LoInf group. These markers were reduced in both groups at follow-up, consistent with reduced stress. However, the attenuation level was significantly different between the two groups. Kynurenate, that indicates activation of the immune system, was higher in HiInf group and remained elevated over 6 months follow-up. Polyamines with anti-oxidant activity and boosting autophagy activities were declined more significantly in the LoInf group presumably indicating more response to bodily anti-oxidant activity compared to the HiInf group. Arachidonic acid-derived eicosanoids, mediators of the immune response, were significantly elevated at baseline in the LoInf while oxidative stress markers were increased more in HiInf group. Branched-chain amino acids (BCAAs), the essential amino acids abundant in muscle, were elevated at baseline in the LoInf compared to HiInf group. Conclusion: Both groups showed an increase in anti-oxidative stress while LoInf group showed more reduction in oxidative stress and immune cell activity. Reduced intermediate compounds of BCCA suggest that their catabolism was attenuated following hip fracture in LoInf.

## THE ASSOCIATION BETWEEN D3CR MUSCLE MASS AND MORTALITY IN COMMUNITY-DWELLING OLDER MEN

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We have shown that men with low muscle mass assessed by D3Cr (deuterated creatine) dilution are more likely to have worse physical performance and incident fractures, injurious falls and disability. However, the relation between D3Cr muscle mass and mortality is unknown. With data from Year 14 Visit of the MrOS study (N=1400, mean age 84.2 yrs), proportional hazards models estimated the risk of mortality (hazard ratio and 95% CI) by quartiles of D3Cr muscle mass (standardized to body mass); we calculated p for trend across quartiles. Models were adjusted for age, race, clinical center, alcohol use, smoking status, comorbidities, activity, percent fat, exhaustion, and cognitive function. Cause of death was centrally adjudicated. Over 3.3±0.8 years of follow-up, 197 (14.1%) men died. Men in the lowest quartile of D3Cr muscle mass/wgt were 2.8-fold more likely to die than men in the highest quartile (HR: 2.8, 95% CI: 1.6, 4.9; p for trend<.001). The HRs for each cause-specific mortality outcome were of similar magnitude to the HR for overall mortality: cancer death (HR, Q1 vs Q4: 2.2, 95% CI: 0.7, 7.1; p trend =0.140); CVD death (HR, Q1 vs Q4: 3.7, 95% CI: 1.3, 10.5; p trend =0.008); or non-cancer non-CVD death (HR, Q1 vs Q4: 2.4, 95% CI: 1.0, 5.6; p trend=0.019). We conclude that low muscle mass assessed by D3Cr dilution is a strong risk factor for mortality in older men, providing additional evidence that low muscle mass is an important risk factor for adverse health outcomes.

## THE PROBLEM OF INTEGRATING OF BIOLOGICAL AND CLINICAL MARKERS OF AGEING

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The number of potential biological markers of ageing increases dramatically especially with the development omics technologies. These biomarkers are not generally independent from each other and also related to clinical markers of aging that also could be markers of some illnesses. We discuss three ways of integrating biological and clinical markers of ageing: a frailty index (FI), indices of biological age, and a statistical distance as a measure of physiological dysregulation. We shows that FI has a strong theoretical support in the complex dynamical network model of the ageing process. The theory allows to explain why the interdependence of variables (representing the attributes of health) is essential for understanding of the basic properties both of the FI and of ageing such as a Gompertz law of mortality. Further progress in the field will go hand-in-hand with the development of new technologies that allow more data to be collected and interpreted.

## THE ASSOCIATION BETWEEN MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY AND MUSCLE OXIDATIVE CAPACITY IN OLDER ADULTS

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Age-related decline in muscle oxidative capacity negatively affects muscle function and mobility, which may lead to disability and frailty. Whether exercise and other life-style practices reduce age-related decline in muscle oxidative capacity is unclear. We assessed whether, after accounting for age, higher daily physical activity levels are associated with greater muscle oxidative capacity. Participants included 384 adults (54.7% women) aged 22 to 92 years from the Baltimore Longitudinal Study of Aging. Muscle oxidative capacity was measured in vivo using phosphorous magnetic resonance spectroscopy. We determined the time constant for phosphocreatine recovery (τPCr, in seconds) after exercise, with lower values of τPCr reflecting greater oxidative capacity. Time spent in moderate-to-vigorous physical activity (MVPA) was assessed using accelerometers that participants wore for 5.9 ± 0.9 consecutive days in the free-living environment. In linear regression models, older age was associated

with higher τPCr (β = 0.39, p-value <.001) after adjusting for sex, race, height and weight. After including MVPA as an independent variable, the standardized regression coefficient for age was attenuated by 40% to 0.22. p-value <.001). MVPA was strongly associated with lower τPCr (β = -0.33, p-value <.001) after adjusting for health status, education and smoking history and was only attenuated by 3% after additional adjustment for age. These results suggest that MVPA is strongly associated with muscle oxidative capacity independent of age, providing mechanistic insights into the health benefits of daily physical activity in older persons.

## HAND2 TRANSCRIPTION FACTOR ENHANCES NMJ ORGANIZATION AND FUNCTION IN OLD MICE

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Over time, declining muscle force and power leads to mobility disability and impaired quality of life. In aging rodents and humans, a denervation and reinnervation process is strongly implicated in sarcopenia: the progressive decline of skeletal muscle mass, composition, and function. We propose that the concomitant decline in expression of Hand2, a key transcription factor (TF) for sympathetic neuron maintenance, induces motor pre- and postsynaptic neuromuscular junction (NMJ) instability and disorganization. To counter the deleterious effect of sympathetic denervation, we developed a novel viral vector (AAV9-Hand2-eGFP, Hand2) carrying Hand2 expression exclusively to sympathetic neurons. Male and female, 16-month-old mice, were examined for signs of muscle denervation and sarcopenia 6 months after IV injection with either Hand2 or control empty virus (AAV9-eGFP, EV). We found that Hand2 increased preterminal synaptic vesicle release, neurofilament phosphorylation (Neurite length: Hand2: 3732±496 μm, EV: 2674±165 μm; P <0.01), NMJ pre/postterminal co-localization, hindlimb muscle mass (EDL: 25%, soleus: 14%, tibialis anterior: 17% and gastrocnemius: 25%; n = 6-8 muscles per treatment group; P < 0.01), myofiber cross-sectional area, and protein kinase-A RIIα/RIα ratio (EV, RIIα:1.05±0.03, RIα:0.93±0.04, ratio: 1.13; Hand2, RIIα:1.81±0.03, RIα:0.94±0.03, ratio: 1.94; P<0.001) which contributes to stability of the NMJ. We also examined Hand2 gene methylation, and RNA-sequencing, muscle metabolomics, and whole body and muscle function with aging in EV and Hand2 injected mice. Our data indicate that expression of Hand2 significantly enhances skeletal muscle adrenergic receptor signaling through the canonical pathway, and prevents in NMJ transmission, and muscle mass and function decline with aging.

## FRAILTY ASSESSMENT BASED ON THE QUALITY OF DAILY WALKING

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Frailty is an increasingly recognized geriatric syndrome resulting in age-related decline in reserve across multiple physiologic systems. An impaired physical function is a prime indicator of frailty. In this study, we aim to implement a body-worn sensor to characterize the quantity and quality of everyday walking, and establish associations between gait impairment and frailty. Daily physical activity was acquired for 48 hours from 125 older adults (≥65 years; 44 non-frail, 60 pre-frail, and 21 frail based on the Fried gold standard) using a tri-axial accelerometer motion-sensor. Continuous purposeful walks (≥60s) without pauses were identified from time-domain acceleration data. Power spectral density (PSD) analysis was performed to define higher gait variability, which was identified by a shorter and wider PSD peak. Association between frailty and gait parameters was assessed using multivariable nominal logistic models with frailty as the dependent variable, and demographic parameters along with the gait parameters as the independent variables. Stride times, PSD gait variability, and total and maximum continuous purposeful walking duration were significantly different between non-frail and pre-frail/frail groups (p<0.05). Using a step-wise model with the above qualitative and quantitative gait parameters as predictors, the pre-frail/frail group (vs. non-frail) was identified with 71.4% sensitivity and 75.4% specificity. Everyday walking characteristics were found to be accurate determinants of frailty. Along with quantitative measures of physical activity, qualitative measures are critical elements representing the stages of frailty. In-home gait analysis is advantageous over clinical gait analysis as it enables cost- and space-effective continuous monitoring.

## LOW-INTENSITY EXERCISE ENHANCES MUSCULAR ANDROGEN/ANDROGEN RECEPTOR TO INHIBIT MYOSTATIN PATHWAY

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Background: Physical exercise is well documented to induce muscle size, strength, and energy metabolism. Although the contribution of systemic or local androgen in exercise-adapted muscle hypertrophy has been suggested, less is known about the molecular pathway of androgen in response to exercise. In the present study, we examined roles of androgen/androgen receptor (AR) after exercise, especially for the suppression of myostatin, a potent negative regulator of muscle mass. Methods and Results: To examine the effects of exercise, we employed low-intensity exercise in mice and electric pulse stimulation (EPS) in C2C12 myotubes. Both mRNA and protein levels of AR significantly increased in skeletal muscle of low-intensity exercised mice and C2C12 myotubes exposed to EPS. Production of testosterone and DHT from EPS-treated C2C12 myotubes was markedly increased. Of interest, we found that myostatin was clearly inhibited by EPS, and its inhibition was significantly abrogated by flutamide, a specific antagonist of AR. Furthermore, IL-6 and phospho-STAT3 (pSTAT3) expression, the downstream pathway of myostatin, were decreased by EPS and this was also reversed by flutamide. Similar downregulation of myostatin and IL-6 was seen in skeletal muscle of low-intensity exercised mice. Conclusion: Muscle AR expression and androgen production were increased by exercise and EPS treatment. As a mechanistical