Aerobic exercise training is a potent intervention for the treatment and prevention of age-related disease, such as heart disease, obesity, and Type 2 Diabetes. Insulin resistance, a hallmark of Type 2 Diabetes, is reversed in response to aerobic exercise training. However, the effect of aerobic exercise training on glucagon sensitivity is unclear. Glucagon signaling at the liver promotes fatty acid oxidation, inhibits De novo lipogenesis, and activates AMP Kinase, a key mediator of healthy aging. Like humans, aging in mice age leads to a decline in physical and metabolic function. To understand the role of glucagon signaling in exercise-induced improvements in physical and metabolic function in the mouse, we implemented a 16-week aerobic exercise training protocol in young and aged mice. 16 weeks of exercise training initiated at 6 months of age increased markers of physical function ($P<0.01$) and attenuated age-related weight gain ($P<0.05$) and fat mass ($P<0.0001$). Additionally, exercise training improved glucose clearance ($P<0.01$), enhanced glucose-stimulated insulin secretion ($P<0.01$) and decreased hepatic lipid accumulation ($P<0.05$). Importantly, exercise training decreased hypoglycemia stimulated glucagon secretion ($P<0.01$), with no effect on hepatic glucagon receptor mRNA expression or serum glucagon. Thus, we propose that aerobic exercise training enhances glucagon sensitivity at the liver, implicating glucagon as a potential mediator of exercise-induced improvements in aging. Studies initiating the same aerobic exercise training intervention at 18 months of age in the mouse are currently underway to establish the role of glucagon receptor signaling in exercise-induced improvements in aging.

Session 4395 (Paper)

Frailty Measurement

CONSTRUCTION AND VALIDATION OF A FRAILTY INDEX IN PRIMARY CARE IN ITALY: THE HEALTH-SEARCH FRAILTY INDEX

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Recognizing frailty in primary care is important to implement personalized care pathways and for prognostication. The aim of this study was to build and validate a frailty index based on routinely collected primary care data in Italy. We used clinical data from 308,280 Italian primary care patients 60+ with at least 5 years of follow-up, part of the Health Search Database. A heuristic algorithm was used to select the deficits to be included in a highly performant frailty index. The fitness of the index was assessed through the c-statistics derived by survival models. Results were externally validated using the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). After testing 3.4 million of deficits combinations, 25 deficits were selected to be included in the Health Search Frailty Index (HS-FI). After adjusting by sex, age and geographical area, the HS-FI was associated with 5-year mortality (HR per 0.1 increase 1.99; 95%CI 1.95-2.02) and hospitalization rate (HR per 0.1 increase 1.25; 95%CI 1.23-1.27). In the external validation cohort, HS-FI independently predicted mortality, hospitalization, incident disability, incident dementia, and incident falls. This is the first frailty index built following a data-driven approach, using national representative primary care data. The implementation of such tool – derived by routinely collected data – in primary care software will ease the prompt, comparable and reliable recognition of frailty at the population level.

METABOLOMICS-BASED BIOMARKERS FOR FRAILTY IN CHINESE OLDER ADULTS

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Background: Frailty is a clinical state characterized by decline in physiological function, and increased vulnerability to adverse outcomes. The biological mechanisms underlying frailty have been extensively studied in recent years. Advances in the multi-omics platforms have provided new information on the molecular mechanisms of frailty. Thus, identifying omics-based biomarkers is helpful for both exploring the physiological mechanisms of frailty and evaluating the risk of frailty development and progression. Objective: To identify metabolomics biomarkers and possible pathogenic mechanisms for frailty with untargeted-metabolomics profiling. Methods: LC-MS-based untargeted metabolomics analysis was performed on serum samples of 25 frail older inpatients and 49 non-frail older controls. The metabolomics profiling was compared between the two groups. Results: We identified 349 metabolites belonging to 46 classes, in which 2 were increased and 3 were decreased in frail older adults. Citrate cycle (with up-regulated cis-Aconitic acid, Fumaric acid, L-Malic acid, and Isocitric acid), fatty acid metabolism (with up-regulated Palmitic acid and L-Palmitoylcarnitine) and tryptophan metabolism (with up-regulated 5-Hydroxy-L-tryptophan, L-Kynurenine, Kynurenic acid, and 5-Hydroxyindoleacetic acid) were significantly associated with frailty phenotype. Conclusions: Our results revealed characteristics of metabolites of frailty in Chinese older adults. The citrate cycle related metabolites (Isocitrate, (s)-Malate, Fumarate and cis-Aconitate), saturated fat (Palmitic acid), unsaturated fatty acid (Arachidonate and Linoleic acid), and some essential amino acid (Tryptophan) might be candidate biomarkers for early diagnosis of frailty. Disorders of energy metabolism, lipotoxicity of saturated fatty acids, disturbances of unsaturated fatty acid metabolism, and increased degradation of tryptophan were potential mechanisms and therapeutic targets of frailty.

THE ASSOCIATION BETWEEN METABOLIC SYNDROME AND FRAILTY IN HEALTHY COMMUNITY-DWELLING OLDER ADULTS

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This study examined the association between metabolic syndrome (MetS) and frailty status in relatively healthy community-dwelling older adults. Participants included 19,114 individuals from the "ASPirin in Reducing Events in the Elderly" (ASPREE) trial. The diagnostic criteria for MetS were according to the International Diabetes Federation Task Force on Epidemiology and Prevention and the American Heart Association/National Heart, Lung, and Blood Institute (2009); and comprised any three of five parameters: waist circumference, triglycerides, fasting blood glucose, high-density lipoprotein cholesterol or hypertension. Frailty and prefrailty were defined using a modified Fried phenotype (FP) comprising exhaustion, body mass index, grip strength, gait speed and physical activity and a deficit accumulation frailty index (FI) of 66 items. The association between MetS and frailty was examined using multinomial logistic regression. At baseline, 51.1% of participants met the criteria of MetS; of those, 41.8% and 2.5 % were prefrail and frail, respectively, according to Fried phenotype, while 49.6% and 11.8 % were prefrail and frail, respectively, according to FI. MetS at baseline was associated with an increased likelihood of prefrailty (RRR: 1.25; 95% CI: 1.17, 1.33) and frailty (RRR: 1.60; 95% CI: 1.28, 2.01) compared to no frailty after adjustment for potential confounders according to Fried phenotype, while the association was stronger for prefrailty (RRR: 2.74; 95% CI: 2.55, 2.94) and frailty (RRR: 5.30; 95% CI: 4.60, 6.11) according to FI. Overall, at baseline, more than half of the participants had MetS, and the presence of MetS was significantly associated with pre-frailty and frailty.

TRANSPLANT CENTERS THAT MEASURE FRAILTY AS PART OF CLINICAL PRACTICE HAVE BETTER OUTCOMES

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Frailty predicts adverse outcomes for kidney transplant (KT) patients; yet the impact of clinical assessments of frailty on center-level outcomes remains unclear. We sought to test whether KT centers that measure frailty as part of clinical practice have better pre- and post-KT outcomes. We conducted a survey of US transplant centers (11/2017-4/2018), 132 KT centers (response rate=65.3%) reported frequencies of frailty assessment at candidacy evaluation and KT admission. Center characteristics and clinical outcomes were gleaned from the national registry (2017-2019). Poisson regression was used to estimate incidence rate ratios (IRRs) of waitlist mortality rate and transplantation rate in candidates and graft loss rates in recipients by frequency of frailty assessment. All models were adjusted for case mix and center characteristics. Given similar center characteristics, centers assessing frailty at evaluation had a lower waitlist mortality rate (always=3.5, sometimes=3.2, never=4.1 deaths per 100 person-years). After adjustment, centers assessing frailty at evaluation had a lower rates of waitlist mortality (always IRR=0.91, 95% CI:0.84-0.99; sometimes=0.89, 95% CI:0.83-0.96) and transplantation (always IRR=0.94, 95% CI:0.91-0.97; sometimes=0.88, 95% CI:0.85-0.90) than those never assessing frailty. Centers that always assessed frailty at KT admission had 0.71 (95% CI:0.54-0.92) times the rate of death-censored graft loss than their counterparts never assessing frailty. Assessing frailty at evaluation is associated with lower transplantation rate but better waitlist survival; centers always assessing frailty at admission are likely to have better graft survival. Research is needed to explore how routine assessment of frailty in other clinical practices benefits broader patient populations.

VALIDATION OF PERCEIVED MENTAL FATIGABILITY USING THE CHINESE VERSION OF THE PITTSBURGH FATIGABILITY SCALE

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Background: Recently we validated the simplified-Chinese version of the Pittsburgh Fatigability Scale (PFS) Physical subscale. Next step is to validate the PFS Mental subscale in order to introduce a reliable measure of perceived mental fatigability among Chinese community-dwelling older adults. Methods: This cross-sectional study was conducted in an urban community in Beijing. Internal consistency of the PFS Mental subscale was evaluated by Cronbach's alpha. The participants were divided in half to evaluate the factor structure validity by exploratory factor analyses and confirmatory factor analysis. Convergent validity and discriminant validity were evaluated against cognitive function (assessed by MOCA) and global fatigue from FRAIL Scale. Results: Our study included 370 participants (mean=83.8 years). The simplified-Chinese version of PFS Mental subscale showed strong internal consistency (total Cronbach's alpha=0.82, each items Cronbach's alpha ranged from 0.78 – 0.83). The results of exploratory factor analysis showed all 10 items loaded on two factors: moderate to high and low intensity activities, which explained 60.8% of the total variance. Confirmatory factor analysis showed fit indices: SRMSR = 0.090, RMSEA = 0.120, CFI = 0.89. PFS Mental scores demonstrated moderate concurrent and construct validity against cognitive function ($r = -0.24$, $P < .001$). Additionally, the PFS Mental subscale had strong convergent validity, discriminating according to established cognitive impairment or FRAIL Scale fatigue testing cut points, with differences in PFS Mental scores ranging from 3.2 to 8.4 points. Conclusions: The PFS Mental subscale