



National Institutes of Health
WORKSHOP PROGRAM

National Institute on Aging Workshop
Causes & Consequences of Age-Related Changes in Gait Biomechanics:
The Metabolic Cost of Walking

September 20-21, 2021

[Register for the workshop](#)

September 20, Day 1 (*All times Eastern Daylight Time*)

<u>Time</u>	<u>Topic</u>	<u>Presenter</u>
10:00 am	• Opening Remarks and Introductions	Lyndon Joseph, National Institute on Aging
10:10 am	• Overview: Refining Our Tools: Applying Exercise Physiology and Physical Therapy Methods to Aging Research	Eleanor Simonsick, National Institute on Aging

Session 1: Gait Biomechanics

<u>Time</u>	<u>Topic</u>	<u>Presenter</u>
10:25 am	✓ <i>Age-related differences in gait biomechanics- what and in whom have they been observed?</i>	Katherine Boyer
10:30 am	✓ <i>The mechanical and metabolic consequences of aging effects on muscle-tendon units powering locomotion: moving beyond observational inquiry</i>	Jason Franz
10:35 am	✓ <i>Helping Identify the Causes of Age-Related Changes in Gait Via Musculoskeletal Modeling & Simulation</i>	Brian Umberger
10:40 am	✓ <i>Adaptation, Compensation, and Restitution in the Context of Post-stroke Gait Rehabilitation</i>	James Finley
10:45 am	<i>Moderator recap and charge to groups</i>	Kharma Foucher
10:50 am	Breakout Session	
11:30 am	LUNCH BREAK	

Session 2: Neuromuscular mechanisms for changes in gait biomechanics

<u>Time</u>	<u>Topic</u>	<u>Presenter</u>
12:00 pm	✓ <i>Aging-related changes in skeletal muscle mass and composition and associations with walking performance</i>	Barbara Nicklas
12:05 pm	✓ <i>Walking with an aging nervous system</i>	Dave Clark

<u>Time</u>	<u>Topic</u>	<u>Presenter</u>
12:10 pm	✓ <i>Bioenergetic and metabolic changes in old age: potential effects on mobility function and gait</i>	Jane Kent
12:15 pm	✓ <i>Age-Related Changes in Muscle Fatigability: Task Matters'</i>	Sandra Hunter
12:20 pm	<i>Moderator recap and charge to groups</i>	Brian Clark
12:25 pm	Breakout Session	
1:05 pm	BREAK	
1:10 pm	Day 1 Synthesis: All-hands discussion	Katherine Boyer and Brian Umberger
2:30 pm	End of Day 1	

September 21, Day 2

<u>Time</u>	<u>Topic</u>	<u>Presenter</u>
10:00 am	• Opening Remarks	Lyndon Joseph, National Institute on Aging
10:05 am	• Overview: Looking inside the aging muscle	Luigi Ferrucci, National Institute on Aging

Session 3: Connective Tissue Function

<u>Time</u>	<u>Topic</u>	<u>Presenter</u>
10:20 am	✓ <i>Effect of ageing on tendon mechanical properties and impact on muscle function</i>	Marco Narici
10:25 am	✓ <i>How does the extra cellular matrix affect muscle mechanical behavior and what are the possible implications for energy cost?</i>	Thomas Roberts
10:30 am	✓ <i>Challenges and approaches for studying biomechanical function and mobility in real-world movement</i>	Peter Adamczyk
10:35 am	<i>Moderator recap and charge to groups</i>	Silvia Blemker
10:40 am	Breakout Session	
11:10 am	BREAK	

Session 4: Interventions and Technologies

<u>Time</u>	<u>Topic</u>	<u>Presenter</u>
11:15 am	✓ <i>Timing and coordination training for improved</i>	Jennifer Brach
11:20 am	✓ <i>Can exoskeletons preserve musculoskeletal structure-function in aging?</i>	Greg Sawicki
11:25 am	✓ <i>The effects of exercise interventions on gait biomechanics</i>	Tibor Hortobagyi
11:30 am	<i>Moderator recap and charge to groups</i>	Jonathan Bean
11:35 am	Breakout Session	
12:05 pm	LUNCH BREAK	
12:35 pm	Day 2 Synthesis: All-hands discussion	Katherine Boyer and Brian Umberger
1:35 pm	✓ <i>Johnson County OA Project; incorporating diversity into study design</i>	Yvonne M. Golightly
1:45 pm	All-Hands Discussion: Prioritizing Inclusivity; Universal Study Design	
1:55 pm	Wrap up Discussion: recommendations and priorities	Lyndon Joseph
3:00 pm	Adjourn	

Index of Speaker Biographies and Abstracts

National Institute on Aging Workshop Causes & Consequences of Age-Related Changes in Gait Biomechanics: The Metabolic Cost of Walking	2
Lyndon Joseph, Ph.D., National Institute on Aging	7
Eleanor Simonsick, Ph.D., National Institute on Aging	7
<i>Refining Our Tools: Applying Exercise Physiology and Physical Therapy Methods to Aging Research</i>	7
Session I	8
Katherine Boyer, Ph.D., University of Massachusetts Amherst.....	8
<i>Age-related differences in gait biomechanics- what and in whom have they been observed?</i>	8
Jason Franz, Ph.D., University of North Carolina at Chapel Hill	9
<i>The mechanical and metabolic consequences of aging effects on muscle-tendon units powering locomotion: moving beyond observational inquiry</i>	9
Brain Umberger, Ph.D., University of Michigan	9
<i>Helping Identify the Causes of Age-Related Changes in Gait via Musculoskeletal Modeling and Simulation</i>	10
James Finley, Ph.D., University of Southern California	10
<i>Adaptation, Compensation, and Restitution in the Context of Post-stroke Gait Rehabilitation</i>	11
Kharma Foucher, M.D., Ph.D., University of Illinois at Chicago.....	11
Session II.....	11
Barbara Nicklas, Ph.D., Wake Forest School of Medicine.....	11
<i>Aging-related changes in skeletal muscle mass and composition and associations with walking performance</i>	12
David J. Clark, Sc.D., University of Florida	12
<i>Walking with an aging nervous system</i>	12
Jane Kent, Ph.D., University of Massachusetts Amherst	13
<i>Bioenergetic & Metabolic Changes in Old Age: Potential Effects on Mobility Function & Gait?</i>	13
Sandra Hunter, Ph.D., Marquette University	14
<i>Age-Related Changes in Muscle Fatigability: Task Matters!</i>	14
Brian C. Clark, Ph.D., Ohio University	15
Luigi Ferrucci, M.D., Ph.D., National Institute on Aging	15

<i>Looking inside the aging muscle</i>	15
Session III	16
Marco Narici, Ph.D., University of Padova, Italy	16
<i>Effect on Aging on Tendon Mechanical Properties and Impact on Muscle Function</i>	16
Thomas Roberts, Ph.D., Brown University	17
<i>How does the extra cellular matrix affect muscle mechanical behavior and what are the possible implications for energy cost?</i>	17
Peter Adamczyk, Ph.D., University of Michigan	18
<i>Challenges and approaches for studying biomechanical function and mobility in real-world movement</i>	18
Silvia Blemker, Ph.D., University of Virginia	19
Session IV	19
Jennifer Brach, Ph.D., PT, FAPTA, University of Pittsburgh.....	19
<i>Timing and Coordination Training for Improved Mobility</i>	19
Gregory Sawicki, Ph.D., Georgia Institute of Technology	20
<i>Can exoskeletons preserve musculoskeletal structure-function in aging?</i>	20
Tibor Hortobágyi, Ph.D., University of Groningen, Netherlands	21
<i>The effects of exercise interventions on gait biomechanics</i>	21
Yvonne M. Golightly, PT., MS., Ph.D., University of North Carolina	22
<i>Johnson County OA Project; incorporating diversity into study design</i>	22
Jonathan F. Bean M.D., MS., MPH., Harvard Medical School	23

Lyndon Joseph, Ph.D., National Institute on Aging

Dr. Lyndon Joseph, Ph.D, an Exercise Physiologist, is a Program Officer at the National Institute on Aging's Division of Geriatrics and Clinical Gerontology. His programmatic and research portfolio covers basic, translational and clinical studies related to musculoskeletal conditions, gait/balance, physical function, the effects of exercise and other interventions on chronic diseases and disability, disability trajectory and prevention, physical therapy and rehabilitation, falls and fall prevention, frailty, obesity, and physical activity/sedentary behavior in older adults. Dr. Joseph received his doctorate degree in Physiology (Interdisciplinary) from The Pennsylvania State University, Master's degree in Clinical Exercise Physiology from Northeastern University, and bachelor's degree in Biology from St. John Fisher College. He completed his Post-doctoral Fellowship at the University of Maryland, School of Medicine in the Division of Gerontology and his Cardiac Rehabilitation internship at Boston University Medical Center.

Eleanor Simonsick, Ph.D., National Institute on Aging

Dr. Simonsick is an epidemiologist and staff scientist in the Longitudinal Studies Section of the Translational Gerontology Branch within the Intramural Research Program (IRP) of the National Institute on Aging (NIA) and an associate professor in the Division of Geriatric Medicine and Gerontology at the Johns Hopkins University School of Medicine. She also serves as affiliated faculty for the Johns Hopkins Center on Aging and Health (COAH). For over 35 years, Dr. Simonsick has conducted aging-related research within the context of longitudinal observational studies and has substantial expertise in the design, conduct and administration of multi-disciplinary longitudinal studies of aging. Currently, she is the Acting Co-Director of the Baltimore Longitudinal Study of Aging (BLSA) and a Principle Investigator and Federal Project Officer of the Health, Aging and Body Composition (Health ABC) study. Her primary areas of expertise include assessment of higher-order physical function including endurance walk performance and fatigability and changes with aging. She also has substantial experience in evaluating the behavioral, psychological, biomechanical and physiologic factors and conditions that impact energetic cost and reserve capacity and how these in turn impact maintenance and decline in function and the overall aging process. She has extensive knowledge of proper design and conduct of longitudinal observational studies of aging and aged individuals and appropriate analysis techniques.

Refining Our Tools: Applying Exercise Physiology and Physical Therapy Methods to Aging Research

Abstract: This session aims to stimulate brainstorming and discussion on the range of factors and systems that impact gait and the energetic cost of walking. The "energy box" paradigm developed and applied in the Baltimore Longitudinal Study of Aging (BLSA) will be presented to provide context for identifying components of the energetic cost of walking. Preliminary data on the relationship between the energetic cost of

walking and energetic capacity as assessed by portable indirect calorimetry during the Long Distance Corridor Walk will be used to elucidate the relationship between the energetic cost and energetic capacity in conditioning usual gait speed. Ongoing analyses of the association of shoulder function limitations with walking endurance and lower extremity physical performance will be used to illustrate how non-traditional sources may help identify under-appreciated threats to efficient gait. Lastly, recently published findings from an ongoing study of energetic reserves and Alzheimer's Disease will be used to exemplify both the importance and possible centrality of brain health in gait mechanics and efficiency.

Session I

Katherine Boyer, Ph.D., University of Massachusetts Amherst

Dr. Boyer is an Associate Professor in the Department of Kinesiology at the University of Massachusetts Amherst. She received her Ph.D. from the University of Calgary and completed a post-doctoral fellowship at Stanford University. Her research program focuses on quantifying mechanisms of mobility declines in aging and with injury and is funded by both the NIH and industry partners.

Age-related differences in gait biomechanics- what and in whom have they been observed?

Abstract: Age-related changes in gait biomechanics are considered key factors leading to the decline in gait speed and mobility in older adults. The prevailing theory on aging gait suggests that older adults experience a distal to proximal shift in mechanical power generation during stance phase of walking, reducing the power produced at the ankle and increasing that generated at the hip. However, the universality and mechanisms for such a redistribution remains unclear. In recent meta-analysis, we found large standardized effects for smaller peak propulsion moments and power in older as compared to younger adults both when walking speeds were and were not similar or matched. However, the overall effect of age on hip kinetics was small and only in studies with similar walking speeds between younger and older groups were significant large standardized effects of age on joint moments and powers found. On average, reported walking speeds for older groups in aging gait biomechanics studies are fast and not different from younger groups (~1.3 m/s). While few studies report the physical activity level of the participants, effect sizes for age differences in several studies focused master's runners and highly active adults who are both mid-life (50 – 65yrs) and older (>65yrs) remain high. While muscle weakness is often suggested as a mechanism's for age-related gait differences, the functional demand on the lower extremity muscles in walking is relatively low (~estimated 20-25% of knee extensor muscle capacity) and large declines in strength would not yet be expected in the active mid-life adults. Together this suggests we have largely studied the biomechanics of high functioning older adults and the suggested redistribution of joint power may be not be characteristic of individuals with incident mobility deficits. Gaps remain in the knowledge of when age-related gait changes begin to emerge and at what rate they

progress and begin to impact mobility function. In addition, the physiological factors that may lead to the initiation of changes in movement coordination and if these initiating factors are the same as those that may contribute to gait deficits in the older old remain unclear.

Jason Franz, Ph.D., University of North Carolina at Chapel Hill

Dr. Franz is an Associate Professor in the Joint Department of Biomedical Engineering at the University of North Carolina at Chapel Hill (UNC) and North Carolina State University (NC State). He also holds faculty appointments in the UNC Human Movement Science Program and the UNC Thurston Arthritis Center. Dr. Franz is the director of the UNC Applied Biomechanics Laboratory, which aims to advance understanding of the neuromuscular determinants of walking ability limitations, instability, and falls, with a special emphasis on aging and neurodegenerative disease. Prior to joining UNC and NC State, Dr. Franz completed an NIH Post-Doctoral Fellowship in the Department of Mechanical Engineering at the University of Wisconsin-Madison, received his Ph.D. in Integrative Physiology from the University of Colorado, Boulder, and received his B.S. and M.S. degrees in Engineering mechanics from Virginia Tech.

The mechanical and metabolic consequences of aging effects on muscle-tendon units powering locomotion: moving beyond observational inquiry

Abstract: Compared to younger adults, older adults exhibit reduced mechanical output from muscle-tendon units spanning the ankle (i.e., plantar flexors) during the push-off phase of walking. Our field posits that insufficient ankle push-off power precipitates slower speeds and redistributes the mechanical demands of walking to muscle-tendon units spanning the hip with significant metabolic penalties. However, there are several significant scientific gaps limiting our potential to advance our mechanistic understanding and treatment of age-related gait changes arising from deficits in plantar flexor muscle-tendon unit function. I intend to highlight three such gaps. First, we must better appreciate that push-off power during walking, and thus deficits therein, arises not from muscle contraction alone, but from complex neuromechanical interplay between active muscle force and passive series elastic tendon. Second, and by logical extension, we must move beyond muscle strengthening alone, and invest in strategies that elicit tissue remodeling and context-specific adaptation to promote meaningful change in habitual biomechanics and gait performance. Finally, I will encourage us all to move beyond purely observational studies in aging biomechanics, toward methodological and computational approaches to establish cause-effect relations critical to moving the field forward.

Brain Umberger, Ph.D., University of Michigan

Dr. Umberger is Professor of Movement Science and Chair of the Movement Science Program in the School of Kinesiology at the University of Michigan, where he is also a faculty affiliate of the Michigan Institute for Computational Discovery and Engineering. Prof. Umberger is a fellow of the NIH National Center for Simulation in Rehabilitation

Research at Stanford University, and he recently served as President of the American Society of Biomechanics. Prof. Umberger's research program is focused on better understanding the mechanics, energetics, and control of human locomotion. He studies fundamental and clinical aspects of muscle function in locomotion by integrating experimental data with advanced musculoskeletal modeling and computer simulation techniques.

Helping Identify the Causes of Age-Related Changes in Gait via Musculoskeletal Modeling and Simulation

Abstract: Simulation of human walking using computational models of the musculoskeletal system represents a powerful approach for studying how and why we walk the way that we do. Studies employing modeling and simulation techniques have made numerous contributions to our fundamental understanding of the biomechanics and energetics of human gait. A clinically-relevant use of gait simulations is to help identify the causal factors in movement impairments, but this approach has been underutilized in studying the causes of age-related gait changes. Modeling studies can help identify cause-and-effect relations by disentangle confounds that exist in the real biological system. Modeling and simulation holds considerable potential for helping address the problem of reduced mobility in older adults, but this potential has not yet been fully realized. Among the many gaps in our current knowledge, there are some that modeling and simulation techniques are well suited to help address. One of these is identifying the neuromuscular changes that are most causal of the slower gait speed and greater metabolic cost in older adults. Likewise, a simulation approach can provide insights on how the task "objective" for walking change in older adults, including factors beyond metabolic cost such as muscle fatigue, stability, smoothness, and joint loading. An additional gap pertains to the appropriate role that modeling and simulation techniques should play in helping solve the broader problem of age-related gait changes. This involves matters such as establishing our degree of confidence in simulation results for this particular application, relative to modeling assumptions and simplifications, and determining how best to integrate simulation results with other sources of evidence. Regular communication and close collaboration among modelers, experimentalist, and clinicians will be necessary to realize the full potential of the modeling and simulation approach.

James Finley, Ph.D., University of Southern California

Dr. Finley is an Associate Professor in the Division of Biokinesiology and Physical Therapy, the Department of Biomedical Engineering, and the Neuroscience Graduate Program at the University of Southern California. Dr. Finley and his research team in the Locomotor Control Lab use experimental studies and computational models to understand how mobility is controlled in healthy individuals and individuals with neuromotor impairments such as stroke and Parkinson's disease. This work relies on principles of engineering, neuroscience, game design, biomechanics, and exercise physiology to ultimately design more effective interventions to improve mobility.

Adaptation, Compensation, and Restitution in the Context of Post-stroke Gait Rehabilitation

Abstract: Lesions to the central nervous system caused by a stroke result in marked gait and balance ability impairments. Because strokes are most prevalent in older adults and the elderly, lesion-related deficits often compound pre-existing, age-related mobility impairments. At a cursory level, the objectives of post-stroke rehabilitation seem clear: to restore the abilities that an individual possessed at an earlier point in life. However, for biomechanists who develop neurorehabilitation interventions, we must carefully consider how best to use our tools to achieve this objective. For example, we might consider using activity-based interventions, such as real-time biofeedback, to help individuals unlearn abnormal muscle activation patterns or minimize gait asymmetries. Alternatively, we may consider employing engineered, assistive solutions such as exoskeletons to compensate for the fact that certain muscle groups have lost their ability to generate mechanical work. Regardless of the researcher's approach, they must also consider and evaluate how a given reduction in impairment or compensatory strategy might benefit the individual. As an example of this concept, I will share recent work from my research team where we evaluate how reductions in a specific measure of impairment, gait asymmetry, impact presumed measures of the "goodness" of an individual's walking pattern such as energetic cost and balance. From there, I will highlight key challenges for identifying personalized targets for intervention in the context of stroke-induced changes in gait biomechanics.

Kharma Foucher, M.D., Ph.D., University of Illinois at Chicago

Dr. Foucher is an Associate Professor in the Departments of Kinesiology and Nutrition and Bioengineering at the University of Illinois at Chicago (UIC) and the Associate Director for Education and Professional Development in the UIC Center for Clinical and Translational Science. She received an S.B. in Engineering Sciences from Harvard University and a PhD in Bioengineering/MD from the University of Illinois at Chicago. Her lab uses biomechanics to understand, predict, and improve person-oriented osteoarthritis outcomes, with current projects particularly focusing on physical activity and falls.

Session II

Barbara Nicklas, Ph.D., Wake Forest School of Medicine

Dr. Nicklas is Professor of Internal Medicine in the Section on Gerontology and Geriatric Medicine at Wake Forest School of Medicine. She has cross-appointments in the WFU Department of Health and Exercise Science and the Translational Science Institute. Dr. Nicklas is an experienced clinical investigator with research and scientific expertise in the fields of exercise physiology, obesity, and aging. She has vast experience in conducting exercise and diet clinical trials in older adults with both clinical and biological outcomes.

Aging-related changes in skeletal muscle mass and composition and associations with walking performance

Abstract: Aging-related changes in whole-body composition are well known and include a loss of total and appendicular muscle mass and an increase in adipose mass. These changes are evident across species and in all individuals, even if highly physically active. Whether the age-related increase in adipose precedes the loss of muscle, or vice versa, is not known; but, loss of muscle mass is accelerated in those with greater adiposity.

If, and how, these aging-related changes in body composition lead to gait abnormalities with aging is not fully understood. Most data show loss of total and/or appendicular muscle mass are not strong predictors of decline in gait speed over time—rather, an increase in adiposity is a better body composition predictor of longitudinal decline. However, decline in walking performance may be related to loss of muscle mass in specific muscle groups and differential loss between legs (asymmetry). With aging, there is also a redistribution of fat from being stored below the skin (subcutaneous) to being stored in and around internal organs and within (intra-muscular) and between muscle fibers (inter-muscular fat, IMF). This occurs even in those losing total adipose over time. Importantly, the accumulation of IMF is the strongest body composition-related risk factor for decline in gait speed and incidence of mobility disability. In fact, the negative relationship between IMF and gait speed is even greater in those with a higher muscle area.

Much more research is needed to delineate how increases in total and regional adiposity alter the metabolic and biomechanical factors involved in walking. Potential mechanisms by which fat accumulation with age may affect walking performance include by altering: joint kinetics, balance, and gait efficiency; muscle structure (capillarization, fiber size and type, motor neuron innervation); and/or muscle function (substrate uptake/usage, mitochondrial function, contractile capacity, fatigability). Research designed to identify how to prevent fat redistribution and IMF accumulation with aging is also needed.

David J. Clark, Sc.D., University of Florida

Dr. Clark is an Associate Professor in the College of Medicine at the University of Florida, and a Research Health Scientist in the Brain Rehabilitation Research Center at the Malcom Randall Veterans Affairs (VA) Medical Center. He leads a collaborative research program in the area of walking control and rehabilitation for older adults and people who have experienced a stroke. His research spans multiple disciplines including neurorehabilitation, neuroimaging, non-invasive neuromodulation, electrophysiology, biomechanics, and exercise physiology.

Walking with an aging nervous system

Abstract: Young adults walk with a complex, stable, and energetically efficient gait pattern that is coordinated largely by pattern-generating circuits in the central nervous

system. This is referred to as “automaticity” of walking. With advancing age, numerous changes occur throughout the body that disrupt this automaticity, which in turn alters biomechanics and energetics of gait. Some prominent factors that disrupt automaticity are reduced afferent inputs to the central nervous system (e.g., due to somatosensory impairment), increased physical effort (e.g., due to neuromuscular weakness and fatigue), and pain (e.g., due to musculoskeletal conditions). Loss of automaticity results in a compensatory shift toward a voluntary control strategy to coordinate walking. This strategy demands real-time attentional processing of movement, which compels the individual to select a less complex gait pattern. This may explain age-related increases in muscle co-activation and increased reliance on proximal muscle groups, as well as slower speed, shorter steps, and wider step widths. This altered gait pattern may be less energetically efficient, exacerbating muscle fatigue and further limiting walking performance. Optimizing walking function in older adults will require multifaceted approaches that account for the intertwined effects of neural control, biomechanics, and bioenergetics.

Jane Kent, Ph.D., University of Massachusetts Amherst

Dr. Kent is a Professor in the Department of Kinesiology, Director of the Muscle Physiology Lab, and faculty in the Institute for Applied Life Sciences at the University of Massachusetts Amherst. Using advanced *in vivo* magnetic resonance spectroscopy and imaging techniques, her work focuses on muscle bioenergetics and fatigue in older adults, and how these may influence mobility function and fatigability in aging.

Bioenergetic & Metabolic Changes in Old Age: Potential Effects on Mobility Function & Gait?

Abstract: Muscle bioenergetics- operationalized here as the production of ATP for use in contraction- is supported by the breakdown of macronutrients in the process of metabolism. ATP production is accomplished via the creatine kinase reaction, glycolysis and oxidative phosphorylation; all of which can be measured in human muscle *in vivo* and noninvasively using magnetic resonance spectroscopy. Studies to date have focused largely on the *capacity* for oxidative energy production; a process that is performed by the mitochondria, requires adequate oxygen delivery to the working muscle, and generates large amounts of energy. A 2016 meta-analysis indicated that several factors moderate muscle oxidative capacity in aging, including sex, health status, physical activity and the muscle studied. Of the locomotory muscles, lower oxidative capacity in aging is generally observed only in the knee extensors. In addition to *capacity*, the *use* of the 3 pathways for ATP in muscle also has been examined, although less widely. These studies suggest greater relative use of oxidative ATP production and lower use of glycolysis in older compared with young muscle, including mobility-impaired older adults. Additional work is needed to determine the conditions (muscle, population, etc.) under which this shift in pathway use occurs. Perhaps most germane to the question of the energy cost of walking in older adults, recent work has shown markedly lower metabolic economy in older vastus lateralis

muscle during dynamic, but not isometric, contractions. The role of poor muscle economy in the energy cost of walking, mobility dysfunction and fatigability in aging remains to be determined. Moving from muscle to the whole body level, evaluation of substrate (carbohydrate, fat) use in metabolism during walking has not been thoroughly evaluated as yet. Given the critical role of metabolism in supporting muscle energetics and overall health, the knowledge gap regarding how potential deficits in carbohydrate or fat metabolism may influence mobility and fatigability in aging should be addressed. Finally, consideration is needed of the variety of factors, such as sex, health status, medications, habitual physical activity level and nutritional status that may work independently or together to alter bioenergetics, metabolism and gait in old age.

Sandra Hunter, Ph.D., Marquette University

Dr. Hunter is a Professor in the Exercise Science program, Department of Physical Therapy, and Director of the Athletic and Human Performance Research Center at Marquette University, Milwaukee, Wisconsin. Her research focuses on understanding (1) the mechanisms of performance fatigability, and (2) the benefits of exercise training and related therapies across all ages and abilities including sex differences, advanced aging and clinical populations. Specific clinical populations include people with diabetes, postpartum women, stroke survivors, people with Achilles tendinopathy and COVID-19 survivors.

Age-Related Changes in Muscle Fatigability: Task Matters!

Abstract: Advanced aging is associated with low and more variable functional performance during daily tasks due to low strength and power of limb muscles that is exacerbated by age-related fatigability (muscle fatigue). Fatigability of limb muscles is an acute reduction in force or power of muscle in response to exercise or muscle activity. The mechanisms for muscle fatigability can originate from a reduction in the central nervous system to adequately activate the muscle, and from within the skeletal muscle, both resulting in a reduction in force and power. Fatigability of limb muscles however is task dependent: this means that the demands of the task, the involved muscles and/or the characteristics of the population can dictate both mechanisms and the magnitude of muscle fatigue. Age-related changes within the neuromuscular system, however, results in muscle fatigue with aging that differs in magnitude across various tasks. Old adults (~65-74 years) for example, are typically less fatigable than young people for isometric contraction tasks but are more fatigable for fast dynamic contraction tasks. Very old adults (>75 years), however are more fatigable than young adults for both isometric and dynamic tasks. Because very old adults have low baseline limb power, they are at high risk for functional deficits when performing tasks that require repeated fatiguing contractions such as walking or stair climbing. Low limb power of leg muscles at baseline is typically associated with impaired functional performance tasks including stair climbing and walking speed. Others at risk for functional deficits during fatiguing tasks include females, sedentary and mobility-impaired older adults who typically exhibit low baseline limb power. The challenge in future research is to determine (1) the mechanisms for age-related fatigability for

dynamic tasks (2) the functional relevance of muscle fatigability during gait in the most vulnerable older adults in the community (3) how fatigability further exacerbates the increased age-related variability within (trial-to-trial) & between older adults impacting functional performance such as mobility, and (4) the effectiveness of physical activity and related 'therapies' to offset age-related muscle fatigability and its impact on mobility in older adults.

Brian C. Clark, Ph.D., Ohio University

Dr. Clark is a Professor of Physiology and Neuroscience in the Department of Biomedical Sciences at Ohio University where he holds the Harold Clybourne Endowed Research Chair. He is also a PI and serves as the Executive Director of the Ohio Musculoskeletal and Neurological Institute (OMNI). The overall goal of his research is to develop effective and implementable interventions that increase muscle function (e.g., muscle strength, motor control, fatigue-resistance) and mobility in older adults. He has expertise and experience with basic and applied science human physiology experiments as well as randomized controlled trials.

Luigi Ferrucci, M.D., Ph.D., National Institute on Aging

Dr. Luigi Ferrucci, Scientific Director of NIA, is a geriatrician and an epidemiologist who conducts research on the biological and phenotypical pathways leading to progressive physical and cognitive decline in older persons. He has made major contributions in the design of many epidemiological studies conducted in the U.S. and in Europe, including the European Longitudinal Study on Aging, the AKEA study of Centenarians in Sardinia, the Women's Health and Aging Study and more recently the GESTALT study. He was also the Principal Investigator of the InCHIANTI study, a longitudinal study conducted in the Chianti Geographical area (Tuscany, Italy) looking at risk factors for mobility disability in older persons. In September 2002, he became the Chief of the Longitudinal Studies Section at NIA and redesigned the Baltimore Longitudinal Study of Aging to create an interface between the rising field of Geroscience and study of age-related changes of phenotypes, as well as physical and cognitive function. He is a member of the Association of American Physicians and has received numerous awards including the "Enrico Greppi" award, the IPSEN Longevity award and the "Cavaliere dell'Ordine della Stella d'Italia". Dr. Ferrucci collaborates extensively with many researchers in the US and Europe, has published more than 1500 peer-reviewed manuscripts on aging and age-related diseases and is considered as the most productive Italian Scientist in the area of medical science.

Looking inside the aging muscle

Abstract: Skeletal muscle tissue undergo profound biochemical, structural and functional changes with aging, and when these changes are overt or accelerated configure the syndrome of Sarcopenia, characterized by a substantial reduction of muscle mass and muscle strength that negatively affect physical function and mobility. At a microscopic view, skeletal muscle tissue has a very well-organized architecture,

with parallel myofibrils that are interrupted by allineated, typically structured sarcomeres. Interlaced between myofibrils and between the muscle tissues and capillaries are intramyocellular and sub-sarcolemma mitochondria that provide the necessary energy for contraction. With aging, this extraordinary morpho-functional structure is slowly deranged, with progressive loss of order of the contractile apparatus and change in the mitochondria number and morphology. In particular, the network structure of the mitochondrial function appears to be progressively more fragmented with aging. Discovery proteomics of skeletal muscle confirms that mitochondrial proteins become under-represented with aging, although physical activity appear to prevent in part this loss. Epidemiological studies show that the decline of mitochondrial function occurs both in men and in women, and are associated both cross-sectionally and longitudinally with loss of mobility, with some hints that muscle strength mediates this association. The causes of decline of mitochondrial changes with aging are unknown, but both metabolomic and epidemiological studies point to a defect in the biosynthesis and/or oxidation of cardiolipin, a mitochondrial specific lipid that is essential to maintain the architectural integrity of mitochondrial crests.

Session III

Marco Narici, Ph.D., University of Padova, Italy

Dr. Narici is Professor in Physiology at the University of Padova, Italy and Chair in Physiology at the Department of Biomedical Sciences, School of Medicine. He has been coordinator of the EC FP5 project BETTER AGEING and Co-I of European Union FP7 Project MYOAGE, he has been part of EU Framework 7 Advisory Panels for Ageing Research (LinkAge, WhyWeAge). He was President of the European College of Sport Science (2013-15). He has published over 240 peer reviewed journal articles (H-factor 66) and book chapters. His present work and interests are focused on the mechanisms of remodeling of human neuromuscular system with exercise, inactivity (including spaceflight) and ageing. He is presently coordinating the NeuAge PRIN Project funded by the Italian Ministry of Education, University and Research (MIUR) focusing on the Mechanisms of Neuromuscular Ageing and its Functional Implications, and coordinator of Italian Space Agency (ASI) project, MARS-PRE, focusing on the identification of early biomarkers of pathophysiological alterations of different organs and systems to simulated microgravity.

Effect on Aging on Tendon Mechanical Properties and Impact on Muscle Function

Abstract: Tendons play a fundamental role in transmitting forces generated by skeletal muscle and in acting as springs during locomotion. Because of their anatomical arrangement, the mechanical properties of tendons impact on those of skeletal muscle, above all, on the length-force relation (1, 2), rate of force development (4) and on gait performance (5). With ageing, tendon matrix composition (collagen types, enzymatic and non-enzymatic cross-linking, hydration, collagen density and crimp) undergo significant changes. While tendon cell number and density seem preserved with ageing, cell proliferation and migration seem reduced (6). These observations are mostly based

on murine models in which it is difficult to dissociate the effects of maturation from those of ageing (6). Scanty data instead exists on matrix and cellular changes of human tendons, however a consistent increase in advanced glycation end-products (AGEs) cross-links has been found (6). While increased AGEs cross-links contribute to tendon dehydration, predicting a decrease in tendon stiffness, the opposite is expected from increased cross-linking. In vivo measurements have shown a decrease in tendon stiffness in older individuals and although the more compliant tendon extends more during the stance phase of the gait cycle, this seems compensated by lesser shortening of muscle fascicles (5). Although possible causes may involve a decrease in hydration status, in collagen content, metalloproteases (MMPs) accumulation, and increased collagen fibril crimp angle, future studies should clarify the role of these factors. Tendons retain considerable plasticity in response to overloading in old age since their mechanical properties can be substantially improved by resistance training (RT) (7). Indeed, after 14-week RT in septuagenarian males, patellar tendon stiffness and modulus and hysteresis were found to improve to values comparable to those of young adults. In the short-term, these improvements seem mostly due to changes in tendon material properties rather than hypertrophy, an increase in stiffness after years of training seems mostly accounted by tendon hypertrophy. Recent findings also show that the increased stiffness induced by RT is independent from the contraction mode and that changes in tendon tissue seem to occur in a coordinated fashion with those of skeletal muscle; presumably in an effort to maintain the efficacy of the muscle-tendon unit.

Thomas Roberts, Ph.D., Brown University

Dr. Roberts is a Professor in the Department of Ecology, Evolution and Organismal Biology at Brown University. His work uses a comparative approach to investigate the link between the mechanical function of muscles and locomotor mechanics and energetics. Much of this work has focused on the central role of tissue elasticity in powering movement.

How does the extra cellular matrix affect muscle mechanical behavior and what are the possible implications for energy cost?

Abstract: Muscle fibers are bound together by an elaborate collagenous skeleton. Several functions of this collagenous extracellular matrix (ECM) have been identified, including lateral transmission of force and the production of passive tension. Changes in ECM properties associated with aging or disease have the potential to alter muscle mechanical function, thus it is important to understand how ECM structure and behavior influence muscle mechanics. Recent modeling and empirical studies identify the mechanical interaction between intramuscular fluid and ECM as having an important influence on how much force muscles produce. A muscle that swells under an osmotic perturbation generates greater passive tension, and an imposed change in muscle pressure can either increase or decrease active force generated during contraction; the direction of effect is length-dependent. This behavior can be explained

by theory of fiber-wound cylinders, highlighting the importance of three-dimensional dynamics in muscle function. A specific prediction from this work is that something as simple as a change in muscle fluid volume could alter muscle force production and possibly impact the metabolic cost of movement. The observation highlights how multi-scale interactions that are sometimes missed by reductionist approaches can have important physiological consequences.

Peter Adamczyk, Ph.D., University of Michigan

Dr. Adamczyk earned degrees in Mechanical Engineering from Case Western Reserve University (B.S.) and the University of Michigan (M.S. and Ph.D.) in the areas of Robotics and Biomechanics. He spent several years running a startup company dedicated to advancing the science and technology of real-world motion assessment and lower-limb prosthetics. He is now an Associate Professor at the University of Wisconsin–Madison where he directs the Biomechatronics, Assistive Devices, Gait Engineering and Rehabilitation Laboratory (UW BADGER Lab, <http://uwbadgerlab.engr.wisc.edu>). Dr. Adamczyk's research aims to enhance physical and functional recovery from impairments affecting walking, running, and standing. Core foci include wearable sensors for movement assessment during real-life activities; the design of semi-active foot prostheses for gait restoration after amputation; and rehabilitation robotics to explore motor learning and neural adaptation.

Challenges and approaches for studying biomechanical function and mobility in real-world movement

Abstract: “Mobility” is a functional outcome describing a person’s effectiveness in moving to participate in everyday life, often studied through metrics of activity level or spatiotemporal gait characteristics. “Movement” is the action of the body’s structures to create mobility, typically studied in detailed laboratory experiments and sometimes in “real-world” settings. But a deep understanding of how age or physiology affects everyday Mobility ultimately requires the study of Movement itself, in as much detail as possible, within that realm of unsupervised everyday life. This presentation will compare and contrast these ideas of Mobility and Movement, real-world environments and everyday life, focusing on the technology, experimental methods, and analytical approaches proper to the study of each. The goal is to advance the development of methods for generating detailed insight about how specific aging-related phenomena or interventions cause specific changes in movement in an everyday context, to the benefit or detriment of individuals’ mobility. A primary issue is the technological challenge of miniaturizing, validating and deploying as much lab-like instrumentation as possible while keeping sensors wearable, unobtrusive and convenient for participants. Another challenge lies in planning experiments to study both typical movement and exceptional events, and applying analysis that appropriately includes, excludes, pools and divides the resulting data to address scientific questions. The presentation will outline recent approaches and advancements in these areas and connect them to technological and methodological questions that must be resolved in any study of everyday movement, as

well as to long-term challenges whose resolution could advance the study of how aging affects Movement and Mobility.

Silvia Blemker, Ph.D., University of Virginia

Dr. Blemker is a Professor of Biomedical Engineering. at the University of Virginia. At UVA, she leads the Multi-scale Muscle Mechanophysiology Lab (“M3 Lab”). The M3 lab group develops advanced multi-scale computational and experimental techniques to study skeletal muscle biomechanics and physiology, and they are currently applying these techniques to variety of areas, including speech disorders, movement disorders, vision impairments, muscle atrophy, aging, muscular dystrophies, and athletic performance.

Session IV

Jennifer Brach, Ph.D., PT, FAPTA, University of Pittsburgh

Dr. Brach is Professor in the Department of Physical Therapy at the University of Pittsburgh. She is a physical therapist and epidemiologist with over 20 years of experience in patient-oriented research in aging and disability prevention. Dr. Brach has served as a principal investigator or co-investigator on multiple NIH/NIA and PCORI grants. Dr. Brach’s current work focuses on developing, testing and implementing exercise programs to improve mobility in community-dwelling older adults. Her long-term goal is to bridge the gap between clinical research, public health, and everyday practice by transferring the findings from clinical trials to practice settings and communities, where the findings will improve mobility and prevent disability in older adults.

Timing and Coordination Training for Improved Mobility

Abstract: Walking is a complex task that requires the integration of multiple physiologic systems. Standard interventions to improve walking primarily target musculoskeletal and cardiopulmonary systems through strength and endurance training, but rarely address the nervous system through timing and coordination training. Standard programs focus on increasing the capacity of the musculoskeletal and cardiopulmonary systems for “maximum performance”, whereas task specific timing and coordination training focuses on integrating movement and postures during walking for “optimal performance”. Task specific timing and coordination exercise that includes practice of smooth coordinated aspects of gait over multiple walking conditions has the potential to improve walking ability greater than a standard program. We combined the two interventions to determine if potential gains in mobility from a standard plus timing and coordination program were larger than the gains obtained from the standard program alone. Participants were randomized to either standard strength and endurance exercise or standard plus timing and coordination training. Exercise sessions were one hour, twice a week for twelve weeks. Both interventions resulted in improved gait speed, but there was some evidence for varying intervention effects and maintenance of effects by baseline walking speed. Future research

should more thoroughly examine the timing and sequencing of exercise interventions to improve walking in older adults and finding/targeting those most likely to benefit from different interventions.

Gregory Sawicki, Ph.D., Georgia Institute of Technology

Dr. Sawicki is an Associate Professor of Mechanical Engineering and Biological Sciences at the Georgia Institute of Technology. Sawicki directs the Human Physiology of Wearable Robotics (PoWeR) Lab where the goal is to combine tools from engineering, physiology and neuroscience to discover neuromechanical principles underpinning optimal locomotion performance and apply them to develop lower-limb robotic devices capable of maintaining musculoskeletal structure-function across the lifespan.

Can exoskeletons preserve musculoskeletal structure-function in aging?

Abstract: Older adults walk slower and with higher metabolic cost than younger adults, changes that reduce mobility, independence, and quality of life. Age-related changes in musculoskeletal structural properties offer one potential mechanism for functional declines observed during locomotion. For example, a growing body of evidence indicates that, as we age, in addition to losing muscle mass and strength, the Achilles tendon (AT) becomes more compliant. A more compliant Achilles tendon may push muscles to operate down the ascending limb of the force-length curve where force capacity is diminished, creating a need to increase muscle activation to produce the force and power needed to propel the body forward. The additional metabolic cost of recruiting a larger volume of muscle could partially explain the age-related increase in the metabolic cost of walking.

Elastic exoskeletons could provide a cheap, simple way to restore stiffness about the ankle joint to overcome structural deficits of an overly compliant Achilles tendon. Indeed, in young adults, it is possible to reduce the metabolic cost of walking by 5-7% across multiple speeds by attaching an external tendon, or 'exo-tendon' of intermediate stiffness (~20% of ankle joint quasi-stiffness) in parallel with the plantarflexors. Follow-up studies using dynamic ultrasound imaging reveal that the metabolically optimal 'exo-tendon' stiffness reduces calf muscle force and muscle activity and also shifts muscles to longer lengths, pushing them to operate up the ascending limb where force production is more economical.

Our current NIA-funded research seeks to apply elastic exoskeletons as an intervention to improve the economy of walking on older adults. By tuning 'exo-tendon' properties to fill the gap in Achilles tendon stiffness between an aged user and their 'younger self', it should be possible to simultaneously offload calf muscles while steering them to longer more economical contractile lengths. If successful, this approach could lay a groundwork for physiologically informed prescription of assistive technology and previews the possibility for long-term adaptive systems that can self-tune to a user's changing muscle-tendon properties over time, or even shape internal structures by applying targeted external loads. A number of key scientific and technological hurdles

must be addressed in order to close the loop between musculoskeletal biology and wearable robotic systems. First, low-profile, non-invasive and high bandwidth measurement systems that can track tissue forces and displacements ‘under the skin’ as well as local metabolic activity associated with cell growth/repair are needed. Next, the cyclical stress/strain patterns that drive tissue hypertrophy/atrophy must be better characterized for both muscle and tendon. Finally, streamlined (i.e. portable and comfortable) exoskeleton or exosuit technology with controllers that can apply torque to oppose rather than assist movement will open up the possible for wearable resistance training on-demand.

More broadly, there are a number of underexplored avenues for applying exoskeleton assistive technology to improve mobility in aging. First, studies are needed to examine whether exoskeletons can address facets of locomotion performance beyond improving economy. These include increasing preferred and/or top walking speed, increasing endurance by reducing fatigue, and improving balance/dynamic stability. These objectives may be best served by exploring interventions at multiple lower limb joints (e.g. hip vs. ankle vs. both).

Tibor Hortobágyi, Ph.D., University of Groningen, Netherlands

Dr. Hortobágyi received his PhD in biomechanics and motor control at the University of Massachusetts, Amherst, in 1990. His work focuses on the neuromechanical and cognitive mechanisms of adaptations to exercise interventions in older adults with and without cognitive impairment. He was a professor and director of the Biomechanics lab at East Carolina University, Greenville, NC until 1990. Currently, he is a professor of movement and healthy aging in the Center for Human Movement Sciences, University Medical Center, University of Groningen, The Netherlands.

The effects of exercise interventions on gait biomechanics

Abstract: Biomechanical mechanisms of motor-cognitive interventions-induced mobility improvements in aging Abstract Walking speed declines during natural aging. Gait slowing at midlife is associated with current and future medical and health-related outcomes. The decline is substantially greater in adults with than without metabolic, orthopedic, neurological, and cognitive impairments. There is a strong research impetus to understand how interventions can prevent gait slowing at midlife and maintain or even increase walking speed in older adults with and without metabolic, orthopedic, neurological, and cognitive impairments. However, the mechanisms of how interventions might improve walking speed are not well understood. Because the mechanisms could differ according to participants’ health and medical status, as comprehensive approach is needed. Some of the gaps in our current understanding of the mechanisms underlying gait-slowing during aging with and without impairments are as follows: 1. Kinetic mechanisms of how motor-cognitive interventions improve walking speed; 2. Effects of exercise dose and type on the kinetic mechanisms of increasing walking speed; and 3. Characterization of responders and non-responders to

interventions. RCTs should preferably compare the effectiveness of 1-2 interventions in reducing mobility disability. Address gaps 1-3 comprehensively by assessing: A) gait behavior (kinematics, dynamical systems outcomes); B) inverse dynamics and musculoskeletal modeling in gait conditions with and without motor-cognitive perturbations (gait adaptability, stability); C) muscle contractile function at rest and during contraction (muscle quality, architecture, MR spectroscopy); C) tendon properties (at rest, during gait), and D) multi-array EMG-based motor unit and EMG-EEG-based corticomuscular coherence outcomes during gait, before and after interventions, and after de-training follow-up periods.

Yvonne M. Golightly, PT., MS., Ph.D., University of North Carolina

Dr. Golightly is a musculoskeletal epidemiologist and a physical therapist with 18 years of research experience and over a decade of clinical experience. Her research focuses on risk factors for osteoarthritis, musculoskeletal injury, health equity, physical function, physical activity, biomechanics, and chronic musculoskeletal pain. She is co-Principal Investigator with Dr. Amanda Nelson of two large diverse community-based studies in Johnston County, North Carolina: 1) the Johnston County Osteoarthritis Project, a study of Black and white adults 45+ years old, and 2) the Johnston County Health Study, a study of Black, Hispanic, and white adults 35-70 years old.

Johnson County OA Project; incorporating diversity into study design.

Abstract: Diversity among research participants is essential in order to have generalizable results, to develop and improve treatment approaches that work in all populations, and to allow all populations to experience the benefits of research advancements. The [Johnston County Osteoarthritis Project](#) (JoCoOA) and Johnston County Health Study (JoCoHS) are community-based studies of a diverse community in a predominantly rural county in North Carolina. Since 1991, these studies collected extensive clinical data to provide important new insights into many factors that affect our health. The JoCoOA enrolled 3,187 adults who identified as Black or white aged 45 years or older from 1991 to 1998. An additional 1,015 participants were enrolled during 2003–2004. In 2019, we began enrolling a new group of 3,000 participants for the JoCoHS. The new group includes individuals 35-70 years old who identify as either Black, Hispanic, or white. By recruiting a diverse sample of the community, the data from these studies have contributed significantly to ongoing, national efforts to better understand osteoarthritis and its associated health conditions. Notable findings from this research include: 1) osteoarthritis was more common than originally estimated, and 2) individuals who identify as Black have hip osteoarthritis (contrary to reports prior to this research). Key elements of success in incorporating diversity into research include improving accessibility to facilitate study participation, fostering and maintaining long-standing relationships in the community, building a multicultural research team, balancing political and research design considerations, and having a shared vision between the study team, the participants, and the community.

Jonathan F. Bean M.D., MS., MPH., Harvard Medical School

Dr. Bean is a Professor in the Department of Physical Medicine and Rehabilitation at Harvard Medical School. He is the Director of the New England Geriatric Research Education and Clinical Center (NEGRECC) at the VA Boston Healthcare System and on staff at Spaulding Rehabilitation Hospital. Dr. Bean is an internationally recognized expert in geriatric rehabilitation. His work focuses on developing innovative approaches to care that position rehabilitation as a model of secondary prevention--optimizing independence and preventing disability for older adults.