the obesity cut point (>=30 vs <30 < kg/m2) and at the median for total muscle mass (21.2±7 kg) to create four categories (non-obese BMI/ low muscle mass; non-obese BMI/ high muscle mass; obese/low muscle mass; obese/high muscle mass. The obese/low muscle mass group was designated as "sarcopenic obese." We measured gait speed (m/sec) as an average of two walk trials of 4 meters at usual pace, and measured grip strength (JAMAR dynamometer) as the best of three attempts per hand. We used sex-specific multiple linear regression, adjusting for age, and height, to determine associations between sarcopenic obesity and both gait speed and grip strength. **Results:** Gait speed in the sarcopenic obese group of women (0.91 ± 09 m/sec), tended to be slower than in women not in the sarcopenic obese (1.02 – 1.21 m/sec), (p=0.0003). Similarly, in the sarcopenic obese men, the gait speed of 0.95 ± 0.21 was slower than men not in this group (1.02 – 1.21 m/sec), (p=0.03). Using sex-specific multiple linear regression, adjusting for age, and height, gait speed in the sarcopenic obese women was 0.12 m/sec slower than the other groups combined (p=0.064). Although the sarcopenic obese women and men had the lowest adjusted grip strength (20.6 kg ±1.4 (SE) and 33.5 ± 2.2 respectively), differences were not significantly different between groups. Compared with obese/high muscle mass men, low muscle mass men had lower adjusted grip strength regardless of obesity status (5.1 kg less in sarcopenic obese and 4.8 kg less in non-obese/low muscle mass). In women there were no differences in adjusted grip strength. **Conclusion:** Older adults who have obesity in the face of low muscle mass walk slower because the amount of muscle to transport the higher body weight is limited. Grip strength is lower in older men with low muscle mass regardless of obesity status, as grip strength does not depend on being able to move the weight of the entire body. Sarcopenic obesity particularly limits physical mobility with aging.