Examining the Association of Chronic Health Conditions and Adverse Health Outcomes:
Knee OA and Recurrent Falls
Knee OA and Mobility Limitations
Sarcopenia and Fractures

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Abstract

Background: The older adult population is growing. Older age is accompanied by multimorbidity.[1] The declines in physical function and mobility that coincide with aging and chronic conditions is a significant reason that our rapidly growing aging population is a public health concern. [2]

Objectives: This dissertation examined the associations of (1) knee osteoarthritis with recurrent falls (2) knee osteoarthritis with mobility limitations and (3) sarcopenia with fractures (any clinical, hip, and major osteoporotic).

Methods: Study populations included community dwelling adults from the (1) Osteoarthritis Initiative Study (N=4,976, age=45-79 years) and (2) Osteoporotic Fractures in Men Study (MrOS) (N=5,995, mean age= 73.7 (+/-5.9)). Generalized estimating equations were applied to aim 1 and 2 and cox proportional hazards models were applied to aim 3.

Results:

Older adults (≥age 65) with KOA were at higher odds of recurrent falls in comparison to individuals without KOA in models adjusting for known covariates (possible OA OR= 2.22, 95% CI= 1.09-4.52; mild OA OR=2.48, 95% CI= 1.34-4.62; unilateral moderate-severe OA OR= 2.84, 95% CI= 1.47- 5.50; bilateral moderate-severe OA OR= 2.52, 95% CI= 1.13-5.62). Middle aged

adults with KOA did not have increased odds of recurrent falls in comparison to those without KOA except for possible KOA (OR= 1.86, 95% CI=1.01-2.78) (KLseverity*age interaction = 0.025).

Overall, 1,413 men had a fracture during follow-up. Slow walking speed was associated with an increased risk for any HR=1.39, 1.05-1.84; hip HR= 2.37, 1.54-3.63; and major osteoporotic, HR= 1.89, 1.34-2.67 in multi-variate adjusted models. Low lean mass and low grip strength were not significantly associated with fracture.

Conclusion: These findings suggest that there are targetable impairments at the body function and structure and at the activities level of older adults to prevent future limitations in participation and disability. The public health relevance of these findings are that identifying potential earlier impairments that are known to lead to disability may inform prevention efforts to prevent incident cases of disability.

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1.0 Introduction

1.1 Demographic Changes: An Aging World

Transformations in global demography will affect public health over the next decade, as the percentage of adults ≥ 65 years of age is increasing world-wide. [3] The number of older persons in the world is expected to exceed the number of people ≤ 35 years by 2050 for the first time. (Figure 1) [4] In the United States, the Census Bureau estimates that by 2030, one in every 5 Americans will be 65 years and older. Additionally, by 2050, the number of US adults 85 years and older will increase over 3 times the amount from 5.7 million in 2008 to 19 million. [3] As the 'baby boomer' generation (birth year 1946-1965) turns 65, both the absolute and relative numbers of older adults (≥ 65 years) will rise quickly. This change in demography has been termed by some as "squaring off" of the age pyramid. This "squaring off" of the age pyramid is expected to affect the nation's healthcare system due to the morbidity experienced by older adults near the end of life.

Older age is accompanied with multiple chronic conditions and poor health. More than one-half of all older adults have three or more chronic medical conditions.[1] Aging is associated with changes in body composition, such as reduced muscle mass, increased visceral fat mass, and changes in the health and quality of bone. [5, 6] These changes in muscle and bone can lead to chronic conditions such as sarcopenia and osteoarthritis which impact the health and physical function of older adults. [5, 6]. The burden of musculoskeletal disorders, such as sarcopenia and osteoarthritis, are significant as they represent causes of disability world-wide. The cost associated with care for musculoskeletal disorders is greater than the combined cost for breast cancer,

cardiovascular diseases, and stroke care in the United States. [7] The declines in physical function and mobility that coincide with aging and chronic conditions, such as sarcopenia and osteoarthritis, is a significant reason that our rapidly growing aging population is a public health concern. [2] Therefore, it is important to understand the role that sarcopenia and osteoarthritis have on the health and physical function of older adults.

The purpose of this dissertation will be to review the epidemiology of sarcopenia and the most common form of osteoarthritis, knee osteoarthritis. We will specifically aim to investigate the association of sarcopenia on incident fractures and the role of knee osteoarthritis on recurrent falls and physical performance in middle and older aged adults. With the aging population, the number of older adults diagnosed with osteoarthritis is expected to increase. Knee osteoarthritis is the most common form of osteoarthritis, with estimates that 29% of the adult population aged 45 years and older have knee OA. [8] The prevalence of knee osteoarthritis increases with age and is currently not reversible through treatment. The information from this dissertation will aid public health and medical professionals by providing insight into a population at higher risk of falls, fractures, and disability.

1.2 Common Language

The World Health Organization proposed a framework, the International Classification of Functioning, Disability, and Health (ICF) in 2001 to describe function and disability. (Figure 2) The goal of this framework was 4-fold. First, to provide a scientific basis for understanding the varying health statuses, health outcomes, determinants of health, and changes within function

related to health. Second, to establish common language across health professions and improve communication between various users including health care workers, researchers, and the public. Third, to permit comparison of data in a common way across health care disciplines and researchers within and across countries. Fourth, to provide a systematic coding scheme to correspond with the International Classification of Disease (ICD) system.

The ICF model states that function and disability are multi-dimensional and that all persons can have some level of disability. Both function and disability are related to body function and body structures and impairments in both, activity engagement and limitation, participation in life events and restrictions in participation, and the environmental and personal factors that may impact these events. Body function and structures occur at the level of the body for a person. Activity participation occurs at the level of function for a person. Participation occurs at the level of a societal role for the person. Environmental and personal factors may act as barriers or facilitators across these levels. The ICF model is a biopsychosocial model of disability that is both multi-dimensional and interactive.

Use of this framework and understanding the concepts this framework can aid healthcare workers and researchers in utilizing a common language and optimize available prevention and treatments for chronic conditions. Muscle loss in aging, sarcopenia, is a multi-faceted condition that impacts body structure and function by loss of muscle density and strength, that causes challenges in mobility and increases likelihood of falls, which may result in decreased participation in life-events that are important to a person (e.g. attending grandson's birthday party). Interventions that may be aimed at increasing participation may only target one level and may not wholly resolve the limitations and disability experienced. A specific exercise or rehabilitation program may improve function of a body system but may not improve

participation, as this may require more of a behavioral intervention to align with personal and environmental factors. Identifying areas that can be targeted for prevention of disability are important as we enter this demographic transition.

1.3 Conceptual Framework

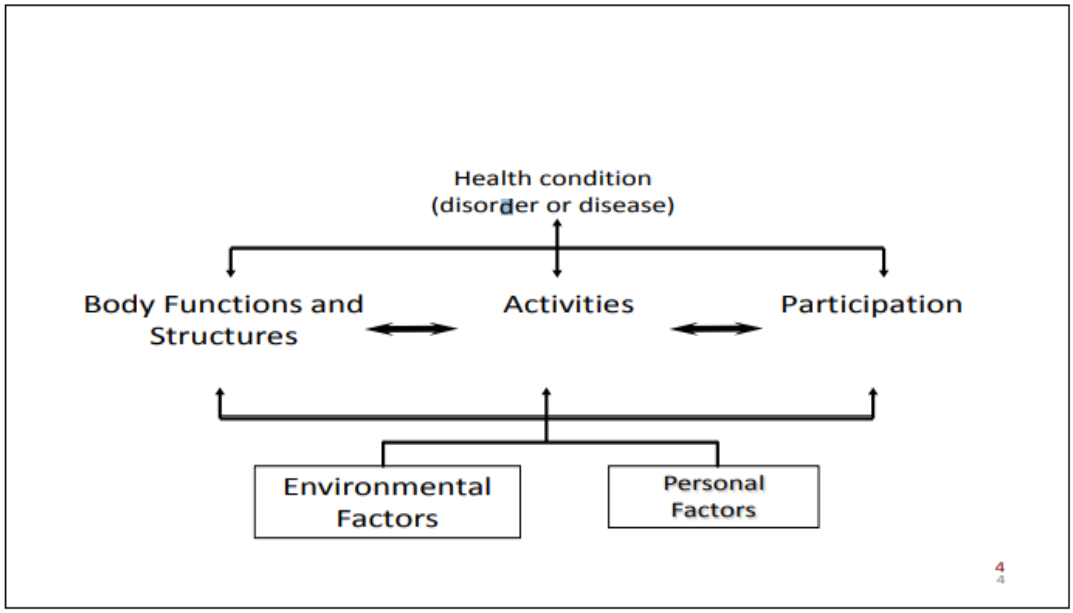


Figure 1. International Classification of Functioning, Disability, and Health Model

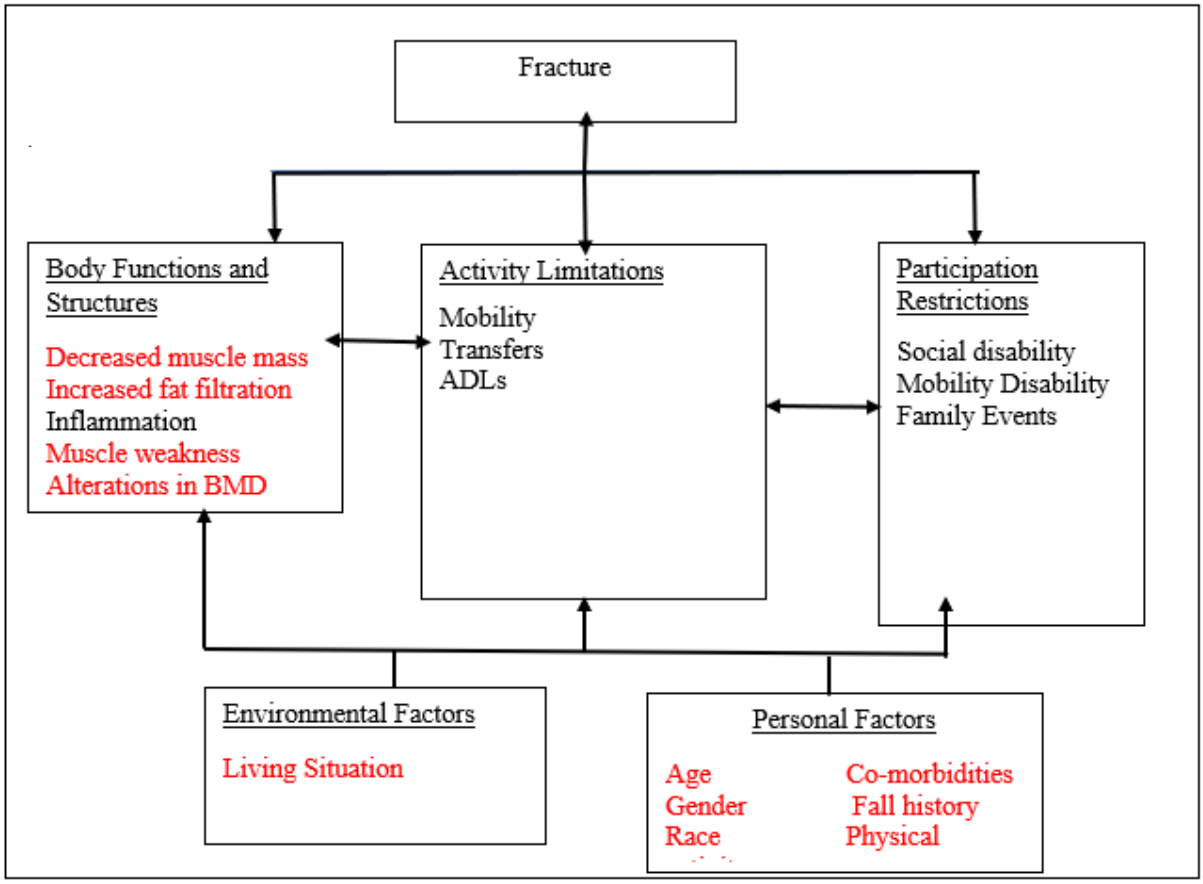


Figure 2. Sarcpenia and Risk Factors for Fracture

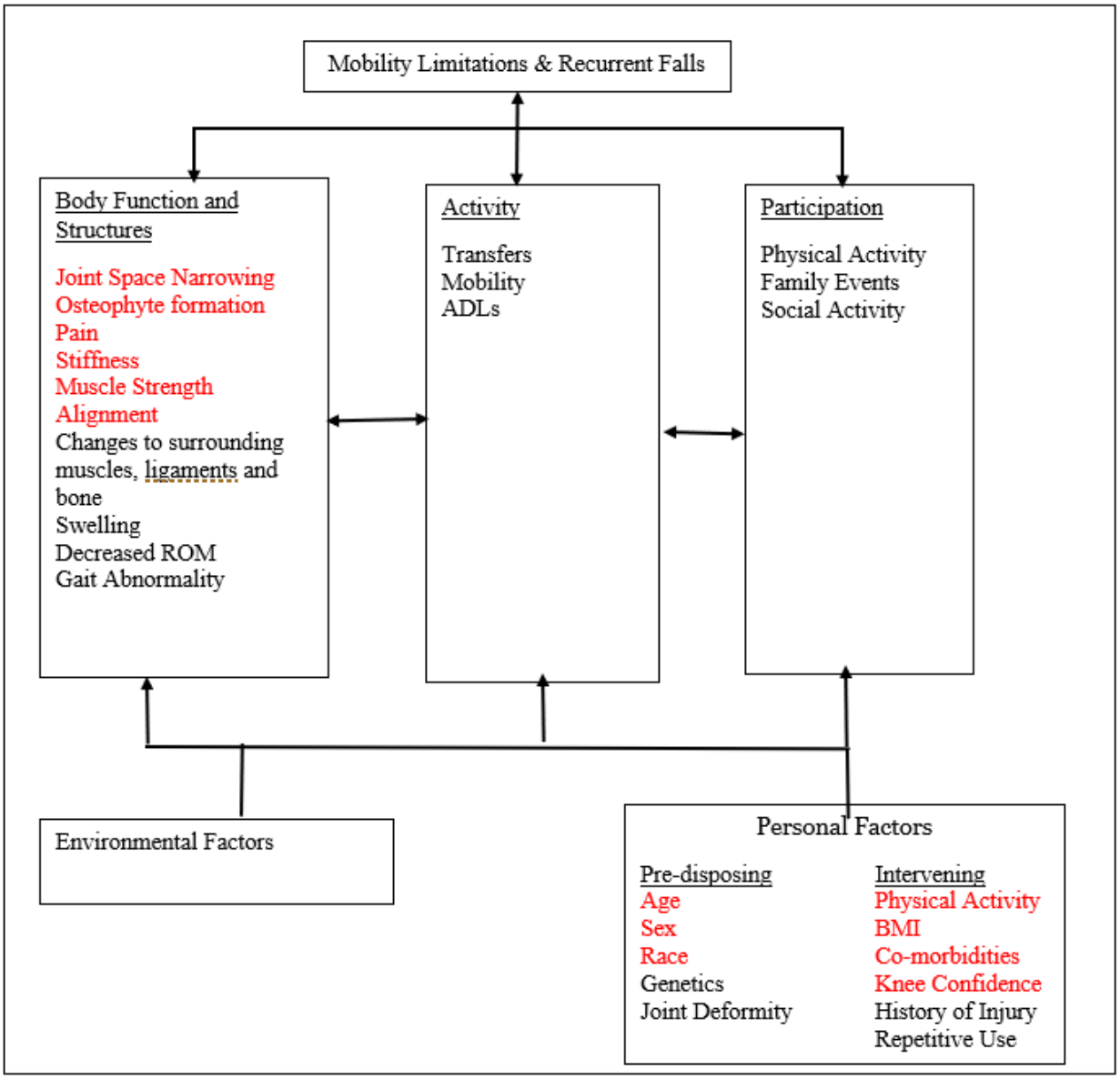


Figure 3. Knee Osteoarthritis and Risk Factors for Recurrent Falls and Mobility Limitations

2.0 Age Related Changes in Body Composition

2.1 Muscle Fibers

As we age, changes occur in the size and number of muscle fibers, the contractility of the fibers, the infiltration of fat into the fibers, and modification to the motor unit. [9-11] Normal muscle is illustrated by a uniform distribution of type I and type II fibers. Type I fibers have higher concentrations of mitochondria, myoglobin, and surrounding capillaries resulting in their ability to be more resistant to fatigue and having higher aerobic capacity. Type II fibers are larger sized fibers and can produce more force with contractions. Type II fibers additionally have quicker contractions and fatigue more easily. [9, 11] Both the amount of muscle fibers and the size of muscle fibers play a role in the decline of muscle mass. Type II muscle fibers are impacted the most in both scenarios. [10, 12, 13] The overall muscle fiber size is 10-40% lower in older adults compared to younger adults. [12] The satellite cell response that normally occurs with signals of damaged muscle is blunted in aging. The chronically increased level of inflammatory marker interleukin-6 mediates this pathway and promotes muscle catabolism. [12] Additionally mitochondrial induced apoptosis may also promote the loss of muscle fibers. [12] Age related changes in muscle fibers contribute to the decline in strength and power in older adults.

2.2 Fat Mass

Aging is also associated with a decline in fat free mass and an increase in fat mass that begins in the fourth decade. [14, 15] Both of these trends continue through to late life when body composition begins to shift again to declines in both fat free and fat mass. [15] The change in cross-sectional area of muscle decreases between the ages of 20-80 by roughly 40%. [13, 16, 17] Relative increases in intra-abdominal fat storage as compared to subcutaneous fat storage occur with aging. [15] Fat distribution however has been shown to vary by gender and race. [18] Women have greater amounts of total body fat than men, generally more subcutaneous fat in the abdominal and gluteo-femoral regions. [19] Men generally have greater amounts of visceral fat tissue, which includes intra-abdominal fat. [19] Asian women tend to have greater amounts of visceral fat tissue as compared to white and African American women while controlling for total body fat. [20] African Americans tend to have less visceral fat than whites, controlling for total body fat. [21] Body composition differences are evident across gender and ethnicity and therefore may contribute differently to the development of sarcopenic obesity.

Research has examined the changes in weight, lean mass, fat mass, and strength with increasing age. Newman et al studied changes in weight and lean mass and demonstrated that older adults lose both lean and fat mass with age. [22] When weight loss occurs in older adults, a greater proportion lean mass is lost in comparison to fat mass support any development of sarcopenic obesity in older adults. This finding was stronger in men, with a 5.8% loss of lean mass with weight loss and a 2.0% gain of lean mass with weight gain. Men who gained weight experienced a 17.9% increase in fat mass. For men who lost weight, there was a 10.6% loss of fat mass. In women, the results are similar with both weight loss and weight gain. For women who lost weight, there was a 5.0% loss of lean mass and 12.7% loss of fat mass. For women who gained weight, there was a

3.0% gain of lean mass and 13.7% gain of fat mass. [22] The difference between gender may be due to women experiencing changes in body composition earlier in life in comparison to men. Changes in body composition were validated in other studies and demonstrate the importance of weight loss in older adults. [14, 23]

2.3 Body Composition Changes and the Association with Muscle Strength

The loss of lean mass may be a predisposing factor for muscle weakness which can lead to functional limitations and disability. Cross-sectional assessment of lower extremity muscle strength however decreases between 20-40% with increasing age, comparing those in their 60s and 70s to those in their 20s and 30s for both women and men. [24-30] Longitudinal assessment of lower extremity muscle strength also demonstrate decline in muscle strength with age. [31] In the Health ABC study, annual percent declines in muscle strength were 4.1% and 3.4% for white and black men and 2.7% and 3.0% for white and black women respectively. [14] The differences in rate of decline were significant between both gender and ethnicity. Men have higher levels of strength at baseline in comparison to women and as a result have more to lose. White men and black women appear to have greater declines in strength in comparison to their counterparts. Additionally, the longitudinal assessment of strength suggests that the rate of decline may be greater than the rates estimated through cross-sectional assessments. The participants included in the longitudinal assessments had a higher baseline age than the participants included in the cross-sectional assessments. The loss of muscle strength may be accelerated in old age and may account for some of the difference between the cross-sectional and longitudinal estimates. Goodpaster et al also demonstrated that the decline in strength is 3 times higher compared to the decline in muscle

mass. [14] The decline in muscle mass has been shown to be associated with a decline in strength; however, this is not a linear association. [14, 32, 33]

The difference between loss of muscle mass and strength with aging suggests that a component of muscle quality is important in this association. [14] Muscle quality is defined as the functional capacity of a tissue and depends on the composition of the muscle tissue and the architecture and structure of the contractile unit. The quality of the muscle is affected by the infiltration of fat deposits. These fat deposits can inhibit the strength of the contraction produced by the muscle. [14, 34, 35] Despite the muscle mass not appreciably decreasing, this compromise of the muscle quality may reduce the amount of force and strength through muscle contraction. [14, 32] Architectural changes include decreased length of the muscle fiber and alteration in the angle of the fiber within the muscle. The result of such changes is reduced force capacity. Understanding the changes in the quality of muscle will aid in identification of adults at higher risk for decline and appropriate treatment to maintain strength.

2.4 "Inflammaging"

Fat deposits and adipose tissue are metabolically active and produce adipocytes and adipokines, as well as other pro-inflammatory markers such as M1 macrophages and senescent cells. [36, 37] [38, 39] [40, 41] The increased inflammatory response is referred to by some as "inflammaging". [38, 39, 42-44] Adipocytes further produce the pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- alpha for example. Adipokines produce hormones, leptin and adiponectin, that up-regulate the inflammatory response. [40] Leptin serves in a negative feedback loop to the hypothalamus to control appetite. With weight gain or obesity, the adipocytes

undergo hypertrophy and activate a cascade of events that reinforce a pro-inflammatory state. [41] In this process it has been shown that levels of leptin will increase and the levels of adiponectin will decrease. [41] This inflammatory response may also contribute to the decline in muscle mass and strength by increasing the ability of lipids to infiltrate the muscle cell. [35, 41, 45, 46] The increases in the number of fat cells within the muscle cell, along with a chronic inflammatory state, have been shown to induce mitochondrial dysfunction. [14, 33] This evidence suggests that a pro-inflammatory state may be a component of decreased strength in persons with increased amounts of fat tissue. [38]

3.0 Definitions of Sarcopenia

The term sarcopenia was coined in 1987 by Rosenberg as the loss of muscle mass that is associated with aging. [47] Multiple age-related processes are associated with accelerated muscle loss including but not limited to muscle fiber denervation, oxidative stress, and decreasing regenerative potential of the muscle cells. [42, 48-50] The age-related processes are thought to be distinct from the age-related decline in physical activity that may result in changes in muscle with age. Based on the current definitions, several algorithms exist that have been proposed to diagnose sarcopenia. While a universally accepted definition of sarcopenia is not available, the clinical relevance of the condition is recognized.

3.1 Basic Epidemiology of Sarcopenia

Each definition of sarcopenia may provide different estimates on the prevalence of the condition. (Table 3 & 4). The prevalence of sarcopenia varies widely from 1 to 52 percent of the older adult population. Variation exists in the prevalence of the condition not only due to the different definitions but also the demographic and characteristics in the populations of older adults represented within the research studies. The cross-sectional assessments of sarcopenia tended to include adults in their 60s and 70s who volunteered to participate, which does not represent the oldest old and frail adults, suggesting a healthy participant bias. The prevalence of sarcopenia shows an increasing trend with increasing age in both men and women. Given that older adults who are healthier than the general population of older adults tend to participate in research studies

an underestimation of the prevalence may exist as these adults may have experienced less atrophy than the regular older adult who has a worse health status and inability to meet the inclusion criteria for the research. Differences arise based on the measurement tools used to calculate total lean mass in the study population as well. Use of bioelectrical impedance in comparison to DXA or CT imaging can produce less accurate results of total lean mass. [51-53] Lack of a consensus definition of sarcopenia and methodology for assessment create challenges, such as who is at risk and in understanding how the condition impacts bone health and risk of falls in aging adults.

3.2 Definitions of Sarcopenia

3.2.1 Baumgartner

The original definition of sarcopenia considered only the amount of lean mass for a given height. Baumgartner originally defined sarcopenia as appendicular lean mass divided by height squared. [54] Cut points for defining sarcopenia were two standard deviations below the referent population mean. The referent population was a younger group of healthy adults and like defining osteoporosis, a cut point of 2 standard deviations below the mean was established.

3.2.2 Newman-Residuals

Improving on the Baumgartner definition, Newman et al also defined sarcopenia using lean mass alone. [55] In this method, appendicular lean mass is adjusted for both fat mass and height.

The 20th percentile of the regression residuals is considered the cut point for sarcopenia. [55] The residuals method has been proven to be a better predictor of functional disability in the Health Aging and Body Composition (Health ABC) and the Framingham cohort. [55] Maintenance of lean mass is important in aging as it is correlated with strength and may represent a target for intervention and prevention of disability. [33, 55, 56]

3.2.3 European Working Group on Sarcopenia in Older People (EWGSOP)

The EWGSOP, in 2009, defined sarcopenia as the loss of skeletal muscle mass and strength associated with risk of negative health outcomes including physical disability, poor quality of life, and mortality. [57, 58] The definition divides total appendicular lean mass by height squared and has set cut points for each gender to define sarcopenia. In addition to low lean mass, persons must have either weakness or slowness as both are considered clinically relevant factors. Grip strength is used as the measure for weakness and usual gait speed is the measure for slowness. A gait speed of 0.8 m/s is indicative of mildly abnormal gait and is associated with the number of predicted years of remaining life at the median life expectancy for most ages and genders. For men and women ages 65-74 years, the mean predicted years of remaining life at 0.8 m/s are 12.6 years and 16.8 years respectively. [59, 60] Gait speed values below 0.8 m/s vs $\geq$ 0.8 m/s have association with poor health outcomes, functional dependence, and institutionalization. [59-62] Stages of sarcopenia have also been developed based on severity- pre-sarcopenia (low lean mass only), sarcopenia (low lean mass and either slowness or weakness), and severe sarcopenia (low lean mass with both slowness and weakness). [57] This practical clinical definition incorporated parameters thought to define the condition of sarcopenia.

3.2.4 International Working Group on Sarcopenia (IWG)

The International Working Group on Sarcopenia defined sarcopenia as the "age-associated loss of skeletal mass and function" and developed a consensus definition at that time. [63] [64] The operational definition divides total appendicular lean mass by height squared and has set cut points for each gender to define sarcopenia as with the definition developed by Baumgartner. Physical performance in this definition was measured through usual gait speed alone. A gait speed less than 1.0 m/s defined poor physical performance. [64] Gait speed that is greater than 1.0 m/s is associated with survival that is longer than expected for age and gender (5 year survival gait speed overall for men & women 65-74 years: 87 years (95% CI= 82-91) for men; 93 years (95% CI= 91-94) for women; 5 year survival gait speed ≥ 1.0 m/s for men & women 65-74 years: 90-95 years (95%CI= 85-97) for men; 96-97 years (95% CI= 94-97) for women). [59] The IWG developed a concise clinically practical definition of sarcopenia that could be adopted in research and medical settings to screen all older adults who have declines in strength, function, and health status.

3.2.5 Foundation for the National Institutes of Health Sarcopenia Project (FNIH)

The FNIH definition of sarcopenia uses data driven cut-points of weakness and low lean mass and applies these standards to populations that are at increased risk of functional limitations (Age, Gene/Environment Susceptibility- Reykjavik Study, Boston Puerto Rican Health Study, 6 clinical trials from the University of Connecticut, Framingham Heart Study, Health, Aging, and Body Composition Study, Invecchaire In Chianti Study, Osteoporotic Fractures in Men (MrOS) Study, Rancho Bernardo Study, & The Study of Osteoporotic Fractures: N= 26, 625; mean age

76.6 years; 41% gait speed ≤0.8 m/s). [65] The project additionally sought to determine whether the low lean mass and weakness criteria were able to predict future mobility limitations in older adults. [66] The equation used for low lean mass accounts for both height and weight through body mass index. This algorithm accounts for the effect of fat mass. Only weakness is included in this definition with data driven clinical cut-points using pooled data from 9 different cohort studies, which is the broadest sample to define sarcopenia, all older adults may not be represented here. [67, 68] The use of a large diverse sample size and multiple validation analyses to maximize sensitivity are strengths of this definition. The use of more stringent clinical criteria minimizes the number of false positives. The FNIH project advances research in this area by developing a validated clinical definition of the condition.

3.2.6 European Working Group on Sarcopenia in Older People 2 (EWGSOP-2)

The EWGSOP met again in 2018 to update the original definition that had been proposed to reflect the updates in research. The EWGSOP2, has developed an algorithm to be more clinician friendly. [69] The pathway would be initiated with a questionnaire, SARC-F. This is a self-report 5-item screen for sarcopenia risk, with all 5 questions based on physical function and ability. The questionnaire was validated in the African American Health Study, Baltimore Longitudinal Study of Aging, and the National Health and Nutrition Examination study. The SARC-F questionnaire has low-moderate sensitivity and high specificity to predict low muscle strength (50% sensitivity and 86% specificity). [70] The questionnaire would be best suited for persons with high risk of negative health outcomes. Following a positive SARC-F, an assessment of muscle strength would be next. If low muscle strength is found, this would be considered ‘probable sarcopenia’. To confirm, examination of muscle quantity or muscle quality would happen. Low quantity or quality

would confirm the sarcopenia. A physical performance measure, such as gait speed, SPPB, TUG, or 400-meter walk test, could be performed to grade the severity of the condition. [69] While the alteration to the initial definition of sarcopenia, appears to be more clinician-friendly, future use and resultant outcomes of this algorithm will prove its usefulness of this new tool.

3.2.7 Strength and Limitations

Table 1 summarizes the definitions of sarcopenia. Volume of lean mass is the consistent component across all definitions. However, the relevant cut points for lean mass vary. The Baumgartner, EWGSOP, and IWG definitions use total appendicular lean mass divided by height squared. This definition to determine lean mass may not be as successful at predicting future disability because it does not consider fat mass, which is accounted for in the Newman Residuals and FNIH definitions. [55] Weakness is incorporated in the EWGSOP and FNIH definitions but with different defining cut-points. The FNIH cut-point for weakness is <26 kg for men has been shown to predict the odds of slow gait speed (≤0.8 m/s) (OR=2.91 (95% CI=2.02-4.17) and the inability to complete 5 sit-to-stands (OR=2.35, 95% CI=1.56-3.55). [67] Using the pooled data from the FNIH Sarcopenia Project, different grip strength measures were compared (<26 kg for men vs 26-32 kg for men). The cut-point of <26 kg predicted the odds of mobility impairment 7.62 (95% CI=6.13-9.49) as compared to men with grip strength >26 kg. The cut point range of 26-32 kg predicted the odds of mobility impairment for men as 3.63 (95% CI=3.01-4.38) compared to those with greater grip strength values. [68] For women, similar results were found. A cut-point of <16 kg predicted the odds of mobility impairment 4.42 (95% CI= 3.94-4.97) as compared to women with grip strength > 20 kg. The cut point range 16-20 kg predicted the odds of mobility impairment for women as 2.44 (95% CI= 2.20-2.71) compared to those with grip strength values

>20 kg. [68] This indicates that grip strength in adults with low lean mass, while a measure of upper extremity strength, is a good indicator of the likelihood of mobility impairment. These cut points by the FNIH did not establish if these defined cut-points independently predicted other important outcomes such as falls, fractures, and mortality. As for the differences in grip strength cut points, both values (FNIH & EWGSOP) are associated with mobility disability with FNIH establishing a more restrictive definition. The EWGSOP and the IWG definitions incorporate gait speed as a component. The IWG cut-point of <1.0 m/s for gait speed demonstrates a difference between "healthy" aging and not while EWGSOP selected a more stringent cut-point of ≤0.8 m/s to signify slowness due to its association with mortality. [59] The Sarcopenia Definition and Outcomes Consortium (SDOC) met in late 2018 and developed standardization to identify older adults that may be at risk for negative clinical outcomes. [71] The SDOC concluded that both weakness, defined by grip strength, and slowness, defined by usual gait speed, should be included in the definition of sarcopenia but there not was not consensus regarding the use of DXA derived lean mass in the definition. [72] Variation exists regarding the clinical definition of sarcopenia, with growing concern regarding the use of DXA defined lean mass is not an accurate assessment of lean mass and more novel methods (D_3-Cr) may become the gold standard. [71, 73, 74]

3.2.8 Comparison of Definitions

Table 1. Definitions of Sarcopenia and Criteria for Men

Name	Lean Mass	Weakness	Slowness	Summary
Baumgartner (1998)	ALM/ht^2 ≤ 7.23 kg/m^2	NA	NA	Low lean mass (2 standard deviations below referent mean value)
Residuals (2003)	Residual – Predicted ALM	NA	NA	Lean mass adjusted for height & fat
EWGSOP (2009)	ALM/ht^2 ≤ 7.23 kg/m^2	Grip Strength <30 kg	Gait Speed ≤ 0.8 m/s	Low lean mass + slowness or weakness
IWG (2011)	ALM/ht^2 ≤ 7.23 kg/m^2	NA	Gait Speed <1.0 m/s	Low lean mass + slowness
FNIH (2014)	ALM/BMI < 0.789	Grip Strength <26 kg	NA	Low lean mass + weakness
EWGSOP 2 (2018)	ASM/ht^2 <7.0 kg/m^2	Grip Strength <27 kg	Gait Speed ≤ 0.8 m/s	(+) SARC-F + weakness + low lean mass

EWGSOP: European Working Group on Sarcopenia, IWG: International Working Group on Sarcopenia, FNIH: Foundation of National Institute on Health Sarcopenia Project; ALM: Appendicular Lean Mass, ht: height

Table 2.Definitions of Sarcopenia and Criteria for Women

Name	Lean Mass	Weakness	Slowness	Summary
Baumgartner (1998)	ALM/ht^2 $\leq$ 5.45 kg/m^2	NA	NA	Low lean mass (2 standard deviations below referent mean value)
Residuals (2003)	Residual – Predicted ALM	NA	NA	Lean mass adjusted for height & fat
EWGSOP (2010)	ALM/ht^2 $\leq$ 5.37 kg/m^2	Grip Strength <20 kg	Gait Speed $\leq$ 0.8 m/s	Low lean mass + slowness or weakness
IWG (2011)	ALM/ht^2 $\leq$ 5.67 kg/m^2	NA	Gait Speed <1.0 m/s	Low lean mass + slowness
FNIH (2014)	ALM/BMI < 0.512	Grip Strength <16 kg	NA	Low lean mass + weakness
EWGSOP 2 (2018)	ASM/ht^2 <5.5 kg/m^2	Grip Strength <16 kg	Gait Speed $\leq$ 0.8 m/s	(+) SARC-F + weakness + low lean mass

EWGSOP: European Working Group on Sarcopenia, IWG: International Working Group on Sarcopenia, FNIH: Foundation of National Institute on Health Sarcopenia Project, ALM: Appendicular Lean Mass, ht: height

Table 3. Prevalence of Sarcopenia Across Definitions

[54] [58, 75]

Definition	Study Population	Prevalence %
Men		
Baumgartner	New Mexico Elder Health Study Community-dwelling, Non-Hispanic white (48%) & Hispanic, Mean age=73.6 years 48% women N=808 (n_{men}= 426)	(70-74 yrs) 19.8 (non-Hispanic white) 18.3 (Hispanic)
		(75-80yrs) 26.7 (non-Hispanic white) 36.4 (Hispanic)
		(>80 years) 52.6 (non-Hispanic white) 57.6 (Hispanic)
Baumgartner	Framingham Heart Study Community-dwelling 100% white	19

	Mean age=78.2 ± 4.3 years (range= 72-92) 64% women N=766 (n_{men}=274)	
Residuals	Framingham Heart Study Community-dwelling 100% white Mean age=78.2 ± 4.3 years (range= 72-92) 64% women N=766 (n_{men}=274)	25
Residuals	Health Aging & Body Composition Cohort Community-dwelling 52% women 41% Black Mean age = 73.6 ± 2.9 years (range=70-79) N=2984 (n_{men}=1435)	20
FNIH	NHANES 1999-2004 Community-dwelling 51% female Mean age=70.5 ± 0.18	(60-69 years) 20.9 NH Whites=19.8

	N=4984 (n_{men}=2453)	NH Blacks=4.3 Hispanic= 43.5
		(70-79 years) 32.4 NH Whites=31.2 NH Blacks=18.1 Hispanic= 54.8
		≥ 80 years 41.9 NH Whites=42.0 NH Blacks=19.1 Hispanic= 62.6
EWGSOP & EWGSOP 2	Korean Frailty and Aging Cohort Study (KFACS) Community-dwelling Mean age=75.9 49.8% women N=2,099	EWGSOP Overall 20.8 Men 25.5 EWGSOP 2 Overall 9.3 Men 11.9
Women		
Baumgartner	New Mexico Elder Health Study	(70-74 years)

	Community-dwelling Non-Hispanic white (48%) & Hispanic, Mean age=73.7 years 48% women N=808 (n_{women}=382)	33.3 (non-Hispanic white) 35.1 (Hispanic)
		(75-80 yrs) 35.9 (non-Hispanic white) 35.3 (Hispanic)
		(>80 years) 43.2 (non-Hispanic white) 60.0 (Hispanic)
Baumgartner	Framingham Heart Study Community-dwelling 100% white Mean age= 78.7 ± 4.4 years (range= 72-92) N=766 (n_{women} =493)	13
Residuals	Framingham Heart Study Community-dwelling 100% white Mean age=78.7 ± 4.4 years (range= 72-92)	24

	N=766 (n_{women} =493)	
Residuals	Health Aging & Body Composition Cohort Community-dwelling 52% women 41% Black Mean age = 73.6 ± 2.9 years (range=70-79) N=2984 (n_{women}=1549)	20
Baumgartner	Epidemiologie de l'Osteoporose Study Community-dwelling 100% women Mean age = 80.5 ± 3.9 N=2725	10.4
Residuals	Epidemiologie de l'Osteoporose Study Community-dwelling 100% women Mean age = 80.5 ± 3.9 N=2725	20
EWGSOP	Epidemiologie de l'Osteoporose Study	5.2

	Community-dwelling 100% women Mean age = 80.5 ± 3.9 N=2725	
IWG	Epidemiologie de l'Osteoporose Study Community-dwelling 100% women Mean age = 80.5 ± 3.9 N=2725	14.3
FNIH	NHANES 1999-2004 Community-dwelling 51% female Mean age=71.6± 0.25 N=4984 (n_{women}=2531)	(60-69 years) 14.1 NH Whites=13.4 NH Blacks=3.5 Hispanic= 32.9
		(70-79 years) 21.6 NH Whites=20.7 NH Blacks=8.5 Hispanic= 48.4
		≥ 80 years

		27.2 NH Whites=28.0 NH Blacks=8.6 Hispanic= 30.5
EWGSOP & EWGSOP 2	Korean Frailty and Aging Cohort Study (KFACS) Community-dwelling Mean age=75.9 49.8% women N=2,099	EWGSOP Overall 20.8 Women 16.2 EWGSOP 2 Overall 9.3 Women 6.7

3.3 Methods to Assess Body Composition in Older Adults

Several tools are available to identify amounts of lean and fat mass. These include computed tomography (CT), magnetic resonance imaging (MRI), dual energy x-ray absorptiometry (DXA), bioelectrical impedance (BIA), anthropometric measurements as common practical options, and D_3-creatine dilution method (D_3-Cr) as a novel approach to assessment of muscle mass.

3.3.1 Imaging

CT and MRI both discern fat from other soft tissue within the body. Because of this, these tools are considered a gold standard for lean tissue assessment. However, the high radiation, high expense, and limited accessibility are reasons that neither is used commonly in clinical or in large scale research settings. [57] DXA is considered the most common and reliable technique used to measure body composition. DXA imaging provides fat and lean mass data on the entire body. [57, 76, 77] DXA additionally does not expose persons to the high radiation levels making it a safer option. Some limitations in using DXA exist. DXA assumes that all fat free mass has the same hydration which may not be accurate in persons with chronic disease. Vital organs and other non-fat soft tissue are also included in the lean mass measurement. A weight limitation for use of the machine prohibits very large persons from testing. [78] The size of the subject may introduce bias in the fat and fat free mass result based on the influence of the depth of the tissue. Fat that is located within the muscle fibers is not detailed with the DXA measurement either. [78, 79] Nevertheless, DXA has become commonly accepted and utilized tool body composition.

3.3.2 Bioelectrical Impedance

Bioelectrical impedance measures fat and lean mass. BIA bases measurements on the concept that water conducts electricity and fat does not. Total body water, fat-free mass, fat mass, and percentages of fat and appendicular lean mass can be obtained through BIA. Prediction equations that are specific for gender and ethnicity with reference values have been established. [80, 81] The prediction equations used in these methods, particularly with older adults or obese adults, are not the most accurate methods due to differing volumes of water within tissues in these

populations. The differences in hydration will bias the results of total lean and or fat mass creating inaccurate results. [51, 52] BIA is not as commonly used given the higher accuracy of DXA scans.

3.3.3 Anthropometric

Anthropometric measurements are the simplest and cheapest methods available to indirectly measure body composition. These methods include measuring height, weight, skin folds, and waist circumference. Body mass index is calculated by dividing weight by height squared and can determine if an individual is underweight, normal weight, overweight, or obese. BMI is an indirect measure of body fat and has been shown to have fair to good correlation with it (males $r=0.44- 0.75$, $p<0.01$; females $r=0.71-0.82$, $p<0.01$). [82, 83] BMI does not provide detail regarding body composition. [84-86] BMI may not be the most reliable method to measure obesity in older adults as it may provide inaccurate estimates because of the loss of height. [83, 85, 87, 88] Using BMI $\geq$30 kg/m^2 to define obesity, has a sensitivity of 43% and specificity of 96% to detect an obese body fat percentage obesity (>25% for men and >35% for women). [83] Waist circumference is another type of anthropometric measurement established by the World Health Organization as high cut-points of 88 centimeters for women and 102 centimeters for men that indicate increased risk for poor health outcomes. [89-92] Waist circumference measurements may present methodological challenges as variation in how the measurement is performed. Standards for obesity using waist circumference vary based on gender and race. While anthropometric measurements are simple and effective in clinical and research settings, these tools do not provide the detail of body composition and are not preferred when studying body composition.

3.3.4 D_3-creatine dilution method (D_3-Cr)

The novel method of D_3-Cr may be the most accurate measure to assess muscle mass. In this process a person ingests creatine (deuterium) and excretes D_3-Cr in urine after approximately 30 hours. [93] Creatine in the body is converted into creatinine and is not synthesized in the muscle. 95% of the creatine in our bodies is found in muscle, making this type of assessment a likely estimator of the muscle mass in our body.[93] The assumption of this method is that D_3-Cr solution is 100% bioavailable and transported to the contractile fibers within the muscle. The amount of creatinine excreted in the urine is used within an equation to determine the creatine pool within skeletal muscle, giving an estimation of muscle mass. Muscle mass estimates from this method have strong correlation with MRI and found to be more accurate than DXA. [94] In cross-sectional analyses from the Osteoporotic Fractures in Men Study (MrOS), older men with the lowest amount of muscle mass per body weight measured by this method, have the highest risk of incident mobility limitations and falls. [95]

3.3.5 Strength and Limitations

Determining the risks and benefits to each tool is important in developing methods for research and for comparison of findings. While CT and MRI measures provide the most detail on body composition these tools are not common in large scale epidemiologic studies because of the cost and risk. DXA was not originally designed to measure fat and lean mass, but it has become a widely accepted tool in cohort studies despite previously mentioned limitations. Anthropometric measures are common to epidemiological studies because of the efficiency, low cost, and low risk

but lack detailed body composition information. No measurement tool of body composition has been universally accepted in the aging populations given the strengths and limitations of each one.

3.4 Methods to Assess Strength and Function in Older Adults

Measures of muscle strength and performance are components of newer definitions of sarcopenia. Common measurements of strength in older adults are grip strength and lower extremity isokinetic muscle strength. Common measurements of physical performance in older adults are usual gait speed and the Short Physical Performance Battery (SPPB). Tests of muscle strength and physical performance have been included into definitions of sarcopenia to help characterize clinical aspects of the condition.

3.4.1 Grip Strength

Handgrip strength is a measure of upper extremity strength. However, handgrip strength is often used in epidemiological studies as an indicator of overall muscle strength. As weakness tends to be correlated throughout the body with aging, this is a simple measure to employ. [96, 97] In the assessment, isometric maximal force is applied to the dynamometer. [98] Hand grip dynamometry correlates well with lower extremity power, knee extension torque, and calf muscle mass area. [99-102] Hand grip strength is also associated with self-reported activities of daily living disability and mortality. [99] Grip strength is easy to administer in both clinical and research settings and most older adults are able to complete this test thus minimizing missing data.

3.4.2 Lower Extremity Isokinetic Strength

Lower extremity muscle strength may also be reliably measured through knee flexion or extension isokinetic tests. [96, 103] In the Health, Aging, and Body Composition study (Health ABC), assessment of quadriceps strength was performed using the Kin-Com isokinetic system, though the reliability of strength assessment with this method has not been established in older adults. These methods are not common in clinical settings due to the need of special equipment (e.g. Biodex machine), the time to complete the tests, and certain co-morbidities may preclude testing (e.g. recent total knee replacement, stroke, advanced osteoarthritis). [57]

3.4.3 Short Physical Performance Battery (SPPB)

The SPPB is based on 3 components- balance tests (stand with feet together, stand with feet semi-tandem, and stand in full tandem), usual gait speed, and chair stands. Established cut-points have been determined to measure high and low physical function. [104] Use of the SPPB is recommended by the International Working Group on Sarcopenia (IWG) as part of the screening process for sarcopenia. [63] The SPPB is a well-established, reliable, and valid measure of mobility; however, it does have a ceiling effect for adults with higher levels of function. The SPPB may not be sensitive to change in adults with higher or lower levels of function over time. [105]

3.4.4 Gait Speed

Usual gait speed is a common, simple clinical measure that can be used with many older adults to assess their function. Slow usual gait speed (<1.0 m/s) has been associated with disability,

poor health outcomes, and mortality. [59, 106] Changes in gait speed over time of 0.1 m/s can indicate a decline in self-reported function (each 0.1 m/s faster HR=0.92; $p<0.001$) and increased 5 year mortality (each 0.1 m/s faster HR=0.90; 95% CI= 0.89-0.91). Strengths of usual gait speed are that it can be used as a measure of physical performance, a predictor of disability and mortality, and can detect small change over time. The European Working Group on Sarcopenia in Older People, IWG and SDOC recommend usual gait speed measurements in their diagnosis of sarcopenia. [57, 64, 71] Measures of physical function and performance are valid tools that provide additional information (i.e. balance) and are commonly used in both clinical and research settings with older adults.

3.4.5 Strength and Limitations

Grip strength has been used more widely in epidemiological studies due to ease of administration and few exclusion criteria in comparison to other tools that measure strength and power such as a biodex or leg press machine. A limitation with use of grip strength is that it is a measure of upper extremity strength alone. With measures of lower extremity strength, limitations include the positioning required during testing, the rigor required to perform the test, and the common medical co-morbidities that all may exclude participants from completing the measure. This may result in higher amounts of missing or potentially unreliable data based on the assessment protocol. Measures of strength do not include assessment of muscle power which is an important contributor to mobility limitations in adults. [107-109] Measures of physical function and performance, such as the SPPB and gait speed, have been most readily adopted in rehabilitation and research settings because of their ease of use, the brief time required to administer the tests, and the predictive ability for major geriatric outcomes. [59, 62, 110, 111] Also, performance-based

tests are composed of activities that are common to daily life in older adults and may provide information regarding whole body functioning. Each measurement of strength and physical function adds value to the assessment of older adults by identifying areas that can be addressed through routine clinical interventions.

3.5 Strength and Limitations

In summary, the various definitions of sarcopenia create challenges when comparing the literature for varying health outcomes and for prevalence of the condition. For medical professionals, this variation presents challenges in diagnosis and how the risks associated with the condition will impact patients. Generally, sarcopenia has not been recognized as a medical/billing code until the updated ICD-10 version (code: M62.84), which may aid in the advancement of research and treatment by removing a previous barrier. [112] The work in this dissertation will add to the literature through comparison of the components of sarcopenia definitions and their association with clinically relevant outcome of fractures.

4.0 Factors Contributing to Declines in Muscle Strength in Aging

Many factors can influence alterations in muscle strength that are attributed to the aging process. Muscle structure changes as type 1 fibers (slow twitch) increase and type 2 fibers (fast twitch) decrease.[113] Aging also reduces the size, elasticity, and power of all muscle tissue. Muscle tolerance for exercise can also diminish, causing muscle to fatigue at a faster rate. [113] These physiologic changes in muscle can lead to decreased function and may contribute to poor health outcomes.

4.1 Atrophy from Disuse

Declines in total energy expenditure due to lower physical activity likely cause disuse atrophy in muscle. In 2007, 51.2 % of US adults age 65 and older self-report regular physical activity, which is lower in comparison to those 18-24 years (74%). [114] This decline may translate into functional declines over time. [115] Muscle atrophy leads to a decline in resting and activity metabolic rates in adults. [116] These changes may perpetuate a cycle of weight gain or increases in fat mass. Common chronic diseases such as cancer, diabetes, and renal failure may also contribute to muscle atrophy. [117-119] Muscle atrophy may occur as a result of various causes and is a concern in aging adults.

Muscle atrophy can occur as a result of aging. Muscle mass decreases approximately 3–8% per decade after the age of 30 and this rate of decline is even higher after the age of 60. In 1,880 participants from the Health ABC cohort over 3 years follow up, decline occurred in total

lean mass across both genders that was significantly different. The mean kg change in overall lean mass was -0.87 ± 1.96 for white men, -1.19 ± 2.30 for black men, -0.31 ± 1.49 for white women, and -0.30 ± 1.97 for black women ($p<0.001$ for gender difference). The mean kg change in leg lean mass was -0.27 ± 0.47 for white men, -0.37 ± 0.54 for black men, -0.16 ± 0.36 for white women, and -0.21 ± 0.47 for black women ($p <0.001$ for gender difference; $p = 0.001$ for race difference). [14] The loss of leg lean mass was significantly different in men vs women and in white vs blacks and may contribute to future functional decline. In a small sample of community-dwelling older adults (n=12) comparing pre intervention to post 10 days bed rest, a significant decline occurred in whole body lean mass (-1.50 kg, p=0.004), lower extremity lean mass (-0.95 kg, p=0.003), and isometric lower extremity strength (-15.6 newton-meters/second, p=0.001). [120] An additional study examining the effects of bed rest (N= 23, 5 days of bed rest) demonstrated that healthy community dwelling older adults (60-75 years) had nearly a 4% decrease in leg lean mass and 11% decrease in isometric leg strength in comparison to young adults (18-35 years) that was statistically different. [121] Following the best rest, both groups underwent high intensity resistance exercise rehabilitation for 8 weeks. The older adults regained leg lean mass and isometric strength to pre-bed rest levels. The young adult group gained greater amounts of leg lean mass in comparison to baseline levels. [121] The results are not generalizable as this is a small sample of "healthy" older adults but the results demonstrate that muscle atrophy occurs with limited activity in a short period of time. The results also demonstrate that the skeletal muscle can recover from the losses induced from bed rest with high intensity resistance training. Differences exist in the loss of lean mass in older adults across gender and race, which may contribute to differences in lower extremity function and risk of fracture. Gaining understanding

on this association is important because potential exists to intervene and prevent further decline in at-risk older adults.

4.2 Insulin-Resistance

Insulin resistance (IR) increases with age and obesity. IR acts on a cellular level to impair muscle mass and strength as glucose in necessary for adequate muscle contraction. IR increases mitochondrial dysfunction, impairs oxidative capacity, creates a state of hyperglycemia, and increases reactive oxygen species production. [115, 122] Declines in physical activity that are common in aging, also play a role in declining strength. Decreased levels of physical activity will decrease the total energy expenditure and may increase insulin resistance. Insulin resistance also results from the increased release of fatty acids that in turn cause insulin-receptor dysfunction. [115, 123] A pro-inflammatory state can also mediate insulin resistance in obese persons through the pathway between cytokines and insulin receptors. [41] Insulin resistance in obese adults may promote muscle catabolism through the action of insulin on protein, which can produce a catabolic state. [122] IR has a negative impact on health and increases the risk of type 2 diabetes.

Insulin resistance results in loss of lean mass and strength. Lee et al reported a greater loss of lean mass and appendicular lean mass in community-dwelling older adult men with diabetes in comparison to men without diabetes. Men with IR had greater odds of higher lean mass (OR=2.09, 95% CI=1.60-2.73) and appendicular lean mass (OR=1.59, 95% CI=1.27-1.95) loss in models adjusted for age, race, clinic site, weight, physical activity, change in physical activity, and medications. [124] Park et al demonstrated that men with diabetes were weaker than those without diabetes despite having greater muscle mass in both their upper and lower extremities. In analyses

adjusted for age, race, clinic site, physical activity level, BMI, number of co-morbidities, vision, renal insufficiency, and lifestyle factors, for men with diabetes, upper extremity strength (β= -0.5 SE=0.16, p=0.002) and lower extremity strength (β= -0.8 SE=0.22, p<0.001) was negatively associated with diabetes. [125] In the same Health ABC cohort, women with diabetes, despite greater muscle mass were not stronger than women without diabetes (upper extremity β=-0.84, SE=0.22, p=0.11 and lower extremity β=-.015, SE=0.24, p=0.524). [125] In the sex-specific models, BMI attenuated 17-37% of the association between diabetes and muscle strength in men and 49-69% of the association with muscle quality. The overall results indicate that muscle strength and muscle quality are diminished in men and women with diabetes compared to those without diabetes. [125] Barzilay et al reported from the Health ABC study that isometric quadriceps strength per kilogram of muscle mass was negatively (r= -0.089) associated with insulin resistance (defined by homeostasis model assessment (HOMA)) in non-diabetic ambulatory community-dwelling men independent of total body fat mass, level of reported physical activity, age, impaired fasting glucose, and quadriceps muscle fat content (p<0.001). [126] Results from the InCHIANTI study, show a sex-specific negative correlation between strength (grip) and insulin resistance (HOMA-IR) in women with r= -0.140 (p=0.02). In adjusted linear regression for the association with grip strength, the highest tertile insulin resistance had a greater negative association (β= -10.087 SE=4.52, p=0.027) compared to the lowest tertile for women only. [127] These results suggest that IR in old age may be associated with sarcopenia, low lean mass and weakness.

4.3 Sex-steroid Hormones

Low muscle strength has been associated with low levels of anabolic hormones, such as testosterone and growth hormone, and this may contribute to muscle impairment. [128-130] Testosterone is considered the primary anabolic steroid and is associated with increased muscle protein synthesis, muscle mass, and strength. A decline in testosterone may reduce protein synthesis and as a result decrease muscle mass. A small double blind RCT (n=50, ≥65 years) that followed men for 36 months reported that men receiving testosterone or testosterone + finasteride had greater increases in lean mass and strength in comparison to men on the placebo. The changes in lean mass were nearly 4 kg greater in both groups receiving testosterone (testosterone only 3.77 ± 0.55, testosterone + finasteride 3.64 ± 0.56. placebo -0.21 ± 0.55 $p<0.0001$). The increases in grip strength were 4-5 kg greater in the groups receiving testosterone ($p<0.05$). [131] In the Testosterone Trials of males ≥ 65 years, no significant difference was found between the placebo and treatment group regarding physical function tests but self-perceived walking ability was higher in the treatment group compared to the placebo group. (effect size=0.15, p=0.002). [130] A decline in anabolic hormones with age in men may be associated with their significantly greater loss of lean mass in comparison to women and may increase their likelihood of experiencing pre-clinical mobility limitations, fall events, and risk of fracture.

Insulin like growth factor is important for growth within the body. Swiecicka et al reported from 4.3 years of follow up in the European Male Ageing Study (n=3,369, age 40-79 years) that insulin-like growth factor was associated with a frailty phenotype and frailty index. The odds for a worsening frailty phenotype for a 1 standard deviation increase in insulin-like growth factor was 0.82 (95% CI=0.73-0.93). This association was attenuated when the models were adjusted for its binding protein. The results suggest an association between non-androgenic anabolic hormones

and weakness or frailty. Results from a 26-week RCT including both older adult men and women (n=131, 65-80 years) reported an increase in lean body mass and decrease in fat body mass with growth hormone alone and in conjunction with sex-steroids ($p<0.001$). Lean mass in women had the highest increase in the growth hormone + hormone replacement therapy (2.1 kg) followed by hormone replacement therapy (2.1 kg), growth hormone (1.0 kg) and lastly placebo (0.4 kg). [132] Lean mass in men had the highest increase in the growth hormone + testosterone (4.3 kg) followed by growth hormone (3.1 kg), testosterone alone (1.4 kg) and lastly placebo (0.1 kg). [132] Changes in strength were not significant for men or women. Hormone levels may have a greater impact on the volume of lean mass in comparison to strength. Alterations in sex-steroid hormones are another contributing factor to declines in lean mass and strength in aging adults.

The age-related decline in sex-steroid hormones and decline in mechano-transduction between low lean mass and bone are potential important etiologies that may be mechanisms for fracture and fall risk. The impact of the declining levels of sex-steroid hormones may not directly impact physical function potentially because in addition to strength other factors such as, balance, proprioception, and neuromuscular control are involved in functional activities.

5.0 Knee Osteoarthritis (OA)

Knee OA is a chronic condition and a major contributor to physical limitation in the United States. [133, 134] Knee OA accounts for 15-16% of disability related to stair climbing, walking, and household activities and is as great as that of cardiac disease and higher than any other medical condition in older adults (% of disability attributed to heart disease: 5.2% for stair climbing, 9.3% for walking & 13.4% household activities). [133] Consequences of knee OA include pain, functional limitations, and disability. [135] The effects of this disease are irreversible at this time. The estimated lifetime direct medical cost of treating knee OA $134,900 per person. [136] The burden of this chronic condition is likely to increase in the aging population since this sector of the population is increasing in number and the functional limitations and disability that accompany the disease may require increased demand of physical assistance and healthcare burden.

5.1 Basic Epidemiology of Knee Osteoarthritis

The 2017 Global Burden of Disease report indicates a global point prevalence of 3754 per 100,000 (95% interval 3389 – 4188). [137] These estimates have risen approximately 9% since 1990. Estimates from 2013-2015 report that 7.1% of adults 18-44 years, 29.3% of adults 45-64, and 49.6% of adults ≥ 65 years report doctor diagnosed arthritis in the US. [138] Knee osteoarthritis (OA) is the most common form of arthritis with prevalence estimates ranging from 19.2% to 27.8% in US adults ≥45 years. [139] Nearly 27 million US adults are estimated to have

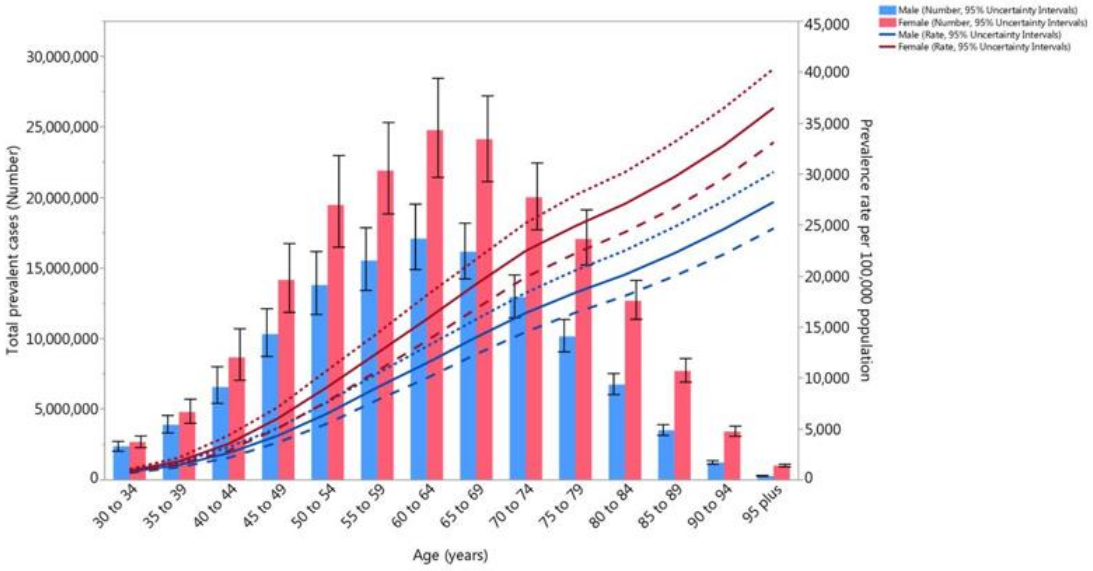
clinical knee OA based on the 2005 US Population estimates from the census bureau. [139] The median age of diagnosis in the US is 55 years and the prevalence of knee OA continues to increase with age according to the 2007-2008 National Health Interview Survey. [140] The Framingham Osteoarthritis Study reported an age related trend in radiographic knee OA for adults 63-94 years with a prevalence of 27.4% in adults less than 70 and 43.7% of adults aged 80 years and older (p for trend <0.01). [141] There was a marginally higher prevalence of radiographic changes that occurred in women compared to men (34% vs 31%) and there was a significantly higher proportion of women experiencing symptomatic OA in comparison to men (11% vs 7%, p =0.003). [141] The exact etiology for the age associated increase is unknown but is thought to be associated with age related susceptibility to damage to the cartilage and surrounding structures. The third National Health and Nutrition Examination Survey 1991-1994 study also reported an estimated 37% of adults > 60 years of age had evidence of radiographic knee OA. [139, 142] The presence of radiographic knee OA is important because the x-ray images may aid medical practitioners in decisions regarding treatment options for patients and how healthcare options will be utilized. Radiographic knee OA rates generally only define tibio-femoral rates of knee OA as the posterior-anterior image is most used. Patello-femoral knee OA would not be included in these images and ultimately not included in the prevalence rate of the condition either. The prevalence does vary by the definition used to diagnose OA, with definitions including only radiographic evidence of OA, only symptomatic evidence of OA, or using a combination of both radiographic and symptomatic evidence. Based on data from NHANES, radiographic knee OA prevalence was 37% whereas symptomatic knee OA prevalence was 12% among US adults ≥ 60 years. [139] Use of only joint symptoms as a definition of knee OA may be provide inaccurate results given that there is potential for other

mechanisms to cause pain at the joint (i.e. bursitis). A clear understanding of the definition being used to define knee OA in comparison of the prevalence is important.

Limited data exists on the incidence rates of knee OA. The 2017 Global Burden of Disease report indicates a global annual incidence of 181 per 100,000 (95% interval 163 – 202) and reports the US has the highest age standardized incidence rate of 317 per 100,000 (95% interval 295- 341). [137] This is approximately an 8% increase since 1990. For symptomatic knee OA, the age and sex standardized incidence rate was 240 per 100,000 person years based on data from the late 1980s. [143] The incidence of knee OA is higher in women compared to men, especially after the age of 50. Women 60-69 years had an incident rate of 658 per 100,000 person years (95% CI= 508-808) which increased to 1082 per 100,000 person years (95% CI= 876-1288) in women age 70-79 years. Men 60-69 years had an incident rate of 487 per 100,000 (95% CI = 351-623) which also increased in men 70-79 years to 839 per 100,000 (95% CI= 638-1040). [143] These rates provide important information but may not be applicable to the general population given that the participants are those specifically seeking out medical care for suspected OA. The Framingham Study reports a RR=1.79 (95% CI=1.08-2.94) for females in comparison to males for developing incident radiographic knee OA over a mean of 8 years. [144] In the United States blacks appear to have similar likelihood of developing knee OA in comparison to whites (OR=1.08, 95% CI=0.86-1.34). [145, 146] A gender difference is found in the development of knee OA among adults living in the US. The incidence of knee OA increases with age for men and women. For males the incidence rate has been reported 5/100,000 person years for 20-29 years and the highest at 839/100,000 person years for men 70-79 years. For women, the lowest rate was 20-29 years at 0/100,000 person years to the highest at 1,082/100,000 person years for the 70-79 age group. [143, 147] Figure 5 summarizes the incidence of knee OA across age. The incidence of knee OA for

both men and women increases through the 8th decade and then declines likely due to death from other competing risks.

Global number of prevalent cases and prevalence estimates of osteoarthritis per 100 000 population by age and sex, 2017; Dotted and dashed lines indicate 95% upper and lower uncertainty intervals, respectively (generated from data available from http://ghdx.healthdata.org/gbd-results-tool).



Saeid Safiri et al. Ann Rheum Dis 2020;79:819-828

Figure 4. Global number of Prevalent cases of Hip & Knee Osteoarthritis per 100,000 population by Age & Sex

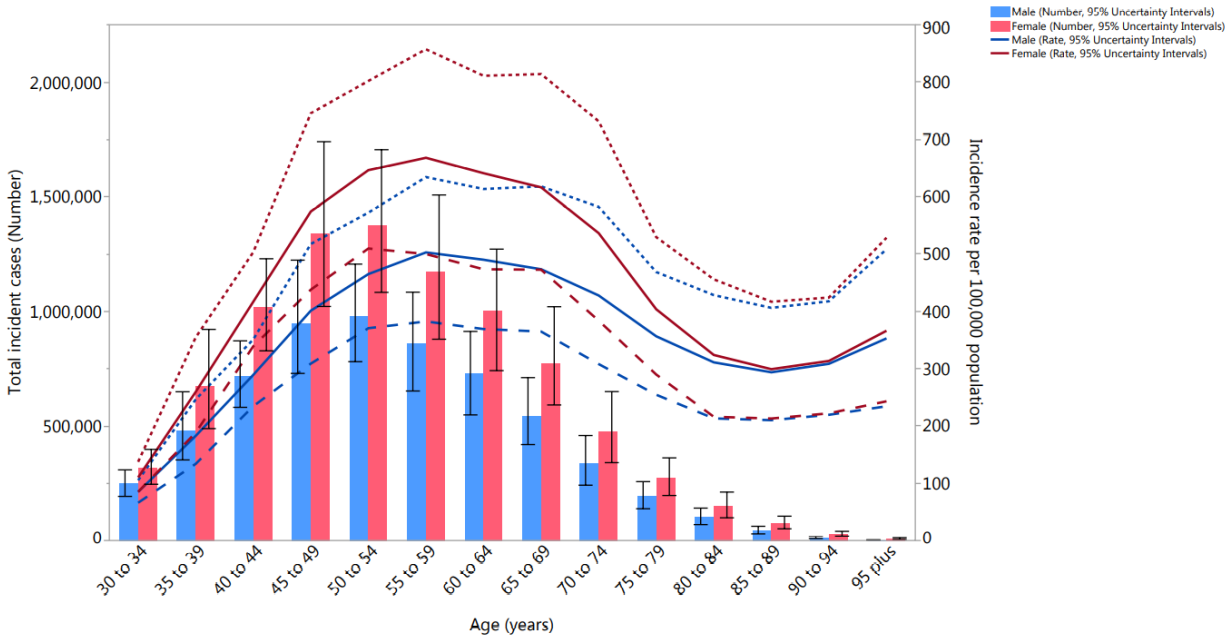


Figure 5. Global Incident Cases of Hip and Knee Osteoarthritis, 2017

5.2 Definitions of Knee Osteoarthritis

Knee OA can be defined using radiographic evidence, symptomatic report, and imaging from MRI films. However, the diagnosis of knee OA is generally based on symptoms (pain, stiffness), the presence of classic radiographic features, and the presence of intermittent soft tissue swelling in the joint. [148] The characterization of OA in the knee joint is principally defined by the loss of articular cartilage with associated changes in the remodeling of the subchondral bone. In clinical settings, knee OA is primarily defined by radiographic films and joint symptomology. In research settings, knee OA has been defined in various ways including radiographically and symptomatically, as well as self-reported physician diagnosis, and by changes in the joint and tissue identified through MRI images. Variations regarding the definition of knee OA may create

differences in the literature regarding prevalence of the condition as well as differences in outcome measures.

The American College of Rheumatology (ACR) criteria to clinically define knee OA are based on clinical signs and certain radiographic features of OA. These criteria include age >50, stiffness lasting < 30 minutes, bony tenderness and enlargement, crepitus, joint warmth, and the presence of osteophytes. [149] Epidemiological studies generally define OA as a self-report of symptoms including pain, aching, or stiffness around the knee joint for nearly most days of a month or a self-reported physician diagnosis of knee OA. [150, 151] Joint pain and stiffness are the dominant symptoms associated with OA. Bedson et al reported in a systematic review that the associations between knee joint pain and radiographic evidence of knee OA have been inconsistent. Adults (age 19-92 included) with knee pain who also have radiographic evidence of knee OA varied from 15-76%. [152] From this same report, adults with radiographic knee OA 15-81% also report knee pain. [152] Hannan et al reported from the NHANES I data (N=6880, 25-74 years) that adults with radiographic knee OA (Kellgren Lawrence grade ≥ 2, n = 319) only 47% report knee pain and only 61% report a physician diagnosis of knee OA. [153] From the entire sample, 14.6% report knee pain (n=1004). From the adults reporting knee pain, 15% had radiographic evidence of knee OA and 59% report a physician diagnosis of knee OA. [153] From the entire sample, 25.6% report a physician diagnosis of knee OA (n=1762). From adults reporting a physician diagnosis, 11% had radiographic evidence of knee OA and 34% report having knee pain. [153] [150, 154] This may be due to the variability in the development and progression of the disease versus symptomology. [155] The variability created may also be due to the x-ray viewed used within the study, the definition of pain included, the grading of the OA status, and demographic factors such as age and ethnicity. The differences between the definitions of knee

OA (radiographic, symptomatic, radiographic + symptomatic) create challenges when comparing the literature and understanding which sub-populations may be at greatest risk of adverse health outcomes.

5.3 Methods to Assess Knee Osteoarthritis in Adults

5.3.1 Radiograph Images

Radiograph films are considered an indirect measure of cartilage pathology in knee OA which illustrate changes in joint space narrowing and are considered a surrogate for articular cartilage loss. However, radiograph films are frequently used to assess the quality of the structures within the joint clinically. The detection of abnormalities on radiographs generally detects a stage late in the disease process. The Kellgren-Lawrence grading system is commonly used to define the quality of the joint. This system was developed over 60 years ago. [156] This grading system is based on joint space narrowing (JSN), osteophyte formation, bone sclerosis, and bone deformity. [156] The Kellgren-Lawrence (KL) ordinal grading system ranges from 0 – 4. A standardized atlas developed by the Osteoarthritis Research Society International (OARSI) is used as a template to define the joint status and provide an improved scoring system for the features of OA. [157] Grade 0 in the KL system indicates no features of knee OA within the joint. A grade 1 would indicate minute osteophyte formation but it would be of doubtful significance in association with OA. Grade 2 is considered definite OA, with definite osteophyte formation but without impairment of the joint space narrowing. Grade 3 is considered moderate level OA with definite multiple osteophyte formations and joint space narrowing, which is acting as a surrogate for articular

cartilage loss. Grade 4 is considered severe OA with significantly impaired joint space, often bone on bone, and sclerosis of the subchondral bone. Radiographic knee OA is defined as a Kellgren-Lawrence grade ≥ 2. [149] The KL grading system has features that may be challenging to assess and are based on an assumed progression of increasing severity, which may not be true in all cases of knee OA. The OARSI developed an alternative scale, along with the atlas, to allow for separate scoring of each feature (osteophyte, joint space narrowing). Bone attrition and sclerosis are graded as present or absent according to the template images in the OARSI atlas. [156, 157] This allows for changes in severity of disease and differentiation in staging. Radiographic features of OA rarely improve with time but may remain stable over many years. [151]

5.3.2 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) has provided insight into the pre-radiographic OA changes and been able to highlight additional morphologic changes that occur and may be important. [158] MRI may identify changes in the tissue within the knee such as cartilage, meniscus, subarticular bone, and the synovium. Several semi-quantitative scoring systems exist that have been proposed to assess the changes in a systematic manner. Whole-Organ Magnetic Resonance Imaging Score (WORMS) is one method used. A total of 14 features are scored which include cartilage and meniscus integrity, subarticular bone abnormalities and joint effusion. The knee joint and tissues are divided into sub-regions and the features of each are scored. [159] Another similar tool to evaluate early changes is the Boston Leeds Osteoarthritis Knee Score (BLOKS). One difference is that BLOKS accounts for changes in bone marrow lesion size, surface area, and percentage in a separate score. [160] A more recent tool that has been introduced is the MRI Osteoarthritis Knee Score (MOAKS). In this assessment tool, the knee joint is divided into

14 sub-regions and grades 10 features. These features include size of cartilage loss, depth of cartilage loss, bone marrow lesion size, bone marrow lesion size relative to the associated bone cyst, number of bone marrow lesions, meniscus integrity, meniscus extrusion from the joint, osteophyte formation, Hoffa-synovitis, and effusion synovitis. [161] The WORMS, BLOKS, and MOAKS have good to excellent inter-rater and intra-rater reliabilities. [159-161] The changes in features or how much abnormality needs to be present to be predictive of knee OA has not been fully established at this time. No individual feature has added more predictive ability to distinguish painful or non-painful knee joints above the KL grade at this time. [162, 163]

5.4 Strength and Limitations

MRI has generally not been the acceptable method to diagnose knee OA in clinical settings. Many studies do not include MRI images on a large scale, with exception of the Osteoarthritis Initiative study, given the high cost and limited availability of the technology in research settings. Radiographic images or self-report are generally used in large scale epidemiologic studies to assess for OA. Radiographic knee OA is not generally detected until late in the disease process, evaluating the selected outcomes for each study will be important in determining how OA will be assessed. However, understanding the risk that knee OA may pose for recurrent falls and declines in physical performance across the stages of knee OA is important in adults and may provide targets for prevention or intervention for functional decline.

5.5 Pathophysiology of Knee Osteoarthritis

Joint pathology of knee OA is varied and involves both loss of articular cartilage as well as abnormal remodeling responses, attrition of the subarticular bone, osteophyte growth, ligament laxity, weakening of periarticular muscles, and synovial inflammation. The entire joint is commonly involved in OA. [164, 165] OA is considered joint failure that may be due to a variety of pathways. Cartilage is a tissue that has compressive and viscoelastic properties that are created by the extracellular matrix that frames the tissue. The extracellular matrix is composed of collagen and proteoglycans. [166, 167] Under normal conditions, the cartilage is exposed to a dynamic remodeling process. During this process, there are balanced levels of degradation and synthesis that occur to maintain the volume of the cartilage. In the disease process of OA, the degrading enzymes are overexpressed, and the matrix degradation exceeds the matrix synthesis. [168, 169] This process results is a net degradation and loss of cartilage volume. In the early stages, the chondrocytes proliferate and synthesize greater amounts of proteoglycan and collagen molecules. However, with progression of the disease, the reparative processes become limited and eventually ineffective. Early on in the disease process erosion and cracking happens in the superficial layers of the cartilage. [167] Over time, these defects or cracks within the cartilage progress to deeper levels and result in observable erosions or defects in the cartilage. [166, 168] The thinning and loss of the articular cartilage leaves areas of bone exposed and subject to damage. The disease progression of OA is generally slow and many of these alterations within the knee joint are occurring prior to the onset of patient symptoms.

5.5.1 Meniscus

The role of the meniscus in normal function is to improve tibio-femoral congruence, joint lubrication, stability, and distribute loads across the joint. [170] [171] The menisci of the knee are crescent shaped wedges that are located in both the medial and lateral aspect of the joint. The peripheral borders are thick, vascular, and attached to the joint capsule. The superior surfaces of the menisci are concave to allow congruence with the femoral condyles while the inferior surfaces are flat to accommodate the tibial plateau. These features improve the congruence and stability of the joint. [171] Greater compressive force on the joint occur with flexion (85-90%) as compared to extension (50%) allowing the meniscus to serve as a shock absorber. [172] [172] Proteoglycans and the collagen fibrils within the menisci help to maintain its health and function. [173] Damage or loss of the menisci affects the articular cartilage and may increase the risk of OA (OR=5.7, 95% CI= 3.4-9.4. [171, 173] [174] In a prospective case control study, damaged menisci was present in 84% of cases that developed radiographic knee OA (KL grade ≥ 2) and present in 18% of cases that did not develop radiographic knee OA ($p<0.001$). [174] Structural damage to the menisci is a potential risk factor in the development of tibiofemoral OA.

5.5.2 Ligaments

Ligaments are dense bands of collagenous fibers that are anchored to bone at end of the joint. Their function is to provide passive stability to the joint throughout the range of motion. The collagen fibrils that compose the majority of ligaments are aligned in the direction of tension applied during normal motion. [175] Motion is allowed in flexion, extension, and minimal rotation in the knee. There are 4 major ligaments in the knee to aid in stability. These ligaments are the

anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial cruciate ligament (MCL), and the lateral cruciate ligament (LCL). Damage to the ligaments is the most common form of injury to the knee. [176] Disruption of this stability mechanism can increase the risk and the progression of OA. [175]

5.5.3 Bone Attrition and Osteophyte Formation

Bone attrition is the remodeling of the bone that will result in a change of shape or a loss of bone. [177] Attrition has generally been considered a change only seen in advanced stages of OA. Recent evidence has suggested that attrition can be seen in more mild cases of OA on MRI. [178] However, reading and deciphering these bone changes can be challenging and are not seen easily with radiographic films as compared to MRI. [178] The thinning and loss of cartilage allows the subchondral bone to thicken and develop bone marrow lesions (BMLs), subchondral bone cysts, osteophyte formation, and bone remodeling. [148] These changes in bone shape can alter the biomechanics of the joint further increasing the risk of OA and the progression of the disease.

Osteophyte formation is a common feature of OA and is an integral part of the definition. Osteophytes generally form near the margins of the joint and are considered an outgrowth of cartilage and the result of new bone formation that occurs in response to the degradation of the articular cartilage. [148, 149] Osteophytes can further undergo ossification. The development of osteophytes can be accelerated by growth factors (growth factor beta). [179, 180] In a longitudinal assessment by Felson et al, the effect of the osteophyte score moderately increased the risk of OA progression. [181] The effect of the osteophyte on disease progression was partially mediated by mal-alignment of the joint. Osteophytes are associated with ipsilateral mal alignment (medial > lateral). Mal-alignment has also been shown to be a strong risk factor for OA progression. [182]

5.5.4 Synovial Fluid

The synovial fluid is important for normal cartilage and joint function. In normal physiology, the synovium membrane contains macrophages and fibroblasts. [183] This membrane is an essential source for the synovial fluid. The synovial fluid contains two molecules that are important for maintaining the integrity of the joint in addition to lubrication of the joint. These molecules are lubricin and hyaluronic acid. [184, 185] In OA, the synovium reacts and becomes inflammatory. There is hyperplasia of the synovial lining, infiltration of other macrophages and lymphocytes, and fibrosis can occur. [183] The concentration of lubricin and hyaluronic acid in OA are altered and adversely impact the joint integrity. [185] Breakdown of the synovium tissues will also add to the clinical symptoms that are common with OA: joint swelling, synovitis, and pain. [186] While the fundamental feature of knee OA is the ongoing loss of articular cartilage with accompanying remodeling of the subchondral bone, other features of the joint are involved with the disease and related symptoms.

5.5.5 Muscle

Muscle weakness, particularly in the quadriceps muscle has been shown to be associated with knee OA. [187] Two mechanisms within the progression of OA are thought to be involved in this process: declines in mass or size of the muscle and dysfunction in the nervous system to activate the muscle. [187, 188] The decline in size or mass may be due to disuse atrophy. Alteration in the function of the nervous system is commonly known as arthrogenic muscle inhibition. [189] Weakness of the quadriceps muscle has ranged from 10-70% depending on the mode of testing in persons with knee OA compared to healthy controls. [187, 188, 190] Methodological limitations

with testing quadriceps strength in knee OA is that symptoms such as pain or laxity and persons with more advanced stages of OA with mal-alignment or limited range of motion may be restricted from participating in the test. [191] Muscle impairment is not limited to the quadriceps but has been shown to involve the hamstrings and muscles of the hip. [192, 193] These modifications in muscle strength are significant because they are determinants of both self-report and performance based physical function. [194-196] Limitations in muscle strength are important in knee OA because it is associated with impaired dynamic stability of the knee and overall physical function. [197-200]

5.6 Risk Factors for Knee Osteoarthritis

5.6.1 Person-Level Risk Factors

5.6.1.1 Sociodemographic

Older age is a well-documented risk factor for OA. [201, 202] Age may increase the risk of knee OA as well as impair the reparative processes of the body to prevent the progression of OA. [139, 141, 147, 151, 203] Women are more likely to develop knee OA than men. [201] The higher risk of knee OA in women compared to men is assumed to be multifactorial including anatomic, kinematic, and hormonal factors. [204] Women have an increased likelihood of OA, especially after the age of 50 (OR = 1.84, 95% CI 1.32 – 2.55). [205-207] Gender differences exist between the length and thickness of the femur, patella, and tibia but a substantiated link to explain the sex difference in risk has not been found and no confirmed evidence with biomechanics exists. [204, 208] African-Americans are more likely to develop symptomatic knee OA compared to other

races. [202] Recent work in 2018, from the Osteoarthritis Initiative, revealed that African-American men, experienced a higher risk of medical joint space loss, suggesting race is linked to progression of the disease as well. In this analysis, adjustment for known risk factors including obesity, history of a knee injury and bony finger enlargements primarily explained the difference between races in progression of the disease. [209]

5.6.1.2 Body Mass Index

Obesity is a well-known risk factor for knee OA. [201, 210] Obesity has been shown to be a strong independent risk factor for the development and progression of knee OA for both symptomatic and radiographic definitions of knee OA. [135, 211] [212, 213]. Obesity expedites the structural deterioration of established knee OA and often precedes development of knee OA. [206, 212] The odds of developing knee OA for a BMI that was higher than 30 kg/m^2 was 2.6 times greater than a BMI within the normal weight range 18.5-24.9 kg/m^2 (OR= 2.63, 95% CI = 2.28 – 3.05). [205] Weight loss has been shown to reduce the symptoms associated with OA, suggesting a lower BMI may delay progression of the disease, in data from the Osteoarthritis Initiative. [214]

5.6.1.3 Nutrition and Vitamins

Nutritional factors, such as low vitamin D levels, have been associated with OA through its role in bone metabolism, suggesting low levels increase risk. [215] This however, is not clearly shown in the literature. Evidence from longitudinal studies and clinical trials have shown no improvement between vitamin D3 supplementation and joint space width or symptoms of pain and stiffness.[216, 217] Research on high fiber diets have shown a reduction in symptoms associated

with this type of diet but no difference on radiographic imaging, suggesting high fiber diets may slow the progression of symptoms. [218]

5.6.1.4 Metabolic Syndrome

Recent systematic reviews have found increased risk of cardiovascular disease and risk profiles in adults with OA, but it is unclear whether the OA precedes the cardiovascular risk or vice versa. [219, 220] Data from the Osteoarthritis Initiative (OAI) has shown an increased risk of incident knee OA in adults with higher systolic blood pressure. [221] Additionally from the OAI study, adults (n=2938) with use of cholesterol lowering medications had less structural changes in their knee and lower reports of pain symptoms compared to those not taking the medication over 3 years of follow up. [222] There is not support for an association with incidence or progression of symptoms of knee OA and diabetes. [223-225] While there may appear to be evidence of an association between true metabolic syndrome and osteoarthritis, there has not been clear evidence of this. In most analyses, when accounting for BMI, the associations are attenuated. [223]

5.6.1.5 Physical Activity

Physical activity has been shown to be beneficial to improve health outcomes and prevent disability.[226, 227] The Centers for Disease Control recommend at least 150 minutes of moderate to vigorous intensity aerobic training in addition to 2 days of strength training for all adults. [228] Kraus et al in a systematic review found no evidence of disease progression for adults with OA who participated in varying amounts and intensities of physical activity. [229] Dunlop et al found that adults, free of mobility and activities of daily living disability at baseline, who participated in 55-56 minutes per week of moderate to vigorous intensity, were most likely to stay disability free

over 4 years of follow-up in the Osteoarthritis Initiative study. [230] These findings suggest that regular physical activity is beneficial to those with OA.

5.6.1.6 Genetics

Genetics have also been associated in the susceptibility of OA, with data from twin studies suggesting the heritability is between 37-39%. [231-233] The presence of OA in other joints, particularly the hand, has shown to increase the odds of developing knee OA by nearly 50% (OR = 1.49, 95% CI = 1.05 – 2.10). [205] Genome wide associated studies have identified 21 different loci for susceptibility of OA that have been highlighted in a review article from 2017. [234] Associations with the gene ALDHIA2 have been made in both Chinese and European populations for both knee and hand OA. [234, 235]

5.6.2 Joint Level Risk Factors

5.6.2.1 Joint Shape and Alignment

Bone and joint shape has primarily been explored in the development of hip OA.[236] In data from the Osteoarthritis Initiative, Hunter et al has shown that in adults with mild to moderate knee OA, changes in the bone area and shape were associated with radiographic changes and progression of pain symptoms over 2 years. [237] In the Tasmanian Older Adult Cohort, irregular shape of the proximal tibiofemoral joint are associated with osteoarthritic changes in the lateral compartment of the knee only.[238] Overall, irregular joint shape is associated with progression of OA.

Alignment of the joint has been inconsistently shown to be a predictor of incident knee OA, as it may alter the distribution of the load across the knee joint. [182, 239-241] Sharma et al

reported from the Multicenter Osteoarthritis study (MOST) that varus knee alignment is associated with incident knee OA, in adults at greater risk for OA (adjusted OR= 1.49, 95% CI= 1.06-2.10), with no difference noted by gender. [241] Differences in findings, however, may be a result of variation of positioning for radiographs or length of the films to include the hip, knee, and ankle joints. Knee alignment may also be a marker of disease severity or progression. Data from the MOST study shows that varus alignment is associated with 3.5 fold likelihood of medial knee OA progression (95% CI= 2.62-4.92) and valgus alignment is associated with a 4.8 fold likelihood of lateral knee OA progression (95% CI = 3.17-7.42). [241] In an OAI study sample of 2,284 adults varus thrust was shown to be associated with progression of knee OA over a 7 year period. [242] Although gaps still exist as to how the change in limb alignment across the lifespan and if gender differences exist, there is a probable role for limb alignment contributing to the incidence and progression of knee OA.

5.6.2.2 Muscle Strength

Muscle weakness has been implicated in the disease process of knee OA. In both aging adults and in adults with OA, a greater loss in strength exists than would be expected in relation to the reduction in muscle size. This difference may suggest that there is a component of muscle quality that is important to consider. Cross-sectional results from Conroy et al in a Health ABC investigation (N=858) found that absolute strength did not differ across participants with and without knee OA, but that lower extremity specific torque did (0.86 vs 0.94, $p < 0.001$). [243] Specific torque is a measure of muscle quality that is calculated by dividing peak strength by the total muscle area. These results were like those reported by Slemenda and Thorstensson. [244, 245] Limitations of the study include the cross-sectional design and inability to infer a causal relationship. Strengths of the study include a well-designed cohort of both white and black race

and the use of CT scan to determine the quality of the muscle tissue. In longitudinal assessment of the association between strength and incident symptomatic + radiographic knee OA from the Multicenter Osteoarthritis Study, men and women in the highest tertiles of knee extensor strength had reduced risk of symptomatic + radiographic knee OA (OR_{men}= 0.7, 95% CI= 0.5-0.9; OR_{women}= 0.7, 95% CI=0.6-0.9) but not radiographic knee OA alone. [246] Results from this study as indicate that leg strength does not influence the progression of knee OA but greater strength was associated with less knee pain (symptoms) and better physical function. [246]

5.6.2.3 History of Injury

In a systematic review, previous injury increased the likelihood of OA by nearly 4 fold (OR= 3.86, 95% CI = 2.61 – 5.70). [205] Injury and its association to knee OA holds across race and gender. [213, 247] Injury to the articular cartilage, meniscus, and ligaments have all been associated with incident knee OA. [201, 236] Injuries directly alter the biomechanics of the joint, stability of the joint, and the modification of load distribution across the joint, which may predispose the joint to development of OA. [182, 248]

5.6.2.4 Bone Mineral Density (BMD)

High BMD has been associated with lower extremity knee OA (radiographic and symptomatic) in both incident cases and progression of the disease. [202, 249] In 2017, Teichtahl et al found in a sample of 153 adults, that higher systemic BMD was associated with early clinical changes in knee cartilage, suggesting high BMD is associated with the incidence of knee OA. This study also found that higher BMD in the hip and spine were associated with progression of the changes in knee cartilage. [250] The biologic mechanism by which BMD may influence OA risk

has not been elucidated and some limitation exists as previous significant findings may result from not controlling for unmeasured confounders, such as bone shape and genetic factors.

5.6.2.5 Occupation

Occupations that have repetitive joint loading have been associated with increased risk of developing knee OA (OR = 2.22, 95% CI = 1.38 – 3.58). [201, 251-253] The commonly included professions in these studies are firefighters and construction workers. A recent cohort (n=3442) of airport baggage workers revealed increased risk of incident knee OA with a dose-response association with increased years of working as an airport baggage worker (adjusted IRR for 20+ years 2.18, 95% confidence interval 1.01 – 4.70).[254]

6.0 Fractures

The increase in the aging population will lead to increases in osteoporosis related fractures even if the rates of fracture remain stable. Age related fractures are expected to increase in the US from 2.1 million in 2005 to over 3 million in the year 2025. [255, 256] Currently an estimated 10 million Americans age 50 years and older meet the criteria for osteoporosis based on the World Health Organization definition. There are over 33 million Americans 50 years of age or older who meet with criteria for osteopenia, or low bone density. [257] The cost of treating incident fractures in the US in 2005 exceeded $17 billion dollars. If fracture rates remain the same, with the aging of the population, the anticipated number of fracture events is expected to be greater than 3 million with costs soaring over $25.3 billion dollars by 2025. [255] The risk of fracture in the aging population is a real public health concern.

6.1 Basic Epidemiology of Fractures in Older Adults

In 2005, over 2 million incident fractures were reported in the US alone. [255] Low bone mineral density is related to most fractures, including traumatic fractures. The distal forearm, vertebrae, and hip regions of bone have high percentages of trabecular bone and are common sites of osteoporotic fractures. Vertebral fractures account for 27% of all fractures, wrist fractures 19%, hip fractures 14%, and pelvic fractures 7%. [255] Using the data from the Olmsted County, Minnesota fracture 2009-2011 study, the incidence of all fractures is estimated to be 4,017 per 100,000 person years (95% CI= 3,908-4,127). Based on the most recent fracture rates from the

Olmsted County, Minnesota fracture project, adults age 50 and greater experienced 2,704 fractures per 100,000 person-years (95% CI= 2,614 -2,793). The age adjusted annual incidence of fractures for women was 3,199 fractures per 100,000 person years (95% CI= 3,068-3,330) and for men was 2,107 fractures per 100,000 person years (95% CI=1984-2230), with a ratio of 1.5:1 for women to men incident rate of fracture. In both genders, an increase in the incidence rate of fractures with age and is highest in the 85 years and older age group. For women the highest incident is 15,415 fractures per 100,000 person years and for men 9,302 fractures per 100,000 person years. Age-adjusted fracture rates were significantly greater in women compared to men for most fracture sites. All fracture sites except, the proximal forearm, tibia/fibula, and ankle showed a strong age-related increase in incidence in both men and women. Overall, the age and sec adjusted incidence of fractures in the 2009-2011 time period was 11% greater in comparison to the 1989-1991 time period (4,017 fractures per 100,000 person years, 95% CI= 3,908-4,127 vs. 3,627 fractures per 100,000 person years, 95% CI= 3,485-3,768). This increase is driven by the increase in certain sites of fractures. [258]

6.1.1 Distal Forearm Fractures

The incidence rate of fractures in the distal forearm overall are significantly decreasing from the 1989-1991 rates. The change in distal forearm fractures went from 400 fractures per 100,000 person years (95% CI=353-447) to 328 fractures per 100,000 person years (95% CI=297-359). The incidence rate in women continues to be higher than that in men, 475 fractures per 100,000 person years (95% CI=424-526) and 152 fractures per 100,000 person years (95% CI=120-183) respectively. The rates in women have declined since the 1989-1991 survey but have increased slightly in men during this same time frame. The highest incidence of distal

forearm fractures was shown to occur in older ages (≥ 75 years), which may potentially be due to fall-related events. [258, 259]

6.1.2 Humeral Fractures

The incident rate of fractures in the shaft or distal humerus decreased and fractures of the proximal humerus increased from 1989-1991 to 2009-2011 but were not statistically different. The rates of distal/shaft humeral fractures decreased in both men and women with significant changes only seen in men from the 1989-1991 to the 2009-2011 data (35 fractures per 100,000 person years to 15 fractures per 100,000 person years). The rates of fracture at the proximal humerus have remained similar over time in both men and women. The incidence of any humeral fracture is greatest in the oldest old (≥ 85 years of age). [258]

6.1.3 Vertebral Fractures

Vertebra

While vertebral fractures are the most common osteoporotic fracture, only 1/3 of these fractures are clinically recognized. [260] The incidence rates of vertebral fractures has significantly increased over time from 659 fractures per 100,000 person years (95% CI=600-718) to 968 fractures per 100,000 person years (95% CI=914-1,022). Vertebral fracture rates continue to be higher among women than among men. The rates in women have significantly increased to 1,092 fractures per 100,000 person years from 812 fractures per 100,000 person years. Vertebral fracture rates in men have increased significantly as well from 460 fractures per 100,000 person years to 798 fractures per 100,000 person years. The rates of vertebral fractures increase with age

in both men and women peaking in the oldest old. [258] The prevalence of vertebral fractures is consistent in older women (≥ 65 years) across the world. In white women the prevalence is 70%, 68% for Japanese, 55% for Mexican, and 50% in African American women. [261, 262]

6.1.4 Hip Fractures

Hip fractures account for less than 20% of the total osteoporotic fractures world-wide. [263] Majority of hip fractures require medical care and are easy to track. In addition, hip fractures are associated with more disability and mortality than all other fractures combined Because of this hip fractures are often used to assess overall burden of osteoporosis. [264] The overall rates of hip fracture have significantly declined since from the 1989-1991 survey to the 2009-2011 survey. This has been shown in other reports as well. [265] The rate of hip fracture in 1989-1991 was 357 fractures per 100,000 person years (95% CI=314-400). The current estimated rate is 294 fractures per 100,000 person years (95% CI=264-323). The rate of hip fracture in women has significantly declined as well from 438 fractures per 100,000 person years (95% CI=378-498) to 327 fractures per 100,000 person years (95% CI=286-367). The hip fracture rate in men has remained stable. Hip fracture incidence rates increase with age and have the highest incidence in those aged 85 years and older. [258] Variability exists with hip fracture incidence world-wide with women experiencing higher amounts than men. Women in Sweden and Norway experience the highest lifetime risk of hip fracture, 28.5 and 24.5 whereas women in Turkey and China experience lower lifetime risks, 1.0 and 2.4 respectively. [266] Potential hypothesized reasons for differences in lifetime risk across populations could be the use of bisphosphonate, the obesity epidemic, lifestyle variation, and differences in the intake of both calcium and vitamin D. [267]

In addition to the significant cost of care for osteoporotic related fractures, the increased risk of disability and mortality following fracture is a significant burden. In a meta-analysis by Haentjens et al (24 studies, all prospective, life table approach) the pooled relative hazards for mortality following hip fracture was greatest in the first 3 months for both men and women (RH=7.95, CI=1.13-10.30 and RH= 5.75, 95% CI=4.94-6.67) respectively. [268] The increased risk of mortality remained after 10 years following the hip fracture (men RH=1.79, 95% CI=1.14-2.81 and women RH= 1.96, 95% CI= 1.30-2.95). [268] Functional outcomes after hip fracture report that at 12 and 24 months, 50% of hip fracture patients were walking disabled (walking across a room or walking 10 feet), compared to 21-29% of age and gender adjusted controls after adjusting for age, sex, co-morbidities, and functional status pre-fracture. [269] The decline in functional ability following fracture also presents burden to our healthcare system.

6.2 FRAX

The World Health Organization has developed a country specific tool that is able to predict fracture risk better than a T-score alone. In addition, bone mineral density measurements, 11 additional risk factors are included in the prediction equation. [270] Risk factors for fracture are varied and include both fixed and modifiable components. The FRAX risk factors include age, gender, weight, height, history of previous fracture, family history of fracture, current smoking status, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol intake of 3 or more units per day. [270] Fixed risk factors, while they cannot be altered, are important to understand clinically because these may impact the choice of treatment. Most of the modifiable risk factors are lifestyle choices and may indirectly impact bone mineral density. The FRAX

calculator is based on data from multiple cohorts and is an easily accessible web-based tool. However, limitations with FRAX include that while web-based, few clinicians have access it. FRAX only accounts for BMD values at the femoral neck. The FRAX calculator, while accounting for many known risk factors for fracture, does not include all factors. It does not adjust for racial or ethnic differences that may influence fracture risk or known risk factors for falls which are independent risk factors for non-vertebral fractures. It also does not account for the increased the risk of fracture after an initial fracture. While FRAX is a commonly used tool, it should be used in conjunction with clinical judgement in medical decisions due to these limitations.

6.3 Risk Factors for Fracture in Older Adults

6.3.1 Non-Modifiable Risk Factors for Fracture

Fixed risk factors for fracture include age, gender, race, family history of fracture, personal history of fracture, long term use of glucocorticoids, hypogonadism in men, menopause in women, and rheumatoid arthritis. [271]

6.3.1.1 Sociodemographic Factors

Most fractures occur in persons age 50 years and older. Declining bone mineral density (BMD) with age partially explains the fracture risk for adults ≥ 50 years but age itself has been shown to be an independent predictor of fracture. [272] The average loss of hip BMD in women 65-69 years is 0.32% and increases to 1.64% in women 85 years and older according to a study from the Study of Osteoporotic Fractures. [273] In addition to the loss of bone, micro-architectural

changes occur in bone tissue that may lead to bone fragility. [274] Changes in cortical bone thickness and cross-sectional area, greater porous cortical bone, and the presence of micro-cracks are part of the structural changes that lead to increased fragility with age. [264, 275-277] Risk of fracture increases significantly in women per 5 years but varies across race. A 5 year age increase, the risk of fracture increases for white women by 1.1 (HR=1.10, 95% CI=1.09-1.12), Hispanic women by 1.13 (HR=1.13, 95% CI=1.02-1.26), Asian women by 1.15 (HR=1.15, 95% CI=1.02-1.29) but not significantly for African American (HR=0.98, 95% CI=0.92-1.05) or Native American women (HR=1.02, 95% CI=0.81-1.28). [278] Fracture risk is highest among women over the age of 50 and women of white race.

Women are at higher risk of fracture compared to men, especially after the menopause transition. The gender difference can partially be explained by men having a higher peak bone BMD in comparison to women. With age, the average rate of BMD loss increases and women tend to lose more bone than men particularly after menopause; which is partially explained by decreased bone formation. [279] [280] Cawthon et al reported from the Study of Osteoporotic Fractures in Men (≥ 65 years of age) that men in the lowest quartile of femoral neck BMD at baseline experienced a greater loss of BMD in comparison to men in the highest quartile of femoral neck BMD at baseline over an average of 4.6 years (-2.11g/cm^2 vs -1.35 g/cm^2, p <0.001). [281, 282] Hypogonadism in men impacts bone density through the hormonal process. Decreased levels of testosterone may not be able to promote proliferation and differentiation of osteoblast cells and inhibit the activity of osteoclast cells. [283] Peak BMD and rate of BMD loss vary by gender with women generally having a lower peak BMD and a greater loss of BMD after the menopause transition.

Differences in BMD exist across race. Whites are more likely to experience a fracture than other races, even accounting for differences in bone mass. [284] Some of these differences may be due to variances in baseline bone mineral density values as well as the rate of bone loss. [274, 279] African American men and women have the greatest peak BMD. [285, 286] The lifetime risk of hip fracture at age 50 in the US is 15.8% in women and 6% in men compared to 2.4% in Chinese women and 1.9% in Chinese men. [266] Among different ethnicities living within the US variations exist in fracture rates. Annual hip fracture rates in the US are highest among white women (140.7 per 100,000) followed by Asian women (85.4 per 100,000), African-American women (57.3 per 100,000) and Hispanic women (49.7 per 100,000). [287] Similar trends are seen across other fracture sites. [278] These differences can be partially explained by differences across race in peak BMD and rate of BMD loss. African American women have the greatest BMD and the lowest risk of fracture. White women though experience higher rates of hip fracture in comparison to Asian women even though Asian women have a lower BMD. [279, 288] Racial differences in bone geometry or higher fall frequency may be contributing to fracture rates in addition to BMD.

6.3.1.2 History of Fracture

A family history of fracture increases the risk of experiencing a fracture. [278] Based on a meta-analysis, the increased risk for any fracture is 1.17 (95% CI=1.07-1.28); the increased risk of any osteoporotic fracture is 1.18 (95% CI=1.06-1.31); the increased risk for hip fracture is 1.49 (95% CI=1.17-1.89). These risks are independent of bone mineral density. [289] Additionally having a personal history of fracture increases the risk of a future fracture event by 1.86 times greater than someone who has not experienced a fracture (95% CI=1.75-1.98). This risk is for both

men and women. [290] Both a familial and personal history of a fracture event increases the likelihood of a future fracture event.

6.3.1.3 Age Related Mechanical Changes

Age related declines in muscle mass and strength impact bone health. Bone responds to the mechanical pressure of muscles, which aids to maintain strength and repair bone. [291] This mechanical pressure or signal is translated into a cellular signal through osteocytes. The osteocytes form a system of interconnected cells that signal and employ other cells to facilitate the bone remodeling. [292, 293] This process also has an indirect pathway through Insulin-like Growth Factor (IGF-1). IGF-1 is a hormone that is involved with the development and repair of bone. Mechanical loading results in an increase of IGF-1, which leads to osteocyte differentiation and bone formation. Aging results in a decline of IGF-1 which in turn leads to a blunted response to the mechanical loading. IGF-1 also acts on muscle cell receptors to promote hypertrophy. [291] Through these pathways, a decline in muscle mass and strength, as seen in sarcopenia, are associated with low BMD. [294-296]

6.3.1.4 Age Related Body Systems Changes

Endocrine function also plays a role as both muscle and bone are endocrine organs. IGF-1 and other growth factors have receptors on the periosteum of the bone, which is the interface between muscle and bone. With declines in the growth factor pathway from aging, a reduction in muscle size and strength, decreased protein synthesis, and decreased bone formation occurs. In addition to IGF, muscle and bone are influenced by testosterone and estrogen. [297] These androgens affect muscle mass as well as bone formation. Estradiol is the main sex steroid hormone that is responsible for bone resorption in both men and women and improving muscle contraction

on bone. [297, 298] As men and women age, the decrease in testosterone and estrogen may place a higher risk for sarcopenia and osteoporosis. Rheumatoid arthritis may also impair bone health by acting on the endocrine system to increase levels of parathyroid hormone, which can increase calcium loss from the bones and weaken the bone over time. [299] The endocrine system is important in bone remodeling and formation.

6.3.2 Modifiable Risk Factors

6.3.2.1 Bone Mineral Density

Low bone mineral density (BMD) remains one of the strongest predictors of fracture in adults of all ethnicities. [284, 300-303] The loss of bone mass and alteration to the composition of the bone increase the susceptibility to fracture. Low BMD is defined by the World Health Organization as hip BMD -1.0 to <-2.5 standard deviations below the mean for the NHANES III reference population. Osteoporosis, which is a more significant loss of bone mass is defined as > -2.5 standard deviations below the mean for NHANES III reference population. Estimates from the NHANES III bone data suggest that approximately 10 million adults greater than age 50 in the United States have osteoporosis and roughly 43.4 million adults have low BMD. [304, 305] These combined estimates are expected to rise to over 71.2 million by 2030. [271] Bone mineral density in combination with other risk factors can increase the risk of fracture even greater than expected. [300] In men, having 3 clinical risk factors such as, a history of fracture after age 50, tricyclic acid use, history of fall, depression, and poor physical performance/neuromuscular function, in combination with low BMD can increase the risk of fracture 15 fold in comparison to men without those clinical risk factors and normal BMD. [300] Low BMD increases the risk of nearly all types

of fractures among older adults and proposes that bone loss is a significant contributing component to the increase in fracture rate with advanced aging. [300, 303, 306]

6.3.2.2 Medication Usage

Long term use of corticosteroids (glucocorticoids) may lead to osteoporosis and be associated with an increased risk of fracture through that pathway. [307] The relative risk for experiencing any fracture was 1.53 times greater (95% CI= 1.37-1.80) for adults using glucocorticoids compared to the population risk with adjustment for bone mineral density. The overall risk for an osteoporotic fracture was 1.61 (95% CI=1.42-1.92) for gluco-corticoid use compared to not and was also adjusted for bone mineral density. The overall relative risk for hip fracture was greatest at 2.13 (95% CI= 1.60-3.15) for corticosteroid users compared to persons not using. [308] Glucocorticoid use may have serious side effects on bone resulting in increased risk of fractures among users.

6.3.2.3 Body Mass Index

A high and low BMI are both considered to increase the likelihood for fracture events. Low BMI or being underweight is a known risk factor given that BMD is generally lower in this sub-population. BMD is moderately positively correlated with BMI (Pearson's r = 0.35, $p < .0001$) and has been shown to mediate the association between BMI and fracture risk. [309, 310] In a meta-analysis (n=398,610 women; average age of 63), the hazard ratio (HR) for osteoporotic fracture for women with a BMI of 35 kg/m^2 compared to women with a BMI of 25 kg/m^2 was 0.87 (95% CI= 0.85-0.90). After adjusting for BMD, the HR was 1.16 (95% CI = 1.09-1.23). [311] Nielson et al in the MrOS Study showed that in age, race, and BMD adjusted models, compared with normal weight, the risk for non-spine fracture was HR=1.04 (95% CI 0.87–1.25) for overweight,

1.29 (95% CI 1.00–1.67) for obese I, and 1.94 (95% CI 1.25–3.02) for obese II. [309] The results were attenuated when adjusting for self-reported mobility limitation of walking 1 flight of stairs or walking 2-3 blocks (obese I HR= 1.12, 95% CI = 0.86-1.46; obese II HR= 1.44, 95% CI = 0.90-2.28) indicating that a deficit in physical performance explains a portion of this association. The associations found between BMI and BMD may indicate that overweight or obese adults have a relatively low BMD and poor bone strength for their given size. Weight changes additionally may increase the risk of fracture compared to weight stable. Over 11 years of follow up in the Women's Health Initiative (n=120,566) both weight loss and weight gain were associated with increased risk of fracture (weight loss for hip fracture- HR= 1.65, 95% CI= 1.49-1.82; weight gain for lower limb fracture HR=1.18, 95% CI= 1.12-1.25). [311, 312] Fat gain has been associated with higher rates of BMD loss and visceral fat has been shown to be negatively correlated with bone structure and strength. [313] Increasing adiposity may negatively affect bone strength and potentially fracture risk. Sowers et al explored the association between lean and fat mass with BMD. An increasing linear trend was noted in BMD with each tertile increase of muscle mass, with a non-linear increase in BMD for each tertile increase of fat mass. BMD was found to be similar and higher among participants with high muscle/high fat and high muscle/low fat groups. This study suggests that an increase in weight alone is not associated with an increase in BMD. High fat mass is only considered to be protective of BMD when a substantial amount of lean mass exists. [314] Theoretically if the muscle is not increasing in size in concordance with the increasing fat mass or body weight, then the benefits associated with BMD through mechanical stimuli will not be optimized. [314] Obesity may increase the risk of fracture among adults with similar BMD values.

6.3.2.4 Lifestyle Factors

Modifiable lifestyle risk factors include high alcohol intake, poor nutrition, insufficient physical activity, and frequent falls. High alcohol (> 2 units per day) intake may influence bone forming cells. [315] The relative risk for any fracture adjusted for bone mineral density increases with greater amounts of reported daily alcohol intake. The relative risk for persons consuming > 2 units per day is 1.24 (95% CI = 1.06-1.45) and for a person consuming > 4 units per day the relative risk is 1.51 (95% CI=1.19-1.93). This trend is also seen for any osteoporotic fracture (RR=1.36, 95% CI=1.13-1.63 for > 2 units vs RR=1.64, 95% CI=1.24-2.17 for > 4 units) and for hip fracture (RR=1.70, 95% CI=1.20-2.42 for > 2 units vs RR=2.39, 95% CI=1.39-4.09 for > 4 units). [316] However, there is conflicting views regarding alcohol intake. Moderate alcohol intake has been shown to be protective against fracture compared to abstainers. [301] Abstinence from alcohol may be a proxy for poor health and consuming alcohol may not be medically safe in certain adults. High alcohol intake and no alcohol intake may increase the risk of fracture.

While nutrition, physical activity, and falls are not incorporated as risk factors used in the FRAX prediction tool, they are important lifestyle factors to consider given their association to bone health and implications of their outcome. Poor nutrition is a risk factor for bone health and fracture primarily through unbalanced levels of protein, calcium, and vitamin D. [317-319] Based on a meta-analysis from Qu et al (cohort studies N=22, N=>1.2 million adults) the highest category of physical activity had reduced risk of fracture compared those in the lowest category of physical activity (pooled RR=0.71, 95% CI=0.63-0.80). [301, 320] In this meta-analysis, physical activity was measured through various questionnaires and interviews indicating that the methods across the studies may not be similar and may have some methodological inconsistency. Decreased physical activity can lead to declines in physical function or performance which can also contribute

to the risk of fracture and the risk of fall events. [300] Fall events can result in a fracture. Over 800,000 persons are hospitalized after a fall for injury and roughly 1 in 10 falls will result in a serious injury, which includes fractures. [321] Fall risk increased with advancing age and results in increased susceptibility to fracture.

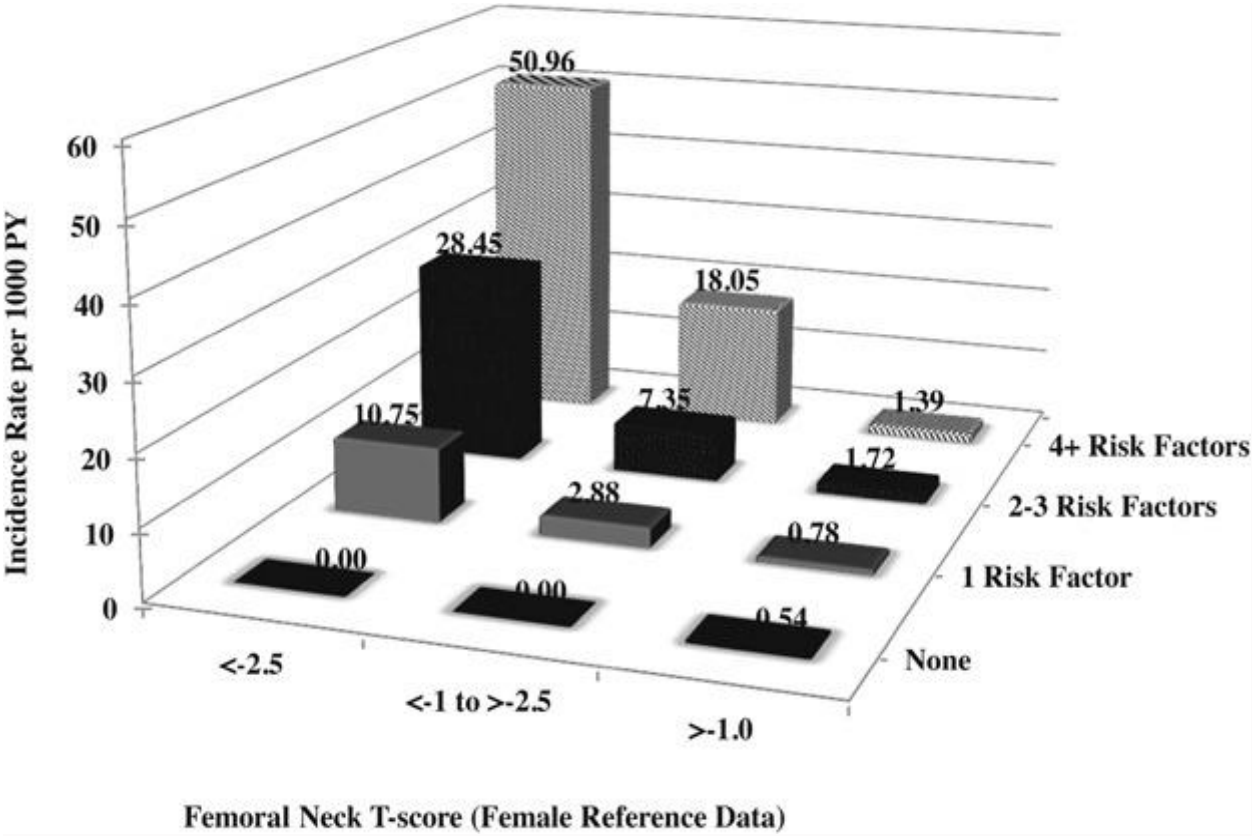


Figure 6. Risk Factors for Hip Fracture in Older Men: The MrOS Study

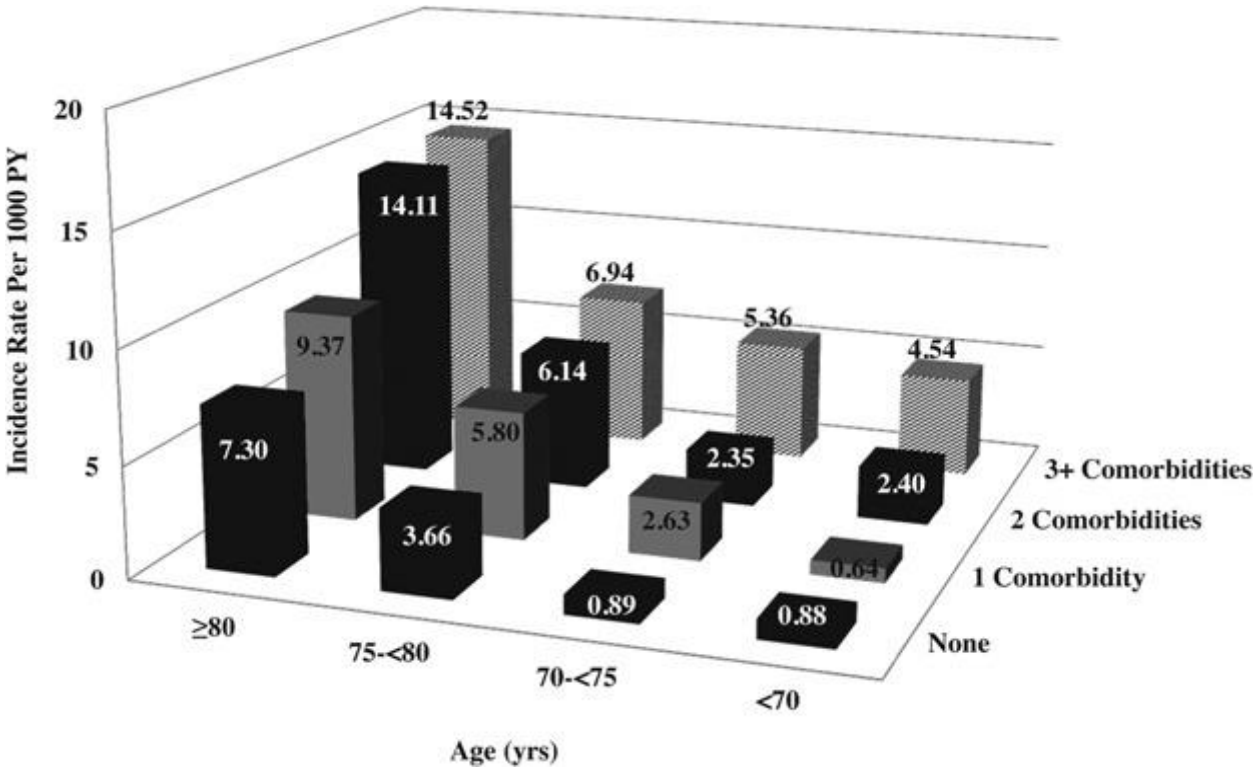


Figure 7. Risk Factors (co-morbidities) for Hip Fracture in Older Men: the MrOS Study

6.4 Bone Health in Aging Adults

As a result of aging, there are changes that occur in the composition and structure of the bone that may impact the function of bone. Bone is dynamic and undergoes constant remodeling, removing old bone and replacing with new bone, throughout our lifespan. Our bone remodeling process is generally equal but with aging turns to a negative one. There is a greater breakdown of bone in comparison to bone formation, resulting in changes that can weaken the structure of the bone.

6.4.1 Bone Remodeling

Bone remodeling is a process highly regulated throughout our lifetime and is essential to preserve bone integrity. The bone matrix is primarily composed of type 1 collagen fibers and non-collagenous proteins. Simplistically, during the bone remodeling process, osteoclast cells are activated, and older bone is resorbed. The resorption occurs as the osteoclast cells adhere to the bone wall and acidify and proteolyze the bone matrix. Osteoblast cells are also activated, and new bone is formed. Osteoblast cells function in a large group of cells and create bone by assisting in production of the bone matrix by laying down collagen and mineral deposits. [322, 323] The bone matrix then matures and is mineralized. These processes normally occur at the same rate. This cycle is regulated by the paracrine and endocrine systems through cytokines, growth factors, and prostaglandins. This close collaboration between the osteoclast and osteoblast cells is known as a basic multicellular unit. [324] Women tend to experience rapid decline in loss of bone mass following menopause. Men, by the ages 65-70, lose bone at the same rate as women, and both genders absorb less calcium. [325]

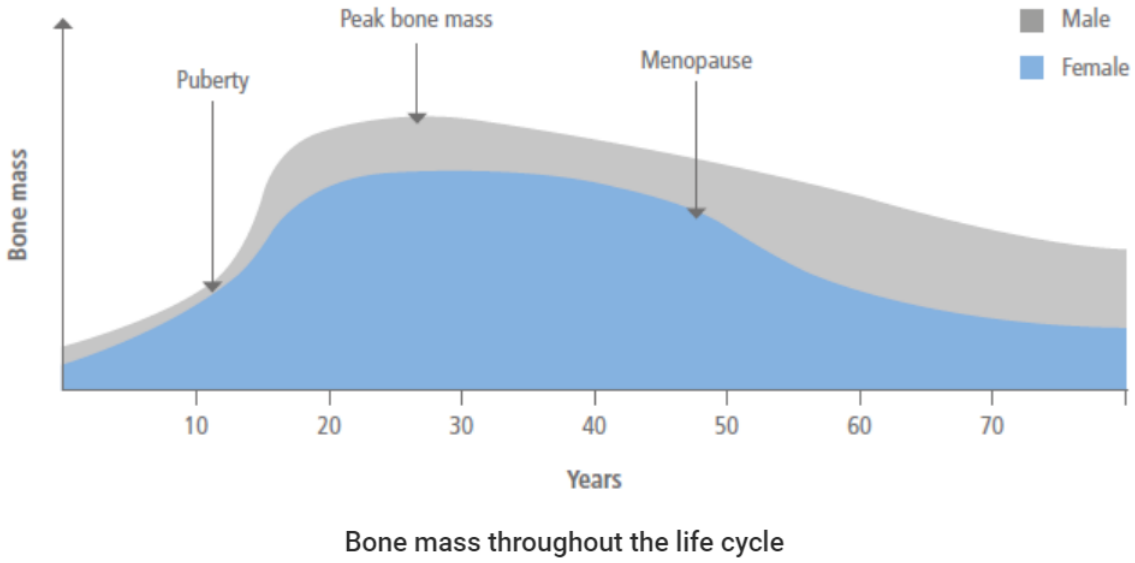


Figure 8. Bone Mass throughout the Life Cycle, via International Osteoporosis Foundation

6.4.2 Inflammation & Bone Health

High levels of inflammation have been linked to several co-morbid conditions and negative health outcomes such as declines in function and cardiovascular disease.[326, 327] In the Health, Aging, and Body Composition cohort, Cauley et al found that high level of inflammatory markers, c-reactive protein, interleukin cytokines (IL-6, IL-2), and tumor necrosis factor (TNF), were associated with increased risk of fracture over nearly 6 years of follow-up. The association increased for the older adults who had elevations in multiple inflammatory markers. [328] The TNF-α factor has been associated with osteoclast stimulation and may alter the bone remodeling cycle to favor breakdown of the bone. Both CRP and IL-6 cytokines have been linked to many co-morbid conditions that may influence physical function and have a more in-direct role in fracture risk.[36, 329]

6.4.3 Osteoporosis

Disruption to the bone remodeling cycle results in unbalanced systems and with aging, this generally results in osteoporosis.[324] Osteoporosis is known as a silent disease because it can be undetected until a problem, such as a fracture occurs. Osteoporosis is a disease that occurs when too much bone is lost or not enough bone is produced, resulting in weakness within the bone. The weakness occurs as a result of decreased numbers of trabeculae, thinning of the trabeculae and decreased thickness of the cortical bone. Osteoporosis is a systemic disease. World-wide, osteoporosis causes over 8 million fractures.[330] As noted, this is a disease that is not limited to women but can impact men as well at a later age in life. [325]

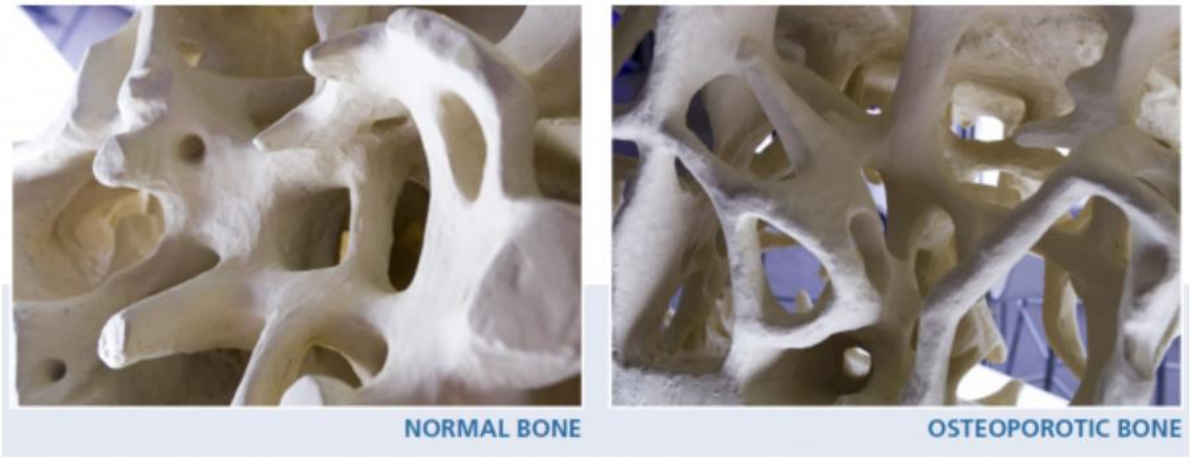


Figure 9. Normal Versus Osteoporotic Bone, via International Osteoporosis Foundation

7.0 Recurrent Falls

Nearly 30% of adults ≥ 65 years of age will experience a fall each year. [321] This equates to an estimated 29 million falls each year. The prevalence increases to 40% for those 80 years and older. [321] Falls are a leading cause of injury, disability, and death among adults. [331] Over half of falls have been shown to result in injury. [332, 333] While the fall may result in physical injury, even without injury a psychological impact that includes a decrease in confidence in mobility and an increase in fear of falling may occur. [332, 334] Fall events are a public health concern due to the frequency, consequences, and the growing aging population.

7.1 Risk Factors for Falls in Older Adults

Risk factors for falls are extensive and often intertwined especially in understanding their role in older adults who often have various and numerous combinations of these factors. Falls may result in diminished physical function, cause injury, activity limitations, and loss of mobility.

7.1.1 Non-Modifiable Risk Factors for Falls in Older Adults

7.1.1.1 Demographic Factors

Higher rates of falls occur in the oldest age groups, with 26.7% of adults 65-74 years of age reporting at least 1 fall in the past year and the percent increases to 29.8% among those 75-84 years and to 36.5% among those 85 years and older ($p<0.01$). [321] [335] Estimates of fall events

from cohort studies report that nearly 28.2% of men ≥ 65 years of age report ≥1 fall over a year (n=2,731, community-dwelling, mean age= 78.9 years) and 14.2% report ≥ 2 falls over a year (n=3,101, community-dwelling, mean age= 76.4 years). [336, 337] Roughly 15% of adults will fall at least 2 or more times per year. [333] Fall events are even greater for adults residing in long term facilities nearing 50% for at least 1 fall and nearly 40% experiencing recurrent falls. [338] The incidence rate of falls increases with age, with the highest incidence seen in the oldest old. The rate for those 70 – 74 years is 47 per 100 person-years and rises to 121 per 100 person-years in those 80 years old and older. [339, 340] The Centers for Disease Control reports the rate of fall injuries in adults 85 and older are nearly 4 times greater than in adults ages 65-74 in the United States. [341] Factors that may be contributing to this are age-related frailty, restricted mobility, more frequent use of multiple medications, and living alone.

Women fall more often and have more injurious falls than men. In women ≥ 65 years, 30.3% report ≥ 1 fall compared to 26.5% of men ≥ 65 years ($p<0.01$). [335] Women are thought to experience a greater number of falls and higher risk of fall injury due to worse lower extremity strength, more difficulty with activities of daily living, and having a higher prevalence of osteoporosis. [342-344]Women have been shown to be more likely to experience an injurious fall (BRFSS 2006; 35.7% of women vs 24.6% of men, $p<0.05$) while men are more likely to experience a fatal fall. [343, 345] Duckham et al reported that older adult women were more likely to experience a fall while indoors and while completing household chores (Indoor fall rate ratio (women/men) = 2.34 (95% CI=1.54-3.57) and household chore rate ratio (women/men) = 3.48 (95% CI=1.41-8.55)). [346] A strength of this study was adjustment for a falls risk index which included age, education, race, BMI, physical activity, blocks walked per week, balance, SPPB, vision, pain, number of co-morbidities, self-rated health, peripheral neuropathy, knee OA,

depression, number of medications, use of psychotropic medications, MMSE, falls efficacy, and number of falls. The falls risk index score is the summation of the products of the person's risk level multiplied by the regression coefficient of the corresponding risk factor, for all risk factors included. Assessment of falls was via a monthly calendar over 4.3 years of follow-up time. Women are at higher risk of experiencing fall events in comparison to men.

Differences in risk of falls exist across race. The proportion of older adults who experienced a fall was reported to be higher among whites (29.6%) as compared to blacks (23.2%) and Asians (19.8%) in the US. [331, 347-349] The Duke EPESE study reported that African Americans have 0.77 lower odds of falling in comparison to whites (95% CI= 0.62-0.94). [350] The Study of Osteoporotic Fractures revealed no differences in age adjusted rates among African-American and white females (African-Americans RR=1.30, 95% CI=0.93-1.85 in comparison to whites). [351] The Hispanic EPESE study reported 31.8% of adults ≥72 years of age reported 1 or more falls over 12 months, noting that the prevalence of falls is similar to that of non-Hispanic whites. [352] The cause for ethnic differences among falls is unknown, though may potentially be due to differences in health and lifestyle behaviors. [335, 353]

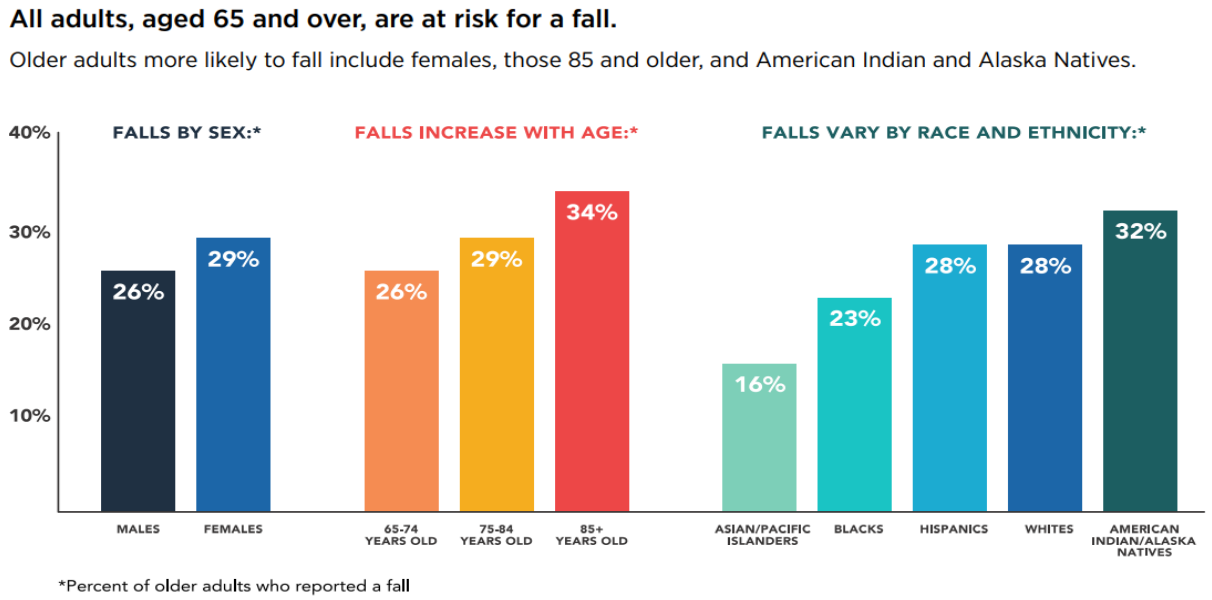


Figure 10. CDC Report, aged 65 and over Risk for Falls

7.1.1.2 Age Related Changes in Vision

Various components of vision are important in navigating potential hazards as well as discerning spatial relationships and distance estimation. Good vision is also important to maintain balance. Declines in visual acuity and contrast sensitivity are components of vision that have been implicated with falls in aging adults. [354, 355] Vision is assessed either through self-report impairment or through testing during a clinic visit. DeBoer et al in the Longitudinal Aging Study (LASA) study reported those with low contrast sensitivity have 2.09 times higher risk of falling compared to those with normal contrast sensitivity (95% CI=1.41-3.20). [354] Falls were assessed through a weekly fall calendar diary minimizing the length of the recall. Differences in the estimates of risk are likely to due to the various methods of assessing fall events which are summarized in Table 10. The differences in the assessment of falls include yearly recall of fall events to weekly fall calendars which fall events are more likely to be recorded.

7.1.1.3 Impaired Cardiovascular Function

Impaired cardiovascular function, such as alterations in heart rhythms and blood pressure (high and orthostatic hypotension), may result in unexplained or syncopal fall events. [356, 357] Additionally, alterations in heart rhythms have underlying mechanisms of decreased cardiac output and impaired baro-reflexes that do not allow for necessary compensation and increase the risk of falls. [358, 359] These cardiovascular impairments can decline as a function of aging or as a result of disease and therefore increase risk for fall events.

7.1.1.4 Altered Neuromuscular Function

The neuromuscular system, which includes both the peripheral nervous system and musculoskeletal system, plays an important role in maintaining upright balance and adequate mobility. Declines in proprioception and nervous systems, impaired reflexes, and dysfunction of muscle innervation may increase fall risk. Given that these systems work in sync to maintain mobility and to keep upright position while moving, when there is declines in one system the other intact systems may not have the reserve to make up for the loss. [360] Declines in proprioception and peripheral neuropathy, which occur as a part of aging or be a consequence of chronic diabetes, increase the risk of falls. [361, 362]. The increased risk of falls in persons with diabetes is estimated to be 1.64 times higher (95% CI= 1.27-2.11) compared to persons without diabetes. [363] Diabetes is associated with alterations in gait. [364] Diabetic peripheral neuropathy starts distally and moves more proximal with progression. The effect on strength and balance are noted in the feet and ankles and also has effect on walking tasks. [364] Diabetic peripheral neuropathy has also been associated with poor physical performance, which is a known risk factor for falls as well. [365] Adults in the Health ABC cohort with diabetes in comparison to adults without diabetes completed fewer chair stands per second (0.34 vs 0.36), worse standing balance (0.69 vs 0.75), slower usual gait speed

(1.11 vs 1.14 m/s), and lower SPPB scores (6.43 vs 6.93) that were all statistically significant ($p<0.05$). [365] In each of these models, after adjustment for peripheral nerve function physical performance values improved for persons with and without diabetes. This finding is important because it reveals that peripheral neuropathy interacts with physical performance directly, not through an indirect pathway through muscle. [365] Additionally, peripheral nerve function is not often accounted for in the assessment of physical performance. The interplay between the neuromuscular and musculoskeletal systems is important to maintain safe mobility and reduce risk of falls

The medical treatment for diabetes increases the risk of falls in older adults. Use of insulin in the management of diabetes has shown to increase risk of any fall, recurrent falls, and serious injurious falls (i.e. hospitalization ICD-9 code). [361, 362] The likelihood of experiencing at least 1 fall in the past year with diabetes being treated with insulin is 2.78 times higher versus without diabetes (95% CI=1.82-4.24) and with diabetes not being treated with insulin is 1.68 higher odds versus without diabetes (95% CI=1.37-2.07). The likelihood of experiencing recurrent falls in the past year with diabetes being treated with insulin is 2.55 times higher versus without diabetes (95% CI=1.45-4.47). Whereas the likelihood of experiencing recurrent falls in the past year with diabetes not treated with insulin is 1.63 times higher versus without diabetes (95% CI=1.22-2.18). [362] Older adults with diabetes, and in particular those treated with insulin, are at higher risk of recurrent and serious injurious falls compared to those without diabetes.

7.1.1.5 Osteoarthritis

Knee osteoarthritis additionally contributes to altered gait patterns through instability, stiffness, malalignment, and pain. [182, 366-368] Knee instability, a frequent symptom in adults with knee OA, is associated with limited confidence in their knees, decreased balance, functional

limitation and fear of falling that are all independent of pain. Nevitt et al reported in the Multicenter Osteoarthritis Study (MOST) (N=1697, age 50-79 years) that knee instability is associated with 1.98 greater odds of recurrent falls than those without this symptoms over a 2 year follow up period (95% CI= 1.35-2.91). [368] Cross-sectionally, knee instability, defined as symptoms of buckling or shifting, had increased odds of 2.0 and 1.5 respectively for recurrent falls as compared to those without knee instability. [368] Knee instability has been shown as an independent risk factor for those with knee OA and/or knee pain. Adults experiencing knee instability are also more likely to have higher fear of falling and decreased confidence in their balance. Data from the Multicenter Osteoarthritis Study (MOST), ages 50-79 years, demonstrate that participants who report knee instability and knee buckling have increased prevalence rates of fear of falling. Knee instability or limited knee confidence is associated with fear of falling with a prevalence rate of 1.4 (95% CI=1.3-1.6) and report activity restriction with a prevalence rate of 5.3 (4.2-6.8) in comparison to those who do not report symptoms of knee instability. [369] Osteoarthritis can additionally be a contributing factor to declines in physical performance. [182, 200, 366] Fear of falling in adults with knee OA can prompt avoidance of activity that leads to physical decline and functional limitation that are independent of the frequency of fall events. [369, 370]

7.1.1.6 Fall History

History of a fall also increases the likelihood of a future fall event. [347] The act of the fall itself is likely not directly causing a future fall but may be a summary indicator of the presence of multiple risk factors. Most falls are consequences of problems with mobility and balance and the risk factors for falls often impact the association through this effect. [338, 347, 348, 360, 371, 372] Fear of falling is considered a risk factor for falls as well. [373] Fear of falling can influence

activity restriction and fall risk. [374, 375] Falls and fear of falling are important barriers to older adults and both increase the risk of falls.

7.1.1.7 Co-morbid Conditions

A higher number of co-morbid chronic conditions can increase the risk of falling in adults. [376] Medical conditions including Parkinson's disease, history of stroke, depression, urinary incontinence, osteoporosis, chronic pain, and cognitive impairment have all been shown to increase the risk of falls. [347, 377-382] Parkinson's disease and stroke increase the likelihood of experiencing falls due to the decreased muscular strength and power output, poor balance, altered posture, and decreased coordination. Parkinson's disease can increase the likelihood of ≥ 1 fall event by 4.61 times (95% CI= 1.34-15.8) and recurrent fall events by OR=9.50 times (95% CI=1.80-50.1) in comparison to persons without the disease. [331, 383] Stroke can increase the likelihood of any fall event by 51% (95% CI= 1.09-2.00) and recurrent fall events by OR=2.59 times (95% CI=1.30-5.16) in comparison to persons without. [383, 384] Mood disorders, such as depression, can increase the risk for experiencing ≥ 1 fall by OR=1.4 (95% CI=1.0-2.0) and ≥ 2 falls by OR=1.6 (95% CI= 1.0-2.5). [385] Multi-morbidity increases the risk of falls in adults.

7.1.2 Modifiable Risk Factors

7.1.2.1 Muscle Weakness

Muscle impairment occurs with aging and in adults with knee OA. Quadriceps strength impairment with knee OA has been documented between 10-56% based on isometric strength testing. Maximal strength testing in persons with knee OA may introduce methodological concerns

because a certain proportion of participants would not be able to complete the testing and would be excluded from the results, which may introduce bias. [187] Eccentric quadriceps strength impairments are more dramatic at 76% deficit in comparison to adults without knee OA. [386] Impaired nervous system activation and decreased cross-sectional area are associated with muscle impairment in knee OA. [187] Arthrogenic muscle inhibition, dysfunction in recruiting all motor units, is common in conditions with joint dysfunction. Strength deficits have been noted in the quadriceps, hamstrings, and hip rotators and abductors. [187] However, maximal quadriceps contraction or that of other lower extremity muscles, are generally not required for gait or other activities of daily living. Abnormal gait patterns and impaired physical function, which arise as a result of impaired nervous system input, decreased lower extremity joint range of motion, or increased weakness in muscular strength may increase the risk of a fall. Older adults exhibit a gait pattern that is less coordinated and efficient. [387] Older adults have a tendency to demonstrate decreased step height and length, have decreased muscle tone and strength, diminished acceleration to adjust to perturbation, and declining body orienting reflexes that all impair the ability to avoid a fall. [387] Muscle impairment increases the risk of falls in adults.

7.1.2.2 Physical Function and Performance

The association between falls and mobility is thought to be an inverted U shape. Adults who are at the ends of the mobility spectrum are at lower risk for falls. This includes those who cannot move themselves independently and are not likely to fall and those with high capacity for movement who are skilled to avoid a fall. [385, 388] Not only is there change in gait performance with aging but there is also a clear decline in other physical performance measures as well. Decreased performance on physical tests including chair stands, narrow walk test, number of steps to complete 180-degree turn, and strength testing all indicate risk for any fall and injurious falls.

[331, 332, 389] Poor lower extremity performance, limited range of motion, decreased strength, and impaired nervous system function, which may manifest as poor physical function, are all considered risk factors for falls. [348, 357, 382, 390]

7.1.2.3 Physical Activity

Physical activity has demonstrated differences for fall risk across age that mimics a reverse J shape. In the Osteoporotic Fractures in Men Study (MrOS), men who were 80 years and older, with the lowest levels of energy expenditure, had 1.43 higher risk of falling compared to those the most active men (p=0.09 for trend). [336] Men who were less than 80 years in the lowest levels of energy expenditure group was less likely to fall compared to the most active group (RR=0.75, p=0.08). This was after adjustment for important covariates in the model. [336] This difference by age may be explained by functional ability and overall health. Men who were ≥ 80 years may demonstrate worse balance and strength and poor health status placing them at a higher risk of falling. Whereas men who were younger and most active, may have the greatest exposure to fall events placing them at highest risk. Other studies have showed that persons who are self-reporting the highest levels of physical activity are at lower risk of experiencing a fall event. [385, 388] Self-report physical activity in older adults is a challenge because of the limited number of leisure activities included, their overestimation of activity, and recall bias in reporting physical activity. The study above from MrOS used objective measures of physical activity which can overcome the limitations of self-report.

7.1.2.4 Body Mass Index (BMI)

Inconsistent results have been found in the association between body mass index and falls. Both low BMI and high BMI have been shown to increase the risk of falls, indicating a U-shaped

association. [391-393] Those who are underweight or frail have an estimated 1.38 increased odds of falling compared to those who are robust (95% CI=1.02-1.88) likely due to poor muscle strength. [392] Hooker et al reported from the MrOS Study that the fall rate was greatest in the oldest age group with the highest BMI (1.47 falls/man-year). [394] In this study across all age groups, men who were obese (BMI ≥30 kg/m^2) had 1.92 increased odds of falling compared to men with normal BMI (18.5 to 24.9 kg/m^2). [394] Additionally, men in the higher classes of obesity (II and III 35-50 kg/m^2) had nearly twice the risk of falls compared to men in the normal BMI group (RR=1.92, 95% CI= 1.28-2.89). [394] Obesity may increase fall risk by altering postural stability, greater amounts of physical limitations, and more obesity-related chronic conditions. Use of different cut-points to define underweight and obesity, such as quartiles of a population, may also create challenges in interpreting and comparing the risks presented in the literature. Use of various cut-points for defining body size may make it difficult to understand who is at higher or lower risk, who is characterized as the referent population, as well as understanding the association with body size.

7.1.2.5 Medication Usage

Medication usage, including both the number of medications used as well as the type of medication used, has been shown to increase the risk of fall events. [390, 395] Medications that are considered central nervous system active, falling into categories known as psychotropic, cardiac, benzodiazepines, analgesics, anti-depressants, and anti-hypertensive are a few types that have been shown to increase falls in older adults. [396, 397] Polypharmacy may be an indicator of multi-morbidity. Medication use and polypharmacy is a modifiable risk factor for falls in older adults.

Medication usage is common in management of OA symptoms. Current guidelines recommend first line use of acetaminophen and non-steroidal inflammatory drugs, antidepressants, and opioids are considered second and third line options. [398] Fully adjusted models from the Osteoarthritis Initiative Study (OAI) study report that persons using any opioid have 1.22 times increased risk of recurrent falls in comparison to persons not taking any pain medications (95% CI=1.04-1.45). [399] This study also reported that participants taking antidepressants had 25% increased risk of recurrent falls compared to persons not taking any pain medications (RR=1.25, 95% CI=1.10-1.41). [399] Among participants with radiographic knee OA (KL grade $\geq$ 2), any opioid use increased the risk of recurrent falls 1.3 times higher compared to those not using any pain medications (RR=1.31, 95% CI= 1.07-1.59). [399] Among these participants with radiographic knee OA, those using antidepressants had 1.23 times higher risk compared to those not using any pain medications (RR=1.23, 95% CI=1.05-1.45). [399] Among those with KL grades <2, possible or no OA group, only antidepressants increased the risk of recurrent falls (RR=1.28, 95% CI=1.06-1.54). [399] Potential explanations for the association between opioids and anti-depressants with recurrent falls are the side effects of the medications (dizziness, drowsiness, cognitive impairment), users were more likely to also use other psychotropic medications, and those taking opioids had a higher burden of co-morbidities and poor self-reported health. Some limitations are that falls were assessed annually through interview, medication information was also collected at annual visits, and dosage of medications was not obtained. These results were adjusted for known important confounders in the association. The study included a 4 year follow up time frame. These findings suggest that use of opioids and anti-depressants in adults with knee OA increases the risk of recurrent falls.

7.1.2.6 Chronic Pain

Chronic pain is considered a risk factor. The severity of pain and number of sites involved are also correlated with falls. [400, 401] The higher the pain and the more sites involved, the higher the risk of falls. In association with symptomatic knee OA, the Johnston County OA Project demonstrated increased odds of falling with higher numbers of painful joints over a 6-year period. Adults with 1 painful lower extremity joint had 53% higher odds and 3-4 painful lower extremity joints had 85% higher odds of falling in comparison to those with no painful joints. [331, 402] As previously mentioned, medication therapy used to manage the painful conditions can also increase that likelihood of falling as well. The combination of multiple painful joints and resultant pain management with opioids will increase the risk of falls in adults.

7.1.2.7 Alcohol Use

Mild alcohol use has been shown to be protective of falls in comparison to abstainers and those with excessive alcohol use. [403] The exact mechanism of this protective effect is not clear. It has been hypothesized that adults who are abstainers from alcohol may have poor health status. Abstaining from alcohol use may be a proxy for health status.

7.2 Assessment of Falls

Assessment of falls in epidemiological studies have had issues with accuracy, recall, and varied definitions of a fall exist. Generally accepted definition in the literature includes coming to rest on the ground, floor, or lower level unintentionally. This definition excludes the position change that may result in coming to rest on a piece of furniture or against a wall. A clear definition

of a fall event may improve accurate reporting and comparison of studies are challenging without comparable definitions. [404]

Falls may be collected through retrospective reporting systems, prospective reporting systems, or surveillance systems. Retrospective reporting includes questionnaires through interview or automated telephone calls that cover various periods of time, which may be from days to a year in length. Prospective reporting includes use of postcards, diaries, or calendars that also range in time period from a day to several months. The frequency of assessment is important as well given that a fall event may have poorer recall over a longer length of time. Use of a more frequent collection of falls data, such as daily to monthly reports, is more accurate than longer time periods of recall. [405] A systematic literature review revealed that a 12 month recall for falls has 87% sensitivity and 93% specificity in comparison to using weekly or monthly fall calendars or postcards. [406] Surveillance systems are passive and would include use of electronic health records. Use of administrative data would likely not provide information unless there was injurious fall or suspected injurious fall. This type of data is valuable in understanding differences within the severity of the insult, however not as useful for non-injurious falls. [404] Inaccuracy with use of medical coding to identify falls exists because the ICD code may be recorded incorrectly or not recorded at all. Prospective assessments of fall events with short time intervals likely provide the most accurate assessment of fall events.

7.3 Background Epidemiology on Recurrent Falls in Older Adults with Knee OA

The association of recurrent falls and radiographic evidence of knee OA has been inconclusive. It has been suggested that it is not presence of OA on radiograph films that is

associated with falls but rather the pain and muscle dysfunction that is associated with the fall. [407, 408] Cross-sectional analyses have demonstrated that an increased risk for any fall events in persons with newly diagnosed radiographic knee OA and radiographic knee OA with symptoms of instability or symptoms interfering with physical function. [367, 368, 409, 410]. Additionally, Tsonga et al in a small study stated persons with moderate to severe knee OA reported 63.2% experiencing at least 1 fall over a year, with 29.4% reporting only a single fall and 33.8% reporting recurrent (≥ 2) falls. [411] Limitations in these cross-sectional studies that include selection bias and a lack of temporal associations between falls and knee OA. In this study, participants included only those seeking medical care for total joint replacement with symptoms of knee OA lasting at least 1 year. From the results of these studies, symptoms of pain and stiffness that are commonly associated with knee OA appear to be related to falls in community dwelling adults vs. radiographic knee OA.

Longitudinal research has demonstrated inconclusive results on which sub-groups of persons with knee OA are at risk for increased falls. Arden et al assessed incident fall events in men and women 75 years and older. Knee OA was assessed through self-report of pain or stiffness on most days of the month or through self-report clinician diagnosis. Those who self-report pain and stiffness have statistically significant increased risk of experiencing a fall event over 3 years (HR= 1.26, 95% CI= 1.17-1.36) as compared to those who do not report knee pain and stiffness. [412] Muraki et al report an increased risk of recurrent falls (≥ 2) in women only who report knee pain or stiffness over most days of the month (OR= 1.87, 95% 1.06-3.28) over 1 year in comparison to those who do not report knee symptoms. [413] Nevitt et al reported that over a 2 year follow up period, persons with radiographic knee OA and symptomatic knee OA who report instability have increased odds of recurrent falling compared to those who do not

report instability (OR= 1.98, 95% CI=1.35-2.91). [368] Dore et al reported on fall risk in the Johnston County OA Project. In a study of 1,619 participants 45 years and older, there is increased risk of at least 1 fall event for persons with radiographic and symptomatic knee OA over 12 months (OR= 1.39, 95% CI= 1.02-1.88) compared to persons without radiographic and symptomatic knee OA. [414] These studies provided framework for the association between OA and recurrent falls and suggest the association of knee OA and falls is stronger among adults who report symptoms in comparison to those with radiographic knee OA alone.

The literature on recurrent falls and knee OA is limited in the length of follow-up for ascertainment of the outcome. The longest follow up period for assessment of falls was roughly 3 years in length. The primary assessment of the outcome is through questionnaire or interview regarding a 12-month period of recall for fall events. This length of recall time may introduce some bias into the participant self-report and bias results towards the null hypothesis. No distinction in these studies between stages of OA status exists or if this differs by incident diagnosis, established diagnosis or if the knee OA is progressing in its course. Potential exists for variation in risk of fall events based on status of the disease. Insight into sub-populations of adults with knee OA may provide understanding as to who would most benefit from intervention to prevent falls.

Table 4. Demographic Variables and Association with Falls

Study	Population	Variable Assessment	Results
AGE			
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years N=1285	Predictor: Age per 10 years Outcome: any fall, recurrent fall, calendar- weekly x 1 year	Age per 10 years & ≥2 fall → OR=1.4 (1.0-1.8)
Ven Hensbroek et al 2009 Cross-Sectional	Dutch Falls Prevention Collaboration, CAREFALL, community-dwelling, age ≥ 65 years N=300	Predictor: self-report age Outcome: medical record of fall event	Age (per year) & any fall → OR=1.06 (1.02-1.10)
GENDER			
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years	Predictor: self-report gender (female) Outcome: any fall, recurrent fall,	Self-report gender (female) & ≥1 fall → OR=1.4 (1.1-1.8)

	N=1285	calendar- weekly x 1 year	
Stevens et al 2005 Cross-Sectional	National Electronic Injury Surveillance System All Injury Program (NEISS-AIP) in US, age ≥ 65 years N=22,650	<u>Predictor:</u> Gender via electronic medical record <u>Outcome:</u> injurious fall via electronic medical record	Females & injurious fall- fracture → RR=2.2 vs males Females & injurious fall- sprain → RR=1.8 vs men
Ven Hensbroek et al 2009 Cross-Sectional	Dutch Falls Prevention Collaboration, CAREFALL, community-dwelling, age ≥ 65 years N=300	<u>Predictor:</u> self-report gender <u>Outcome:</u> medical record of fall event	Gender (female) & any fall → OR=1.06 (1.02-1.10)
Duckham et al 2013 [346] Cohort	Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study, community-dwelling, age ≥ 65 years N=743	<u>Predictor:</u> gender via interview <u>Outcome:</u> any fall, recurrent fall, injurious fall,	Female/Male Rate Ratio → Total Injurious Falls RR= 1.97 (1.44-2.68)

		monthly calendar x 4.3 years	Vigorous Outdoor activity & fall RR=0.42(0.21-0.84) Recreational Outdoor Activity &fall RR=0.30 (0.15-0.58) Snow/icy condition & fall RR=0.57 (0.38-0.87) Walking on sidewalk/street & injurious fall RR=1.66(1.14-2.43) In Kitchen/dining room → any fall RR=2.72(2.42-5.22)

			injurious fall RR=6.37(1.91-21.26) Walking indoors → any fall RR=1.46(1.04-2.06) injurious fall RR=2.51(1.52-4.16) Indoor Stairs & fall RR=0.63 (0.40-0.97) Indoor chores & fall RR=3.48(1.41-8.55) Slip indoors & fall RR=2.34(1.54-3.57)
Nicklett et al 2014 Cohort	Health & Retirement Study, community-dwelling adults, ≥65 years of age N=16,484	Predictor: self-report gender Outcome: self-report falls, interview, 2-	Male & any fall → OR=0.82 (0.69-0.98)

		year recall period, 2000-2010	
RACE			
Nevitt et al 1989 Cohort	Community-dwelling adults, age >60, history of at least 1 fall, 82% female N=325	<u>Predictor:</u> self-report ethnicity <u>Outcome:</u> recurrent fall, weekly post cards x 1 year	Self-report ethnicity(white) & recurrent fall → OR= 2.4 (1.7-5.3)
Reyes-Ortiz et al 2002 Cohort	Hispanic EPESE, community-dwelling; ≥ 72 years; N=1391	<u>Predictor:</u> self-report Hispanic ethnicity <u>Outcome:</u> self-report falls, interview, 1-year recall period	31.8% experienced 1+ falls/12 months
Faulkner et al 2005 Cohort	Study of Osteoporotic Fractures; 100% female; mean age =76 years N=1821	<u>Predictor:</u> self-report ethnicity <u>Outcome:</u> any fall, recurrent fall via triannual post card x 5.7 years	Non-Hispanic white vs African American for any fall RR=1.3 (0.93-1.83)

Hanlon et al 2002 Cohort	Duke EPESE; community-dwelling; 62% female, ≥ 65 years; N=2996	<u>Predictor:</u> self-report ethnicity <u>Outcome:</u> self-report falls, interview, 1- year recall period	African American vs White for 1+ fall → OR=0.77 (0.62-0.94)
Nicklett et al 2014 Cohort	Health & Retirement Study, community- dwelling adults, ≥65 years of age N=16,484	<u>Predictor:</u> self-report ethnicity <u>Outcome:</u> self-report falls, interview, 2- year recall period, 2000-10	African American (vs. white) & any fall → OR=0.65 (0.53-0.80)
Geng et al 2017 Cross-Sectional	Kaiser Permanente Northern California Member Health Survey Ages 65-90 years, 100% female N=6277	<u>Predictor:</u> self-report ethnicity <u>Outcome:</u> self-report any & recurrent fall x 1 year	Asian vs NH-white for any fall → OR=0.64(0.05-0.81) Black vs NH-white for any fall → OR=0.73 (0.55-0.95)

			Asian vs NH-white for recurrent fall → OR=0.62 (0.43-0.88)

Table 5. Associatino of Vision Impairment with Falls

Study	Population	Variable Assessment	Results
Dargent-Molina et al 1996 Cohort	EPIDOS, community-dwelling females, mean age= 80.5 years, N=7575	Predictor: visual acuity in clinic exam Outcome: injurious fall, tri-annual post card, x 2 years	Visual acuity (<2/10) & injurious fall → RR= 2.0 (1.1-3.7)
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years N=1285	Predictor: self-report visual impairment of facial recognition at 4 meters Outcome: any fall, recurrent fall, calendar- weekly x 1 year	Vision impairment & ≥1 fall → OR=1.7 (1.3-2.3) Vision impairment & ≥2 fall → OR=2.6 (1.8-3.8)
deBoer et al 2006 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-	Predictor: self-report vision impairment; vision testing	Low sensitivity contrast & recurrent falls → HR= 2.09(1.41=3.20)

	dwelling; mean age=76 years N=1509	Outcome: any fall, recurrent fall, calendar- weekly x 3 years	Integrated contrast sensitivity & recurrent falls → HR= 1.53(1.03-2.29)
Schwartz et al 2008 Cohort	Health Aging & Body Composition Cohort Ages 70-79 years; N=446	Predictor: vision testing: contrast sensitivity Outcome: any fall, recurrent fall, interview over 12-month recall	Poor contrast sensitivity & any fall → OR= 1.41(0.97-2.04)
Crews et al 2016 Cross-Sectional	Behavioral Risk Factor Surveillance System, nationally representative in US, ages ≥ 65 years N=1,290, 055	Predictor: self-report vision impairment Outcome: self-report fall via interview x 12-month recall	Age-adjusted prevalence of falls with vision impairment 46.7% compared to those with no vision impairment 27.7% ($p<0.001$)

Table 6. Association of Diabetes and Falls

Study	Population	Variable Assessment	Results
Schwartz et al 2002 Cohort	Study of Osteoporotic Fractures, Community-dwelling adults, 100% women, age >65 years N= 9249	Predictor: self-report diabetes, vibration testing, filament testing Outcome: any fall, recurrent fall, tri-annual postcards, mean follow up 7.2 years	DM no insulin & any fall→ OR=1.68 (1.37-2.07) DM & insulin & any fall → OR=2.78 (1.82-4.24) DM no insulin & recurrent falls → OR=1.63 (1.22-2.18) DM + insulin & recurrent falls → OR=2.55 (1.45-4.47)
Yang et al 2006 Meta-Analysis & Systematic Review	Community-dwelling adults, age ≥65 years N=14685	Predictor: self-report DM or use of DM medication Outcome: any fall, injurious fall, triannual	DM & any fall → RR=1.64 (1.27-2.11) DM with insulin & any fall → RR=1.94 (1.42-2.63)

		post card/monthly fall calendar/6-month interview/hospitalization	DM & no insulin & any fall → RR=1.27 (1.06-1.52)
Schwartz et al 2008 Cohort	Health Aging & Body Composition Cohort Ages 70-79 years; N=446	<u>Predictor:</u> self-report DM, AIC measurement <u>Outcome:</u> any fall, recurrent fall, interview over 12-month recall	Low A1C (<6%) in insulin users & any fall → OR= 4.10 (1.24-13.54)
Yau et al 2013 Cohort	Health Aging & Body Composition Cohort Ages 70-79 years; N=3075	<u>Predictor:</u> Self-report DM, medication for DM, fasting glucose ≥ 126 mg/dL <u>Outcome:</u> hospitalization for fall (ICD-9 code)	DM & injurious fall → HR= 1.48 (1.12-1.95) DM with insulin & injurious fall → HR=3.0 (1.78-5.07) DM without insulin & injurious fall → HR=2.18 (1.22-3.93)

Table 7. Association between Cardiovascular Impairment and Falls

Study	Population	Variable Assessment	Results
Kario et al 2001 Cohort	Community-dwelling adults in Bronx, NY, mean age =76 years, 54% women N=266	Predictor: BP in supine & 2 minutes standing, HTN=>140/90 mmHg, untreated Outcome: any fall x 12 months, monthly postcard	2.8 x more fall events greater in lower BP (<140) compared to higher BP (>140) (p<0.0003); 10 mmHg increase in standing BP reduced falls 22% (RR=0.78, p=0.0005)
Heitterachi et al 2002 Cohort	Community dwelling adults, mean age= 77 years N=70	Predictor: continuous BP Head Up Tilt Table at supine & 60 degrees; OH=20 mmHg drop in SBP Outcome: any fall x 2 months, interview, 12-month recall	OH at 3 min → 22% fallers; OH at 3 min & any fall → RR=1.7 (1.1-2.6)
Bergland et al 2003 Cohort	Community-dwelling adults, mean age=81 years, 50% women	Predictor: self-report HTN	HTN & any fall→ OR=1.9 (p<0.02)

	N=307	Outcome: any fall x 12 months, interview, 12-month recall	
Gangavati et al 2011 Cohort	Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study, Community dwelling, mean age= 78 years N=722	Predictor: BP supine, standing 1 min & 3 min; 20/10 OH definition Outcome: recurrent falls (2+ falls), monthly fall calendars x 1 year	39% with uncontrolled HTN & OH had recurrent falls; Uncontrolled HTN +OH at 1 min standing for recurrent falls → HR=2.5 (1.3-5.0)
Stenhagen et al 2013 Cohort	Good Ageing in Skane cohort, Community-dwelling adults, 54% women N=1763	Predictor: Medical record of heart failure (ICD-10 code) Outcome: any fall at 3 & 6 years, interview at 3 &6 years- fall in past 6 months	Heart failure & any fall → OR=1.88 (1.17-3.04) Use of neuroepileptics & any fall → OR=3.30 (1.15-9.43) Slow gait speed & any fall → OR=1.77 (1.28-2.46)

Wong et al 2014 Cohort	Sydney Memory & Aging Study; Community-dwelling; Mean age=80 years, 52% women, N=481	<u>Predictor:</u> BP Head Up Tilt Table at supine & at 70 degrees immediate, 1-5 minutes, 20/10 OH definition; self-report MI <u>Outcome:</u> any fall x 12 months, monthly fall diary	23% falls with OH; OH not significant with any falls → RR= 1.1 (0.9-1.4); high pulse-wave velocity (≥13m/s) & any fall → RR=1.37 (1.06-1.78) 10% of fallers had MI; MI & any fall → RR=1.0 (0.7-1.5)
Rafiq et al 2014 Cohort	127 General Practitioner Offices in UK; Community-dwelling adults, mean age=75 years N=135,433	<u>Predictor:</u> medical record diagnosis of CAD <u>Outcome:</u> fall assessment at any general practitioner	Ischemic heart disease & any fall → OR= 1.2 (1.1-1.2)

		visit (medical record) x 5 year follow up	
Finucane et al, 2017 Cohort	The Irish Longitudinal study on Aging (TILDA), nationally representative of community-dwelling adults ≥50 years; mean age 61.5 years, 54.2% womenN=4127	Predictor: Continuous BP measurements (beat to beat) from supine to standing Outcome: any fall; interview, retrospective 2-year period	Impaired orthostatic blood pressure recovery associated with all cause fall, unexplained falls, and injurious falls → $IRR_{allcause}$= 1.4 (1.01-1.96) $IRR_{unexplain}$=1.81(1.06-3.09) IRR_{injury}=1.58(1.12-2.24)

Table 8. Association between Neuromuscular Impairment and Falls

Study	Population	Variable Assessment	Results
LE Strength			
de Rekeneire et al 2003 Cross-sectional	Health Aging and Body Composition Cohort, community-dwelling adults, age = 70-79 years N=3075	Predictor: isokinetic knee extensor strength (Kin-Com) Outcome: any fall, interview, 12-month recall	Non-significant results knee extensor strength & falls

Tinetti et al 1995 Cohort	Community-dwelling adults, age >72 years N=927	Predictor: Manual muscle test lower extremity (normal/not), chair stand Outcome: any fall, recurrent fall, injurious fall, monthly calendar x 1years	Chair Stands (slower time) & recurrent falls → RR=2.6 (1.7-3.9)
Nevitt et al 1989 Cohort	Community-dwelling adults, age >60, history of at least 1 fall N=266	Predictor: Chair stands, gait speed Outcome: any fall, weekly post cards x 1 year	1 Chair stand (≥2 seconds) & recurrent falls → RR= 3.0 (1.2-7.2)
Graafmans et al 1996 Cohort	Community-dwelling adults, age > 70 years N=354	Predictor: Gait Speed & lower extremity strength Outcome: any fall, recurrent falls	Mobility impairment (LE weakness or slowness) & any fall → OR=2.6 ($p<0.05$)

Pluijm et al 2006 Cohort	Longitudinal Aging Study Amsterdam, community-dwelling, mean age = 75.3 years, 51.1% women, N=1214	<u>Predictor:</u> weak grip strength (≤32 kg female, ≤56 kg male) <u>Outcome:</u> any fall & recurrent fall Weekly calendar x 3 years	Weak grip strength & any fall over 3 year → OR=1.74 (1.19-2.54) Weak grip strength & recurrent falls at 1 year → OR= 1.92 (1.17-3.14)
Physical Performance			
Nevitt et al 1989 Cohort	Community-dwelling adults, age >60, history of at least 1 fall, 82% women N=325	<u>Predictor</u>: single chair stand (≥2seconds), tandem gait (unable or ≥8 errors) <u>Outcome:</u> recurrent fall, weekly post cards x 1 year	Single chair stand (≥2seconds) & recurrent fall → OR= 3.0 (1.2-7.2) tandem gait (unable or ≥8 errors) & recurrent fall → OR=2.7 (1.1-6.2)
Luukinen et al 1995 Cohort	Community-dwelling older adults in	<u>Predictor:</u> Gait speed (<0.77m/s)	Slow Gait speed & recurrent fall → OR=1.79 (1.06-3.00)

	Finland, age ≥70 years N=1016	Outcome: recurrent fall, monthly diary, x 2 years	
Dargent-Molina et al 1996 Cohort	EPIDOS, community-dwelling women, mean age= 80.5 years, N=7575	Predictor: gait speed < 1 m/s), balance (heel to toe walking) in clinic exams Outcome: injurious fall, tri-annual post card, x 2 years	Gait speed & injurious fall → RR=1.4 per 1 SD decrease (1.1-1.6) Balance (per 1 point) & injurious fall → RR=1.2 (1.0-1.5)
Graafmans et al 1996 Cohort	Community-dwelling adults, age > 70 years N=354	Predictor: Gait Speed & lower extremity strength Outcome: any fall, recurrent falls	Mobility impairment (LE weakness or slowness) & any fall → OR=2.6 ($p<0.05$)
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years N=1285	Predictor: Short Performance Physical Battery; self-report functional limitation Outcome: any fall, recurrent fall,	Short Performance Physical Battery (per 1-point increase) & ≥1 fall → OR=1.1 (1.0-1.1)

		calendar- weekly x 1 year	Short Performance Physical Battery (per 1-point increase) & ≥2 fall → OR=1.1 (1.1-1.2) Self-report functional limitation & ≥1 fall → OR=1.6 (1.2-2.0) Self-report functional limitation & ≥2 fall → OR=2.3 (1.6-3.3)
Covinsky et al 2001 Cohort	Retirement community, mean age=81.6 years, men & women N=557	<u>Predictor:</u> self-report balance issue, mobility exam <u>Outcome:</u> self-report fall, interview, 1 year recall	Self-report balance & any fall → OR=1.83 (1.16-2.89) Poor mobility exam & any fall → OR=2.64 (1.64-4.26)

Stalenhoef et al 2002 Cohort	Community-dwelling men & women, ages ≥ 70 years N=311	Predictor: clinic exam timed up & go (TUG), Barthel Index Outcome: recurrent fall, telephone call every 6 weeks for 36 weeks	TUG (<3/5) & recurrent falls → OR=3.6 (1.7-7.4) Barthel Index & recurrent falls → OR=2.5 (1.3-4.9)
de Rekeneire et al, 2003 Cross-Sectional	Health Aging and Body Composition Cohort, community-dwelling adults, mean age= 70-79 years N=3075	Predictor: chair stands, 6-meter gait speed, 400-meter walk Outcome: any fall, interview, 12-month recall	Chair stand (slower time) & any fall → OR_{men}=1.7 (1.3-1.9) OR_{women}=1.4 (1.2-1.6) Gait Speed (slower time) & any fall → OR_{men} = 1.1 (1.0-1.3)
Pluijm et al 2006 Cohort	Longitudinal Aging Study Amsterdam, community-dwelling, mean age = 75.3 years, 51.1% women,	Predictor: weak grip strength (≤32 kg women, ≤56 kg men)	Weak grip strength & any fall over 3 year → OR=1.74 (1.19-2.54)

	N=1214	Outcome: any fall & recurrent fall Weekly calendar x 3 years	Weak grip strength & recurrent falls at 1 year → OR= 1.92 (1.17-3.14)
Nicklett et al 2014 Cohort	Health & Retirement Study, community-dwelling adults, ≥65 years of age N=16,484	Predictor: self-report ADL difficulty, self-report iADL difficulty Outcome: self-report falls, interview, 2-year recall period, 2000-2010	ADL difficulty & any fall → OR=1.32 (1.32-1.33) iADL difficulty & any fall → OR=1.19 (1.06-1.34)

Table 9. Association between Fall History and Falls

Study	Population	Variable Assessment	Results
Nevitt et al 1989 Cohort	Community-dwelling adults, age >60, history of at least 1 fall, 82% women N=325	Predictor: self-report fall history Outcome: any fall, weekly post cards x 1 year	Self-report fall history ≥ 3 falls & recurrent fall → OR= 2.4 (1.3-4.4) Self-report fall history injurious fall & recurrent fall →

			OR= 3.1 (1.5-6.4)
Luukinen et al 1995 Cohort	Community-dwelling older adults in Finland, age ≥70 years N=1016	Predictor: Self-report history of fall Outcome: recurrent fall, monthly diary, x 2 years	History of fall & recurrent fall → OR=3.27 (2.00-5.35)
Covinsky et al 2001 Cohort	Retirement community, mean age=81.6 years, men & women N=557	Predictor: self-report fall history Outcome: any fall, interview 1 yr recall	Self-report fall history & any fall → OR=2.42 (1.49-3.93)
Stalenhoef et al 2002 Cohort	Community-dwelling men & women, ages ≥ 70 years N=311	Predictor: self-report history of fall Outcome: recurrent fall, telephone call every 6 weeks for 36 weeks	≥ 1 fall history & recurrent falls → OR=3.0 (1.3-6.8) ≥ 2 fall history & recurrent falls → OR=3.1 (1.3-6.7)
Pluijm et al 2006 Cohort	Longitudinal Aging Study Amsterdam, community-dwelling,	Predictor: self-report history of falls	history of falls ≥1 fall → OR=2.03 (1.07-3.83)

	Mean age=75.3 years, 51.1% women N=1214	Outcome: any fall, recurrent fall, weekly calendars x 3 years	history of falls ≥2 falls +fear of falling → OR=3.15 (1.16-8.55)
Pohl et al 2014 Cohort	Community-dwelling adults, Mean age=79.5 years N=230	Predictor: self-report history of falls Outcome: any fall, recurrent fall, injurious fall, monthly calendar x 5 years	1 fall with injury & injurious fall → HR=2.70 (1.40-5.50)

Table 10. Association between Physical Activity and Falls

Study	Population	Variable Assessment	Results
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years N=1285	Predictor: Self-report low physical activity Outcome: any fall, recurrent fall, calendar- weekly x 1 year	Physical activity & ≥1 fall → OR=1.1 (1.0-1.2) Physical activity & ≥2 fall → OR=1.3 (1.1-1.5)

Heesch et al 2007 Cohort	Longitudinal study on Women's Health in Australia, ages 70-75 years, community-dwelling N=8188	Predictor: self-report physical activity on tool developed by National Heart Foundation of Australia Outcome: self-reported falls, interview, recall x 12 months, x 2 years	Very high physical activity (>40/80 score) & any fall → OR=0.67 (0.47-0.95)
Sherrington et al 2008 Meta-analysis	Community-dwelling adults, 44 trials N=9603	Predictor: exercise (no walking programs) to emphasize balance Outcome: any fall	Rate Ratio (exercise program/not) & any fall → 0.83 (0.75-0.91)
Cauley et al 2013 Cohort	MrOS Study, 100% men, age ≥ 65 years N=5994	Predictor: Objective physical activity monitor	Men <80 years with lowest energy expenditure vs highest & any fall → RR=0.75 (p=0.008)

		Outcome: any fall, via tri-annual post-card	Men ≥ 80 years with lowest energy expenditure vs highest → RR=1.43 (p=0.009) Lowest quintile energy expenditure vs highest & any fall → HR=1.82 (1.1-3.0)

Table 11. Association between BMI and Falls

Study	Population	Variable Assessment	Results
Tinetti et al 1995 Cohort	Community-dwelling adults, ≥72 years N=568	Predictor: BMI (low= <24kg/m^2) from clinic exam Outcome: injurious fall, monthly report x 36 months	Low BMI (vs. normal) & injurious fall → RR=1.8 (1.2-2.9)
Pluijm et al 2006 Cohort	Longitudinal Aging Study Amsterdam, community-dwelling,	Predictor: Low body weight (≤62 kg females, ≤70 kg males)	Low body weight (vs. normal) & any fall → OR=1.44 (1.05-1.99)

	Mean age=75.3 years, 51.1% female N=1214	Outcome: any fall, recurrent fall, weekly calendars x 3 years	
Ensrud et al 2007 Cohort	Study of Osteoporotic Fractures (SOF), age ≥ 69 years N=6724	Predictor: clinic assessment & interview for frailty (3 of 5 criteria) Outcome: recurrent falls, triannual post card x 1 year	Frail (vs robust) & recurrent falls → OR= 1.38 (1.02-1.88)
Ren et al 2014 Cross-Sectional	Behavioral Risk Factor Surveillance System, Texas Age ≥ 45 years N=13,235	Predictor: self-report BMI (height, weight) Outcome: self-report fall injury	Obese (vs. normal weight) & injurious fall → RR=1.67 (p=0.031)
Hooker et al 2016 Cohort	Study of Osteoporotic Fractures in Men, ages ≥ 65 years N=5834	Predictor: clinic measured BMI Outcome: any fall, recurrent fall, triannual post card x 4.8 years	Fall rate: greatest in the oldest, highest BMI 1.47 falls/man-year Obesity (vs normal weight) & any fall → OR= 1.92 (p <0.001)

Kim et al 2016 Cross-Sectional	Korean Community Health Survey, age ≥ 19 years N=197,973	Predictor: self-report BMI (height/weight) Outcome: any fall, recurrent fall, interview, 12-month recall	Underweight (vs normal weight) & any fall → OR=1.12(1.05-1.19) Obese (vs. normal weight) & any fall → OR=1.06 (1.02-1.10) Underweight (vs. normal weight) & recurrent fall → OR=1.14(1.04-1.26) Obese (vs. normal weight) & Recurrent fall → OR=1.04 (0.99-1.10)

Table 12. Association between Alcohol Use and Falls

Study	Population	Variable Assessment	Results
Cawthon et al 2006	Study of Osteoporotic Fractures in Men	Predictor: self-report alcohol intake	Light alcohol intake (vs. abstainers) &

Cross-sectional	(MrOS); community-dwelling, ≥ 65 years N=5974	Outcome: any fall, recurrent fall, tri-annual post-card, x 1 year	recurrent fall → RR=0.77 (0.65-0.92) History of Drinking Problem & recurrent fall → RR=1.59 (1.30-1.94)

Table 13. Association between Medication Use and Falls

Study	Population	Variable Assessment	Results
Luukinen et al 1995 Cohort	Community-dwelling older adults in Finland, age ≥70 years N=1016	Predictor: Physician interview for medication usage Outcome: recurrent fall, monthly diary, x 2 years	Psychotropic use & recurrent fall → OR=2.05 (1.25-3.37)
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years N=1285	Predictor: medication inventory use of benzodiazepines and antiepileptic medications	Benzodiazepines & ≥1 fall → OR=1.6 (1.2-2.3) Antiepileptic & ≥ 2 falls →

		Outcome: any fall, recurrent fall, calendar- weekly x 1 year	OR=3.5 (1.1-11.5)
Ensrud et al 2002 Cohort	Study of Osteoporotic Fractures, Community-dwelling adults, 100% female, age >65 years N=8127	Predictor: Medication inventory clinic visit Outcome: any fall, recurrent fall, tri-annual post card x 12 month	Benzodiazepines & ≥2 falls → OR=1.51 (1.14-2.01) Antidepressants & ≥ 2 falls → OR=1.54 (1.14-2.07) Antiepileptic & ≥ 2 falls → OR=2.56 (1.49-4.41)
Hanlon et al 2009 Cohort	Health Aging & Body Composition Cohort Ages 70-79 years, 51% female N=3055	Predictor: Medication inventory at clinic visit, Iowa Drug Information System Outcome: any fall, recurrent fall, interview, 12-month recall, x 5 years	1 CNS drug & any fall → OR=1.55 (1.22-1.97) 2+ CNS drugs & any fall → OR=1.95 (1.35-2.01)

			Moderate dose (vs low dose) CNS drug & any fall → OR=1.80 (1.31-2.47) High dose (vs low dose) CNS drug & any fall → OR=2.89 (1.96-4.25) Short Term (vs none) CNS drug & any fall → OR=1.49 (1.11-2.01) Long term (vs none) CNS drug & any fall → OR=1.76 (1.35-2.28)
Lo-Ciganic et al 2017 Cohort	Osteoarthritis Initiative, community-dwelling men & women; age	<u>Predictor:</u> Self-report medication (brown bag method)	Opioid use vs. no pain medication use & recurrent falls → RR=1.22 (1.04-1.45)

	45-79 years (mean age =61.5 years) N=4,231	Outcome: any fall, recurrent fall, interview, 12-month recall, 4-year follow-up	Anti-depressant use vs no pain medication use & recurrent falls → RR=1.25 (1.10-1.41)

Table 14. Association between Other Factors and Falls

Study	Population	Variable Assessment	Results
OSTEOPOROSIS			
Arnold et al 2005 Cross-sectional	Community-dwelling females; ages >60 years, with osteoporosis N=73	Predictor: kyphosis-flexicurve ruler, fear of falling-Osteoporosis Quality of Life Questionnaire Outcome: any fall x 6 months, interview	Kyphosis & any fall → OR=1.17 (1.03-1.34) Low fear of falling & any fall → OR=0.68 (0.38-0.97)
Ven Hensbroek et al 2009 Cross-sectional	Dutch Falls Prevention Collaboration, CAREFALL, community-dwelling, age ≥ 65 years	Predictor: self-report osteoporosis Outcome: medical record of fall event	Osteoporosis & any fall → OR=2.10 (1.27-3.47)

	N=300		
URINARY INCONTINENCE			
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years N=1285	Predictor: self-report urinary incontinence Outcome: any fall, recurrent fall, calendar- weekly x 1 year	Urinary Incontinence & ≥1 fall → OR=1.8 (1.4-2.4) Urinary Incontinence & ≥2 fall → OR=2.3 (1.6-3.2)
Brown et al 2002 Cohort	Study of Osteoporotic Fractures Cohort, community-dwelling adults, mean age= 78.5, 100% female N=6049	Predictor: self-report incontinence Outcome: any fall, post card every 4 months, average follow up= 3 years	Urge incontinence & any fall → OR=1.26 (1.14-1.40)
de Rekeneire et al 2003 Cross-sectional	Health Aging and Body Composition Cohort, community-dwelling adults,	Predictor: self-report urinary incontinence	incontinence & any fall → OR_{male}=1.5 (1.1-2.0) OR_{female} = 1.5(1.2-1.9)

	mean age= 70-79 years N=3075	Outcome: any fall, interview, 12-month recall	
STROKE			
Geng et al 2017 Cross-sectional	Kaiser Permanente Northern California Member Health Survey Ages 65-90 years, 100% female N=6277	Predictor: self-report history of stroke Outcome: self-report any & recurrent fall x 1 year	History of stroke & any fall → OR=1.51 (1.09-2.00)
Chu et al 2005 Cohort	Community-dwelling adults ≥ 65 years, Hong Kong, 49% female N=1517	Predictor: self-report stroke Outcome: any fall, recurrent fall, telephone call every 2 months x 1 year	self-report stroke & recurrent fall → OR=2.59 (1.30-5.16)
PARKINSON'S DISEASE			
Nevitt et al 1989 Cohort	Community-dwelling adults, age >60,	Predictor: self-report Parkinson's disease	Self-report Parkinson's disease & recurrent fall →

	history of at least 1 fall, 82% female N=325	Outcome: any fall, weekly post cards x 1 year	OR= 9.5 (1.8-50.1)
Chu et al 2005 Cohort	Community-dwelling adults ≥ 65 years, Hong Kong, 49% female N=1517	Predictor: self-report Parkinson's disease Outcome: any fall, recurrent fall, telephone call every 2 months x 1 year	self-report Parkinson's disease & ≥ 1 fall → OR=4.61 (1.34-15.8)
CHRONIC PAIN			
Leveille, SG et al 2009 Cohort	Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study, Community-dwelling adults, age > 70 years N=749	Predictor: self-report 13-item joint pain questionnaire, SF-36 questionnaire Outcome: any fall, monthly calendars x 18 months	Highest tertile of pain OR polyarticular joint pain & any fall → RR=1.53 (1.17-1.99)
Stubbs et al 2014 Meta-analysis	Any Pain: 5 studies, Age >60 years N= 4674	Predictor: self-report pain Outcome: any fall, recurrent fall	Any pain & any fall → OR=1.71 (1.48-1.98)

			Chronic Pain & any fall → OR=1.81 (1.26-2.09)
COGNITIVE IMPAIRMENT			
Tinetti et al 1995 Cohort	Community-dwelling adults, ≥72 years N=568	Predictor: cognitive impairment from clinic exam Outcome: injurious fall, monthly report x 36 months	Cognitive impairment & injurious fall → RR=2.8 (1.7-4.7)
Muir et al 2012 Meta-analysis	Community-dwelling adults, >60 years of age, Cohort studies with ≥ 1 year follow up 27 studies	Predictor: any cognitive impairment Outcome: any fall, serious injurious fall	Any cognitive impairment & any fall → OR=1.32 (1.18-1.49) Any cognitive impairment & serious injurious fall → OR= 2.33(1.61-3.36)
Srikanth et al 2009 Cohort	Tasmanian Study of Cognition & Gait	Predictor: white matter lesion volume as measured by MRI	Recurrent fallers greater WMLV than

	Ages 60-86, community-dwelling, N=307	Outcome: any fall, recurrent fall, monthly diary, x 12 months	single fallers & no fallers (p=0.01); WMLV & any fall → RR=2.18 (1.27-3.71) WMLV & incident fall → RR= 2.32 (1.28-4.14)
DEPRESSION			
Whooley et al 1999 Cohort	Study of Osteoporotic Fractures, > 65 years of age N=7414	Predictor: depression via 15 item Geriatric Depression Scale Outcome: self-report falls, interview x 12 month recall x 4 years	Depression & any fall → OR=1.4 (1.2-1.7)
Tromp et al 2001 Cohort	Longitudinal Aging Study Amsterdam (LASA); community-dwelling; mean age=75.2 years	Predictor: CES-D (score ≥16) Outcome: any fall, recurrent fall,	CES-D (score ≥16) & ≥1 fall → OR=1.4 (1.0-2.0) CES-D (score ≥16) & ≥2 fall →

	N=1285	calendar- weekly x 1 year	OR=1.6 (1.0-2.5)
Kerse et al 2008 Cross-sectional	Australian General Practices, >60 years of age, community-dwelling N=21,900	<u>Predictor:</u> depression/depressive symptoms via PHQ-9 <u>Outcome:</u> self-report any fall, recurrent fall, injurious fall x 12 months	Taking anti-depressants & OR_{1fall} =1.34(1.16-1.56) OR_{2+fall} =1.46(1.25-1.7) $OR_{injuriousfal}$=1.29 (1.12-1.49) Possible depression & OR_{1fall} =1.32 (1.13-1.53) Depression & OR_{1fall} =1.50 (1.14-1.70) Taking SSRI & OR_{1fall}=1.55 (1.26-1.90) OR_{2+fall}=1.66(1.36-2.02) $OR_{injuriousfall}$=1.52 (1.25-1.84)
Kvelde et al 2013	>60 years of age, community-dwelling N=21,455	<u>Predictor:</u> depressive symptoms	Highest depressive symptoms & any fall

Systematic review & meta-analysis	20 studies	Outcome: self-report falls (follow up from 3 months-8 years)	→ OR_{pooled}=1.46 (1.27-1.67) → RR_{pooled}= 1.52 (1.19-1.84)

8.0 Mobility Limitations

In order to investigate the classification of function and disability, measures of physical function are used to differentiate functional capacity amongst individuals. Measures of physical function have been shown to be effective in determining treatment outcomes and in predicting adverse health events in older adults. [35, 59, 111, 415-419] Adults may begin to experience early decline before it is recognized clinically or by the individual.

Mobility limitations are one type of early functional decline. Mobility is essential to being able to perform activities of daily living and meaningful social functioning. Mobility limitations can be defined as the inability to complete a 400-meter usual paced walking test within 15 minutes, without having a seated rest break or use of an assistive device more supportive than a single point cane. Mobility disability is a leading cause of health issues in older adults and can cause reduced quality of life in adults as well. [59] Defining mobility impairment or disability can be done in a variety of assessments involving both qualitative and quantitative methods. Objective measures of mobility, such as the usual paced 400 meter walk test, may not be as subject to ceiling effects that may be found with self-report [104] mobility limitations. [420] The use of the 400 meter walk test may also better discriminate older adults with higher levels of physical function. [105] Understanding the etiology and risk factors associated with age-related physical decline is important and a growing concern in public health.

8.1.1 Epidemiology of Mobility Limitations

Aging is associated with has increased risk with impairments in mobility, gait, and activities of daily living. In 2013, over 80% of Medicare enrollees report having at least one ADL or iADL disability or were institutionalized. [421] By year 2030, it is expected that one in every 5 Americans will be 65 years and older. [421]

Mobility disability may have a sudden onset as result of acute or severe disease processes, such as a cerebrovascular accident or lower extremity fracture. Mobility disability is more commonly a gradual progressive process that is a result of chronic conditions and or age-related changes within the body. Depending on the primary cause of mobility disability, the resulting pathway is often dynamic, meaning that generally periods of deterioration and recuperation occur and may be unrecognized clinically until its effects hamper activities of daily living and self-care. [422-424] In a report from the Health ABC Study (n=2324, age range 70-79 years), over a 6 year follow up period, 44% developed persistent mobility limitations (did not complete 400 meter walking test x 2 consecutive visits). [415] A report from Chang et al. stated that 33.9% (n=21) of participants who were able to complete the 400 meter walk test at baseline were not able to at 21 months of follow up. The participants (n=62) were men and women between 75-85 years of age who demonstrated functional limitation (SPPB score 4-9) but were living in the community. [425] Variation in the estimates of mobility limitations may also range due to differences in the definition and the methods used to capture the condition. Overall, poor performance on objective and self-report measures can predict future mobility limitations and increased difficulty with activities of daily living and self-care. [426]

The prevalence of mobility disability and ADL disabilities increase with age world-wide. Mobility disability, according to the Behavioral Risk Factor Surveillance Survey System, is the

most common reported form of disability across older adult age groups.[427] According to NHANES, 20% of adults age 60-69 have ADL disability and 30% in that same age range have mobility disability. 48% of community-dwelling adults age 60-69 years report at least one functional limitation. [428] The InCHIANTI study estimates that 5.5% of adults age 65 years and older have ADL disability and 22% have iADL disability. [429] In the Health ABC study, estimates of a 4% decline in walking speed per year was statistically associated with age over a 5 years period in both men and women (OR=1.06, 95% CI= 1.02-1.12 and OR=1.06, 95% CI= 1.02-1.11 respectively). [430] Disability in older adults is a public health concern because of the aging population, the increased demands and utilization of healthcare services, and the increased costs associated with disability. [431]

FIGURE. Estimated number of adults with any disability, by specific type of disability and age group — Behavioral Risk Factor Surveillance System, 2016

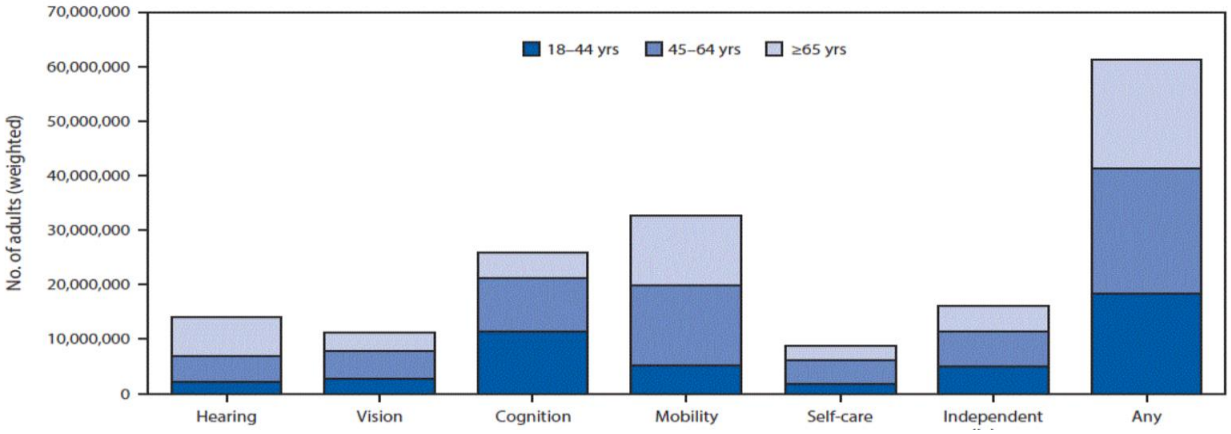


Figure 11. Estimated Number of Adults with any Disability, Behavioral Risk Factor Surveillance System 2016

8.1.2 Assessment of Mobility Limitations and Mobility Disability

The most common definition of mobility impairment is by assessing the ability of an individual to walk without assistance from a device or another person. The occurrence of difficulty with this task or the presence of limitation in walking may also considered. [422] For a range of

severity in mobility disability difficulty getting around outside of the home and in the community would be considered community mobility disability. Limitations moving about inside the home would be considered in-home mobility disability, which is a more serious limitation. The most severe form of mobility disability would be the inability to walk. [426] Varying definitions and the range of severity within the definitions are challenges in comparing the literature in this area.

8.1.2.1 Self-Report

Mobility limitation is assessed through self-report, medical professional report, and objective physical performance measures. Self-report measures vary from questions assessing difficulty in walking or lower-extremity function to questions about the ability and frequency of mobility in the environment. [432] Self-report measures are the most common method used to identify mobility limitations in epidemiological studies as they are simple, inexpensive, and easy to administer to participants. Self-reported measures of mobility impairments have been able to predict incident mobility disability and mortality in older adults. [424, 426, 433-435]. A large amount of variability exists within the self-report questions. For example, single items questions are based on the difficulty of performing a motor task or the dependence of mobility. Many validated questions can identify the impairment and focus in on different levels or stages of the disability (for example, difficulty walking a short (2-3 blocks) or long distance (1 mile)). [422] The Activities of Daily Living questionnaire is one of the more common tools used regarding difficulties with ADLs and mobility. [423, 434, 435] The Instrumental Activities of Daily Living tool contains questions more related to managing finances, meal preparation, managing medications, housekeeping, ability to find a telephone number and make the call, and completing shopping tasks. [435, 436] The Short Form Health Survey (SF-36) Physical Function Subscale (PF-10) examines limitations with difficulty walking 100 yards to a mile, bathing and dressing,

climbing stairs, performing moderately strenuous household chores, to more vigorous activities (running, participating in strenuous sports). The Activity of Daily Living questionnaire and the Instrumental Activities of Daily Living questionnaire provide insight into household mobility that is required to complete ADLs where as some of the single mobility questions and the SF-36 aim to capture mobility beyond the home and into the community.

8.1.2.2 Usual Gait Speed

Short distance usual gait speed (4, 6, 10 meters) has been utilized in multiple studies and has been proven to predictive of negative health outcomes. [59, 61, 437, 438] Various cut-points within the continuum of gait speed have been established to recognize more severe forms of mobility limitations. [59] A gait speed less than 1.0 m/s predicts lower extremity limitations, falls, hospitalization, and death. A gait speed that is less than 0.8 m/s predicts a more severe disability. Additionally, a decline in gait speed of 0.1 m/s over 1 year leads to an increase in 5-year mortality rates. [59, 61, 110]

8.1.2.3 400-meter Walk Test

Longer distance walking tests, such as the 400-meter walk test, have been shown to predict disability in older adults. [415, 416, 422, 439-441] These longer distance walking tests are important in the identification of mobility disability as they have the ability to distinguish mobility limitations in higher functioning older adults and may be able to explain the aerobic fitness component of mobility decline. [415, 442, 443] Additionally, these longer walking tests have been associated with measures of subclinical cardiovascular disease, neurological conditions, and musculoskeletal conditions. [104, 415, 417] Objective measures of physical performance have also

been able to identify populations of older adults at higher risk for developing mobility limitations, disability, and mortality. [415]

8.1.2.4 Short Physical Performance Battery

The Short Physical Performance Battery (SPPB) is another commonly used physical performance measure in both research and clinical settings. This test is a composite of 3 different tests- balance, gait speed, and chair stands. The balance portion consists of 3 different static positions to be held for 10 seconds, side by side, semi-tandem, and tandem stands. The gait speed test is a usual pace 4-meter walk. The chair stands are a timed test to complete 5 repetitions from a sitting position to fully upright without use of the upper extremities. Each component is given a score from 0 to 4, with higher scores indicating better performance. The scores of each component are generally combined to obtain an aggregate score to determine mobility disability. However, the components can be used to evaluate specific functional abilities. This test has been shown to predict mobility disability, activities of daily living disability, future hospitalization, nursing home admission, and mortality in multiple epidemiological studies. [104, 111, 439, 444] In a subset of the Epidemiological Study of the Elderly (EPESE) cohort who self-reported no disability, the SPPB predicted functional decline and hospitalization over a 4 year period. [419, 444] A cut-point of ≤ 9 is considered to be low physical function and a cut point score of ≤ 6 indicates a more severe limitation in mobility. [445] The SPPB may demonstrate a ceiling effect for high functioning older adults and not differentiate initial signs of disability at this level.

8.1.2.5 Strength and Limitations

A potential limitation with self-report questionnaires to capture mobility limitation is that these tools tend to identify persons in a more advanced stage of mobility disability. For example,

those persons who are demonstrating difficulty with basic activities of daily living are easily identified. However, if an individual can still complete the task despite modification or decline in frequency of the task, it may not be recognized as a decline in function. Differentiating limitations at higher levels of physical function may require a more strenuous test. Self-report measures however, do provide valuable information, as the assessment of an individual's perception to complete the task. Self-report measures are best used as an outcome in comparison to identify pre-clinical disability and to understand the impact of impairments on function that lead to disability. Physical performance measures may be able to distinguish limitations in person who do not self-report limitations and serve as a complement to self-report measures. Self-report questionnaires are easier to administer and more cost efficient. These measures also provide a better indication of the person's assessment of ability in their own environment, rather than in an artificial setting.

Some of the limitations with objective measures of physical performance are more intensive training of the staff is necessary, more time and cost is needed in comparison to self-report, greater amounts of dedicated space to complete the tasks is needed, and the tests may not be suitable for more severely disabled persons to complete. The objective measures can, however, identify a spectrum of performance on a variety of persons, identify persons who are at risk for disability, better indicate change in performance over time, predict future disability, need for long term care, and mortality. In a study of 487 older adults (≥ 65 years) from the Veteran's Administration and a Medicare Health Management Organization, gait speed and the Epidemiological Studies of the Elderly physical performance battery test were independent predictors of healthcare use, change in health status, and decline in physical function. [446] Performance measures in this study, with and without self-report measures, were able to predict

the outcomes of hospitalization, health status (Global Health, Euroqol Score), and decline in physical function (National Health Interview Survey and the SF-36). [446]

Table 15. Common Definitions of Physical Function from Epidemiological Studies

Measure	Definition of decline in Physical Function
Self-Report	
SF-36 Physical Function Subscale	Scores range 0-100; mean = 50, standard deviation = 10; higher score = better physical function; disability can be defined as a continuous scale or within specific domains
Self-Report questions	Inability or a lot of difficulty walking ¼ mile
	Inability or a lot of difficulty climbing 1 flight of stairs
	Require assistance with ≥ 2 ADLs
Activities of Daily Living	Categorized as disabled (yes/no); disabled if report difficulty ≥ 1 tasks
	Categorized by difficulty with 1 ADL, 2-3 ADLs, > 3 ADLs
	Create more complex subscales
Instrumental Activities of Daily Living	Categorized as disabled (yes/no); disabled if report difficulty ≥ 1 tasks
	Categorized by difficulty with 1 ADL, 2-3 ADLs, > 3 ADLs
	Create more complex subscales

Objective	
400-meter walk test	Mobility Limitation: Inability to complete 400 meters within 15 minutes
Usual gait speed	<1 m/s is predictive of future health events
	<0.8 m/s predicts more severe disability
	Decline of 0.1 m/s predictive of future mortality
Short Physical Performance Battery	≤ 9 indicates limited physical function ≤ 6 indicates severe limitation physical function

8.2 Risk Factors for Mobility Disability

Majority of research indicates that mobility disability is a multifactorial condition with no primary cause. [447] Age, gender, and ethnicity are non-modifiable risk factors for disability. Some determinants include multi-morbidity, declining neuromuscular system, health and lifestyle factors, and other risk factors. While the treatment for mobility disability has not been firmly established, the approach to prevent and treat this condition will need to be multifaceted.

8.2.1 Non-modifiable Risk Factors

8.2.1.1 Demographic Risk Factors

In the Health ABC study, estimates of a 4% decline in walking speed per year was statistically associated with age over a 5 year period in both men and women (OR=1.06, 95% CI= 1.02-1.12 and OR=1.06, 95% CI= 1.02-1.11 respectively). [430] A gender disparity exists in disability with women reporting disability and developing disability more often than men. [448-450] This difference between genders may be due to women developing disability from different diseases than men. For example, women tend to experience co-morbidities such osteoporosis and osteoarthritis, which are risk factors for physical disability in comparison to men. Women with these conditions compared to men with the same condition tend to report higher prevalence of physical disability at every stage of the disease as well. [450] Men are more likely to experience life-threatening conditions, such as heart disease or even more concerning sudden cardiac death and are possibly more likely to die vs. women rather than develop disability. [451] [448] In addition to the differences in disease processes, women have lower overall lean mass and higher fat mass in comparison to men. [450] However, studies have shown that no differences in incident rates of disability exist between men and women. [452] Women have a greater number of co-morbidities that are risk factors for disability and report higher prevalence of disability in comparison to men.

Ethnic differences also exist in the development of disability. Non-Hispanic blacks have higher prevalence rates of disability in comparison to non-Hispanic whites. [453-455] Results from the Health and Retirement Study report that African-Americans are 1.6 times more likely to develop disability than their white counterparts (95% CI = 1.3-1.9). [456] Results from the Health ABC Study demonstrate that black and white men had similar declines in gait speed (4% per year)

over a 5 year period but the decline was significant for only for differences between black and white women (33% for black women and 27% for white women, p <0.01). [430] Other results from this Health ABC analysis reported that the odds of developing incident mobility limitation over a 5 year period is similar between black and white women after adjusting for age, clinic site, mobility status, and baseline health status however for men, the association between race and incident mobility limitation was attenuated by social economic status. Education level and income were important SES indicators that explained some of the racial differences in the likelihood of incident mobility limitation in older adult men. [430, 457] Data from the EPESE study demonstrated that African-Americans were 2.3 times more likely to develop disability over a follow up period between 7 and 9 years in comparison to whites (95% CI= 1.39-3.71). [457] These differences between race may be partially due to socio-economic differences but not entirely. [455, 456] In addition, African-Americans are more likely to develop chronic medical conditions that are risk factors for disability (diabetes, hypertension, heart disease). [455, 458-460] The mechanism for the disparity may not be fully understood, though it is evident that Blacks develop a higher prevalence of disability in comparison to Whites.

8.2.1.2 Osteoarthritis

Arthritis is a risk factor for decline in physical function. Song et al reported from the Health Retirement Study (N=7758, ≥65 years of age) that adults with self-report arthritis had 1.48 times greater odds of developing disability in comparison to those without arthritis in an adjusted model over a 2 year follow up period (95% CI= 1.21-1.80). [461] The adjusted population attributable fraction for disability due to arthritis is 23.7%. [461] Other longitudinal follow up from the Health Retirement Study (N=7543, ≥65 years of age) reported that those with self-report arthritis have 1.63 increased odds of developing mobility or ADL disability

compared to those without arthritis over a 10 year follow up period in an adjusted model (95% CI=1.43-1.86). [462] Data from the European Project on Osteoarthritis (EPOSA) (N=2886, mean age=74.2 years) demonstrates that either clinical or self-report OA is associated with lower physical performance in unadjusted models but pain and stiffness attenuate the association with self-report OA. [463] Clinical OA was associated with 1.67 higher odds of poor physical performance as compared to those without clinical OA in adjusted models (95% CI= 1.23-2.26). [463] Clinical knee OA was defined through the Western Ontario and McMaster Universities Arthritis Index (WOMAC), age > 50 years, morning stiffness, crepitus with motion, and bony tenderness and enlargement. Low physical performance was defined as a SPPB score ≤9. Low physical performance was associated with stiffness (OR=1.93, $p<0.001$). [463] While this study is cross-sectional and cannot establish a temporal association between OA and low physical performance, the associations found were adjusted for potential confounders. Both self-report and clinical arthritis has been shown to be associated with poor physical function.

8.2.1.3 History of Functional Limitation

Previous functional limitation is also a risk factor. [445, 464] Guralnik et al in the Established Population for Epidemiological Studies of the Elderly (EPESE) cohort, that adults 71 years and older with a SPPB score >7 were 2.8 times less likely to develop mobility disability over a 4 year follow up period (95% CI=1.2-6.7). In addition, older adults with SPPB scores between 4-6/12 were 4.9 times more likely to develop disability in comparison to older adults with scores >10 (95% CI= 3.1-7.8). Older adults with SPPB scores 7-9/12 were 1.8 times more likely to develop disability in the same cohort (95% CI= 1.3-2.5). [444] In the LIFE study, Santanasto et al found that in adults at the highest risk for mobility limitations (SPPB <8 at baseline), the physical activity intervention provided benefit to the overall SPPB score, chair stand score, and balance

score in comparison to the health education intervention over a 36 month period (overall SPPB p= 0.01; chair stand component p<0.001). [465] Previous functional limitation may be associated with disability through the mechanism of decreased strength and power.

8.2.2 Modifiable Risk Factors

8.2.2.1 Neuromuscular Impairment

Deteriorating neuromuscular function, as measured by low muscle strength and power, has been shown to be associated with physical disability. [104] A decline in muscle function is part of the pathway leading to disability as both a precursor to disability and a risk factor for it. Persons with low muscle function are at an increased risk for developing disability and interventions have proven to improve muscle function and then overall physical function. [422, 466, 467] For example, a decline in usual gait speed has been shown to be a strong predictor of incident mobility disability. [59, 62, 66, 110] This measure can be considered a combination of lower extremity strength and neurological functioning as far as the coordination of walking movement and the ability to maintain appropriate balance. However, not all decline in muscle function are due entirely to alterations in the neuromuscular system. Declines in other body systems from disease result in weight loss, physical inactivity, and elevated inflammation, which all impact muscle mass, strength, and physical performance. Lower extremity muscle strength has been shown to be associated with slow gait speed and severe mobility disability in the Health ABC cohort. Manini et al (N=2,784, mean age= 73.6 years ± 2.85, no self-report disability) report results show that men and women with weak knee extensor strength (1.13 Nm/kg for men and 1.01 Nm/kg for women) have moderate increased risk of severe mobility limitations (inability to walk ¼ of mile or climb 10 stairs for 2 consecutive reports; HR=), slow gait speed (<1.2 m/s; HR= 7.0, 95% CI= 5.47-

8.96), and mortality (HR=1.77, 95% CI= 1.41-2.23) in comparison to men and women with greater knee extensor strength (1.71 Nm/kg for men and 1.34 Nm/kg for women). [35, 468] This has been replicated in the InCHIANTI (Invecchiare in Chianti) study that muscle strength and power are strong risk factor for mobility limitations. In both men and women, year 3 assessments of knee extensor strength, lower extremity power, and grip strength were all predictive of incident mobility limitations at year 6 (all measures $p<0.001$ in men; knee extensor strength $p=0.002$, lower extremity power $p = 0.004$, and grip strength $p= 0.02$ in women). Results (n=934, age $\geq$ 65 years, 55% women) demonstrate that men with knee extensor strength <19.2 kg and grip strength <39.0 kg had significant declines in gait speed (0.24m/s) over a 3 year period in comparison to men with leg extensor strength $\geq$ 19.2 kg ($p<0.001$). Men who had lower extremity power < 105 W had 8.7 times greater risk of developing mobility limitations (self-report inability to walk 1 km or climb 10 stairs) over 3 years in comparison to men with lower extremity power $\geq$ 105 W (95% CI = 3.91-19.44). Women with knee extensor strength less than 18 kg had a decline of 0.06 m/s in gait speed over 3 years in comparison to women with knee extensor strength $\geq$ 18 kg ($p= 0.04$). A 3 times greater risk of developing incident mobility limitations in women was found for those with lower extremity power < 64 W in comparison to those with lower extremity power $\geq$ 64 W over the 3 year follow up period (95% CI = 1.79- 5.08). [469] [35] In addition to lower extremity strength, grip strength and declining grip strength over time have also been associated with disability in older adults. [468, 470] In the Lifestyle Interventions and Independence for Elders pilot (LIFE-P), individuals in the lowest sex-specific quartile of grip strength at baseline had 6 times the risk of developing mobility disability in comparison to persons in the highest sex specific quartile of grip strength (HR=6.11, 95% CI=2.24-16.66). [471] Lower extremity muscle power is another predictor for mobility limitations. A study from the InCHIANTI cohort reported that the odds for

poor mobility performance (SPPB ≤ 9) was nearly 9 times greater for those in the lowest quartile of muscle power compared to those in the highest quartile (OR= 8.9, 95% CI = 4.0-20.1). The impact of lower extremity muscle power was 2-3 times greater than lower extremity muscle strength (OR for lowest quartile of hip strength vs highest quartile = 2.9, 95% CI= 1.5-5.6; OR for lowest quartile of knee extensor strength vs highest quartile= 4.5, 95% CI= 2.2-9.2) for predicting poor physical performance. [472] In the Lifestyle Interventions and Independence for Elders (LIFE) study (n=1635, mean age= 78.9 ± 5.2 years, 67% women), a lower rate of major mobility disability was found in adults who received the physical activity intervention in comparison to the adults who received the health education intervention (HR= 0.82, 95% CI= 0.69-0.98). [465] The results were attenuated when adjusted for the change in the SPPB score over the course of the study and the change in the chair stand component of the SPPB. 29% of the effect of physical activity intervention on prevention of mobility limitations was attributed to the change in the SPPB score. 39% of the effect was explained by the chair stand component of the SPPB, which indicates the importance of muscle strength/power as part of the benefit physical activity provides. [465] Maintaining muscle strength and power throughout the lifespan is important to reduce the risk of disability.

8.2.2.2 Physical Activity

Health behaviors that are risk factors for decline in physical performance include low levels of physical activity and obesity. [471, 473-476] Regular physical activity has been shown to have a protective effect on mobility decline. Visser et al demonstrated that adults age 55-85 years who participated in ≤1.3 hours/day of physical activity (including both household and sport) had a decline in objective mobility performance of 0.61 over a 3 year follow up period. Persons from that cohort who participated in ≥ 4 hours/day of physical activity experienced a .28 decline in

mobility performance over 3 years (p=0.008 for trend). [477] The InCHIANTI cohort concluded that older adults who reported higher amounts of physical activity throughout midlife have better mobility than those who did not in older age. [478] Adult men who met or exceeded the recommended levels of physical activity during midlife had statistically higher SPPB scores in comparison to adults who did not meet the guidelines (>10/12 for those who met/exceeded the guidelines, 9.5/12 for those who did not meet guidelines, p =0.059). [478] Adult women who met or exceeded the recommended levels of physical activity during midlife had statistically higher SPPB scores in comparison to adults who did not meet the guidelines (>9/12 for those who met/exceeded the guidelines, 8.5/12 for those who did not meet guidelines, p =0.008). [478] Adult men who did met the recommended physical activity guidelines in midlife were 50% less likely to not complete the 400 meter walk test in comparison to men who did not meet physical activity guidelines (p=0.008). No difference was found among women with the 400 meter walk test in this cohort. [478] Comparing physical performance on a fast paced and usual paced 400 meter walk test in 59 community-dwelling older adults (mean age = 78.4 ± 5.8 years, 58% women), results indicated that older adults with lower physical function (SPPB ≤ 10) had less difference between their completion times in comparison to adults with higher physical function (SPPB >10) (32.8 seconds vs 52.9 second, p= 0.005). [418] Adults ≥80 years also had less difference in their completion times in comparison to those who were <80 years (32.8 seconds vs 56.8 seconds, p=0.003). [418] This may indicate that adults who are older in age and have lower physical function may have been performing at their maximal capacity in the usual paced walk. The usual paced 400-meter walk may be a better option for testing in similar populations, while in a higher functioning and younger population the fast-paced test may serve better to distinguish early changes in mobility. In examining the Long Distance Corridor Walk test (fast-paced 400 meter

walk test), no difference was found in the decline of completion time between those who are physically inactive and those who are exercisers in a Health ABC analysis (N= 3075, ages 70-79 years 52% female) over 8 years of follow up time (Mean decline in completion time: inactive group= 36.1 seconds (95% CI= 28.4-43.8), lifestyle active= 38.1 seconds (95%CI= 33.6- 42.4), exercisers= 40.8 seconds (95% CI= 35.2-46.5)). [479] The exercise group however, consistently had faster completion times ($p<0.001$) which may delay adults reaching a point where aerobic fitness impairs physical function. [479] Maintaining recommended levels of physical activity throughout the lifespan is important to maintain and preserve mobility throughout later life.

8.2.2.3 Obesity

Obesity is a risk factor for developing mobility limitations. In the Health ABC cohort, mobility limitation was defined through self-report difficulty with walking ¼ of a mile or difficulty with ascending and descending 10 stairs. Thorpe et al demonstrated that women who are obese have an increased adjusted odds of 2.51 for developing mobility disability over 5 years in comparison to normal weight women (95% CI= 1.90-3.32). [430] Men who are obese had an increased adjusted odds of 1.91 for developing mobility disability in comparison to normal weight men (95% CI= 1.43-2.58). [430] The LIFE-P results suggest a U shaped association with BMI and the development of mobility disability, was defined by inability to complete the 400 meter walk test. Adults with BMI between 25-29.9 kg/m^2 have 0.48 less risk (95% CI= 0.26-0.90) and <25 kg/m^2 have 0.97 less risk (95% CI=0.45-2.08) in comparison to those who have an obese BMI ($\geq$ 30 kg/m^2). [471] Stenholm et al in the InCHIANTI study showed that adults who were non-obese and had normal strength (leg extensor strength men > 17.1 kg and women >11.3 kg) were 10.53 times less likely and adults with low strength only (leg extensor strength $\leq$17.1 kg for men, $\leq$11.3 kg for women) were 9.43 times less likely to develop mobility disability in comparison to adults

with the combination of obesity and low strength (obesity: BMI ≥30 kg/m^2) ($p<0.0001$ and $p=0.04$ respectively). [480] Obesity and obesity combined with decreased muscle strength increase the risk of developing mobility limitations in adults.

8.3 Background Association between Physical Performance and Knee OA

8.3.1 Cross-sectional Associations

Knee OA has been associated with mobility limitations in cross-sectional studies. [481-484] Ling et al reported from the Women's Health and Aging Study II (n=392, ages 70-79 years) that symptomatic knee (defined by ACR criteria) is associated with slower chair stand times ($p <0.05$), slower stair climb test times ($p<0.001$), and greater self-report difficulty with stairs (OR=2.09, $p <0.05$). [485] Additionally, women with ACR defined knee OA, symptomatic or intermittently symptomatic, required greater time to complete the chair stand test (14.33 seconds vs 13.06 seconds, $p =0.01$) and stair climb test (8.9 seconds vs 7.67 seconds, $p <0.001$) than women without knee OA. [485] In the Johnson County OA Project mild radiographic knee OA (based on KL grades) was associated with self-reported mobility difficulty with stair climbing whereas moderate to severe radiographic knee OA was associated with self-reported mobility difficulty with stair climbing and walking >1/4 mile. These results were attenuated when the models were adjusted for knee pain. [486] Davis et al reported from NHANES, that adults >45 years with radiographic knee OA reported greater difficulty with mobility and activities of daily living in comparison to those without knee OA in both men and women. The association between knee OA and self-reported disability was influenced by the severity grade of knee OA and pain. [487] Knee

confidence or instability in the setting of knee OA is associated with decreased physical function. Poor knee confidence is associated with 1.65 higher odds of poor advanced physical function compared to normal confidence (95% CI= 1.01-2.7). Physical function was measured by the Late Life Function and Disability Index. [199] Knee instability is a common self-reported symptom in those with knee OA. [488] Given that knee stability is important for most activities of daily living and other activities, limited confidence in the knee can result in adults limiting participation in activities due to fear of falling. [369, 488] In 60 adults from the Multicenter Osteoarthritis Study (with radiographic tibiofemoral OA and symptomatic OA), time to complete the Long Distance Corridor Walk did not vary by severity of knee symptoms, age, or activity level. However, when examining adults with bilateral knee OA, there was increased time to complete the walk test (315.6 ± 75.8 vs 293.0 ± 44.5 seconds, p = .188). [489] Astephen et al reported in a cross-sectional analysis of gait biomechanics that adults with moderate or severe tiobiofemoral OA demonstrate varying gait patterns based on kinematics at the hip and knee as well as muscle activation in comparison to adults without OA. [490] This variation may contribute to pre-clinical mobility disability as well as identify a potential intervention for rehabilitation to improve mobility. Knee OA defined radiographically and symptomatically may increase the risk of mobility difficulty in adults.

8.3.2 Longitudinal Associations

The presence of knee OA has been associated with the development of mobility limitations in longitudinal assessments as well. Thorpe et al in the Health ABC cohort reported that women with knee OA have a 1.98 higher adjusted odds of developing mobility disability over a 5 year period in comparison to women who do not have knee OA (95% CI=1.30-3.00). [430] Men did

not have a statistically significant increased odds of developing mobility disability (aOR=1.45, 95% CI=0.83-2.51). [430] In the Women's Health and Aging Study II, women with knee OA were 2.43 (95% CI=1.01-5.87) times more likely to develop both ADL and lower extremity mobility limitations over 72 months of follow up in comparison to women without knee OA with mobility limitations assessed through self-report difficulty with walking ½ mile, negotiating 10 stairs, carrying a 10 pound object, or transferring in and out of a vehicle. [491] Ettinger et al reported from NHANES and the follow up study, that adults >45 years with symptomatic and radiographic knee OA reported greater difficulty with mobility and activities of daily living in comparison to those without knee OA in both men and women. [492] Sharma et al found that in adults with knee OA, those with increasing pain scores (20 mm) on a visual analog scale over a 3 year follow time had 1.48 greater odds (95% CI= 1.12–1.95) of worsening self-reported function (WOMAC), with an increased odds per 5 years of age by 1.34 (95% CI= 1.15–1.57) for poor performance with the chair stand test. [200] Longitudinal analyses demonstrate the association between knee OA and functional disability.

Adults with knee OA have low prevalence of meeting the 2008 aerobic physical activity guidelines (≥150 minutes/week) in a report from the Osteoarthritis Initiative (OAI). In a sample of 1,111 adults, 49-84 years of age, 12.9% of men and 7.7% of women with radiographic knee OA met the public health guidelines through accelerometry assessment of physical activity. Lee et al reported with data from the OAI study that adults with lower amounts of sedentary activity had better physical function that was independent of moderate-vigorous physical activity minutes. Among adults in the most sedentary groups, gait speed, as measured by a 20 meter walk, was significantly slower (1.18 m/s compared to 1.32 m/s) compared to those in the least sedentary group. [493] Additionally, those with more sedentary activity had lower chair stands per minute

compared to the less sedentary groups (25.9 stands per minute vs 31.1 stands per minute respectively). Sedentary behavior was captured through use of accelerometry to provide objective and accurate assessments of physical activity level, though this study is cross-sectional and cannot establish a causal association between sedentary behavior and physical function. White et al reported that adults who took greater numbers of steps each day had lower risk of functional limitation as measured through performance and self-report measures. [494] Adults from the MOST study who walked ≥ 7500 steps/day, had 0.31 and 0.41 times lower risk of performance and self-report functional performance compared to those who walked less than 5000 steps each day. [494] Adults who walked between 5000-7499 steps per day had 0.50 lower risk of performance based functional limitation and 0.51 lower risk of self-report functional limitation compared to those who took less than 5000 steps/day. [494] Steps per day were objectively measured through an ActiGraph tool, which provides an accurate assessment of steps. Each additional 1000 steps/day was associated with a 16% and 18% reduction in incident functional limitation by performance-based (gait speed ≤ 1.0 m/s) and self-report measures (WOMAC physical function score ≥28/68), respectively. [494] This study had a 2 year follow up period and can provide an estimate of risk. Physical activity, whether structured strength training or aerobic activity or as unstructured activity, is important in maintaining physical function in adults with knee OA. [495]

8.3.3 Strength and Limitations

The limitations in the current research are the lack of data on the stages of severity of knee OA and the varying definitions to define disability and mobility limitations. Results from NHANES suggest that there may be differences in risk of disability based on the stage of the knee

OA. There additionally may be gender differences in the role of OA. The work in this dissertation aims to provide information to begin to identify the relevance of stages of knee OA in association with mobility limitations to start to fill this gap in literature. An objective measure of "pre-clinical" disability for mobility limitation, such as the 400 meter walk, may provide greater insight into populations at risk for future disability, especially for those older adults who may not currently walk that distance in their daily routines or have misperception of how far the distance is.

Table 16. Associations Between OA & Disability

Study	Population	Variable Measurement	Results
Lamb et al 2000 Cross-sectional	Women's Health & Aging Study; 100% women N=764	Predictor: self-report symptomatic knee OA Outcome: gait speed (≤0.42m/sec) & chair rise (yes/no)	Self-report OA vs not & slow gait speed in obese → OR= 7.6(2.6-23.0) Self-report OA vs not & no chair rise in obese → OR= 7.1(1.5-23.0)
Ling et al 2003 Cross-sectional	Women's Health & Aging Study; 100% women N=436	Predictor: ACR criteria Outcome: self-report disability with stairs	ACR defined OA vs not & self-report disability → OR=2.09 ($p<0.05$)

Sharma et al 2003 Cohort	Mechanical Factors in Arthritis of the Knee, mean age =68.6 years, KL ≥ 2 N=257	Predictor: self-report OA, pain scores Outcome: self-report function (WOMAC), 3 years follow-up	In OA, 20 mm worse pain score vs no pain change & self-report poor physical function → OR=1.48 (1.12-1.95)
Ling et al 2006 Cohort	Women's Health & Aging Study; 100% women N=199	Predictor: ACR criteria Outcome: self-report mobility disability	ACR OA vs not & self- report mobility disability → OR=2.43 (1.01-5.87)
Song et al 2006 Cohort	Health Retirement Study; ≥65 years of age N=7758	Predictor: self-report OA Outcome: self-report mobility disability, 2 year follow up	Self-report OA vs not & self-report disability → OR=1.48(1.21-1.80).
Covinsky et al 2008 Cohort	Health Retirement Study, ≥65 years of age N=7543	Predictor: self-report OA Outcome: self-report mobility & ADL	Self-report OA vs not & self-report disability → OR=1.63 (1.43-1.86)

		disability, 10 year follow up	
Thorpe et al 2011 Cohort	Health ABC 70-79 years N=2969	Predictor: self-report OA Outcome: self-report mobility disability	Self-report OA in women vs no OA in women & self-report disability → OR=1.98 (130-3.00)
Edwards et al 2014 Cross-sectional	European Project on Osteoarthritis (EPOSA), mean age=74.2 years N=2886	Predictor: ACR criteria Outcome: physical performance (SPPB ≤ 9)	ACR defined OA vs not & low physical performance → OR=1.67(1.23-2.26)

9.0 Summary of Gaps in the Literature

It is important to find modifiable risk factors that influence body structure and function and modifiable risk factors that influence activity in order to prevent limitations in participation and disability. While disability is not a fixed state, preventing a catastrophic decline in older adults is a public health concern.

Previous research has shown mixed associations between knee osteoarthritis and falls. [496-498] Dore et al in a cross-sectional analysis has shown that adults with symptomatic knee OA have increased risk of falls, that increases with the number of involved joints with a mean follow-up of 6 years but with only a single follow-up assessment. [497] Barbour et al reported increased risk of injurious falls in men with symptomatic OA over 6 and ½ years of follow up.[499] Aspects of disease progression including knee instability, reduction in knee range of motion, increased pain and other symptoms of knee OA, and muscle weakness may be important factors to consider when assessing the association between knee OA and falls [497, 500-502]. However, previous studies have not considered whether these factors influence the associations between severity of radiographic knee OA and fall risk.

Knee osteoarthritis (KOA) is a major cause of disability. The World Health Organization (WHO) ranked OA as a top 10 contributor to years lived with disability from 1990-2013.[503] Clinical treatment or recommendations for management of disability with KOA is challenging because these recommendations (exercise, consistent physical activity) are often difficult for persons with KOA to perform. Persons with KOA are often limited by their pain and other symptoms resulting in reduced capacity to participate in activity, which further perpetuates this cycle. Over 43% of individuals with arthritis experience arthritis-attributable activity

limitations.[504] The ability to walk a distance of 400-meters is associated with independence while walking in the community and inability to complete mat indicate risk for future decline that may not be evaluated by shorter walking tests. [415, 416, 505, 506] Walking endurance, similar to walking speed, has been shown to be a predictor of health outcomes such as mobility limitations, disability, and death.[415] Understanding if any sub-group of KOA is at most risk for mobility limitations is of value for prevention of disability.

The lack of a consensus definition of sarcopenia has limited its use clinically and has hindered the development of appropriate therapeutic interventions.[71] Sarcopenia was initially defined as the loss of lean mass associated with aging.[507] Lean mass, measured by dual energy x-ray absorptiometry (DXA), has variable associations with adverse health outcomes including fractures. [74, 508-510]Current definitions of sarcopenia include varying cut-points for body composition, strength, and functional performance further creating challenges for clinical utility. [71, 511] It is not clear whether all the components of sarcopenia definitions (slow walking speed, low lean mass and low grip strength) each individually predict adverse outcomes, particularly fractures, in older adults. Previous work has demonstrated that once BMD is accounted for, appendicular lean mass divided by height square (ALM/ht^2) mass is not an independent risk factor for fracture. However, whether an alternative measure of lean mass, which accounts for body fat mass in addition to height and has shown a stronger association with lower function in older adults is unknown. Worse performance on functional measures and weakness has been associated with increased risk of fracture and are recommended components of sarcopenia definitions by the Sarcopenia Definitions and Outcomes Consortium. [71, 72, 512, 513] The association between this alternative measure to assess low lean mass and various fracture types has not been explored.

Aging causes various impairments at the body function and structure level. Understanding how these changes influence activity and participation in aging adults is critical to find targetable risk factors to intervene on.

10.0 Associations Between Severity of Radiographic Knee OA and Recurrent Falls: The Osteoarthritis Initiative

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10.2 Abstract

Background: Knee osteoarthritis is the most prevalent type of osteoarthritis (OA) and a leading cause of disability in the United States. Falls are a major cause of morbidity and mortality in older adults. Our aim is to examine how the severity of radiographic OA impacts recurrent falls in a cohort of middle and older aged individuals enrolled in the Osteoarthritis Initiative (OAI).

Methods: 3,972 participants, mean age of 63 years, 58% female were assessed for worst severity of knee OA (KOA) from baseline to 36 months. Participant characteristics were summarized by worst OA severity with appropriate descriptive statistics. We used generalized

estimating equations for repeated logistic regression to model the association between KOA severity and the likelihood of recurrent falls over follow-up of 5 years.

Results: Older adults (≥age 65) with KOA were at higher odds of recurrent falls in comparison to individuals without KOA in models adjusting for known covariates (possible OA OR= 2.22, 95% CI= 1.09-4.52; mild OA OR=2.48, 95% CI= 1.34-4.62; unilateral moderate-severe OA OR= 2.84, 95% CI= 1.47- 5.50; bilateral moderate-severe OA OR= 2.52, 95% CI= 1.13-5.62). Middle aged adults with KOA did not have increased odds of recurrent falls in comparison to those without KOA except for possible KOA (OR= 1.86, 95% CI=1.01-2.78) (KLseverity*age interaction = 0.025).

Conclusions: Older adults with radiographic evidence of KOA have an increased likelihood of experiencing recurrent falls in comparison to their counterparts without KOA independent of known risk factors. Results suggest fall prevention efforts should include older adults with all stages of KOA.

Key Words: Falls, Osteoarthritis, Physical function

10.3 Introduction

Falls are a leading cause of morbidity and mortality in older adults and have a major public health impact [514, 515]. Approximately 30% of adults 65 years and older in the US fall at least once per year and this number rises to 50% in adults 85 years and older [408, 516]. The cost for care after a fall contributes significantly to healthcare expenditure, over $31 billion dollars in 2015 [517, 518] . Beyond the healthcare expense, falls can pose a variety of consequences such as

injury, functional decline, increased need for long-term care and death [331, 356, 519]. While a fall may not always result in physical injury, there is often subsequent fear of falling and decreased confidence that may result in activity modifications [347, 520]. With the rising rates of falls, which increased 31% from 2007- 2016 amongst those 65 years and older, and fall related injuries and deaths, which have increased 3% per year amongst those 65 years and older from 2007-2016, a more in-depth understanding of risk factors contributing to falls is warranted [521].

Knee osteoarthritis is the most prevalent type of osteoarthritis (OA) and a leading cause of disability and lost work days in the United States [522]. In the US, the prevalence of radiographic knee OA in adults ≥ 60 years of age was estimated to be 37% [135]. The presence of knee OA contributes significantly to functional limitations in participation and performance of weight bearing activities such as walking, stair climbing, and household chores, which may lead to negative health outcomes and declines in quality of life [523, 524].

Cross-sectional studies have shown mixed associations between falls and knee OA [407, 413, 525]. Dore et al have shown that adults with symptomatic OA of the lower extremities, defined as radiographic evidence plus corresponding joint symptoms, have an increased risk of a fall event that trends up with the number of joints involved [526]. This study provided strong support for the association between OA and falls but this longitudinal assessment is limited by a single follow-up time point with a mean of 6 years after baseline. Other longitudinal studies have found a null association [496]. Severity of knee OA may also impact falls, with higher fall risk associated with greater severity of knee OA [527]. Aspects of disease progression including knee instability, reduction in knee range of motion, increased pain and other symptoms of knee OA, and muscle weakness may be important factors to consider when assessing the association between

knee OA and falls [497, 500-502]. However, previous studies have not considered whether these factors influence the associations between severity of OA and fall risk.

The objective of this analysis was to examine whether the severity of radiographic tibiofemoral OA in both knees may impact recurrent falls in a cohort of middle aged and older adults, while being able to adjust for the important confounding variables. We also aimed to test whether these associations differed by age. We hypothesized that adults with increasing severity of tibiofemoral knee OA(KOA), taking into account radiographic severity in both knees, will have higher likelihood of recurrent falls compared to adults without evidence of radiographic tibiofemoral OA in either knee and that the associations will be more pronounced in older individuals.

10.4 Methods

10.4.1 Participants

The participants were enrolled in the Osteoarthritis Initiative (OAI) cohort, a prospective study investigating risk factors and biomarkers associated with the development and progression of KOA. Briefly, OAI recruited 4,796 adults aged 45-79 years with or at high risk to develop KOA at 5 clinical sites (John Hopkins Bayview Medical Center and the University of Maryland, Baltimore, Maryland; Ohio State University, Columbus, Ohio; University of Pittsburgh, Pittsburgh, Pennsylvania; and Memorial Hospital, Pawtucket, Rhode Island) between years 2004-2006. Approval was obtained from the Institutional Review Board at each participating OAI site. Each participant provided written informed consent. Participants enrolled in OAI either had

symptomatic OA in at least one knee or risk factors for developing knee OA, including being overweight or obese, knee symptoms, history of knee injury, history of surgery, history of repetitive knee bending, family history of knee replacement, or the presence of Heberden's nodes. Persons with rheumatoid or inflammatory arthritis were excluded from the OAI study. Additional reasons for exclusion included: findings of severe joint space narrowing in both knees on baseline knee radiographs, unilateral total knee arthroplasty and severe joint space narrowing in the other knee, bilateral total knee arthroplasties, plans to have bilateral knee arthroplasties in the next 3 years, inability to undergo a 3.0T magnetic resonance imaging of the knee due to contraindications, positive pregnancy test, inability to provide a blood sample, use of ambulatory aids other than a single straight cane for 50% of the time during ambulation, co-morbid conditions that may interfere with the ability to participate in a 4 year study, or current participation in a double-blind randomized trial. The data and additional details are publicly available at: https://nda.nih.gov/oai/.

10.4.2 Primary Independent Variable: Radiographic Severity of OA

All OAI participants underwent knee radiography at baseline, following the posteroanterior fixed flexion weight-bearing protocol with a SynaFlexer^{TM} frame.

The presence and stage of OA in the tibiofemoral joint was based on the Kellgren-Lawrence (KL) grading system using annual radiographs from baseline to the 36-month visit. Serial radiographs were graded on an ordinal scale 0 (normal) to 4 (most advanced). Participants were divided into mutually exclusive groups based on their worst radiograph disease status through the 36-month visit. The groups included those with no radiographic knee OA (0/0), possible knee OA (0/1, 1/1), mild radiographic knee OA unilaterally or bilaterally (0/2, 1/2, 2/2), unilateral moderate to severe radiographic knee OA (0/3, 0/4, 1/3, 1/4, 2/3, 2/4), or bilateral moderate to

severe radiographic knee OA (3/3,3/4, 4/4). For those with a total knee arthroplasty prior to the baseline visit, the KL grade was given a zero [528]. In centralized readings, experts (weighted kappa inter-reader agreement 0.79), blinded to other's reading, hypothesis, and all other data, assessed KL grade. Adjudication for KL 0-1 vs 2 included a third reader.

10.4.3 Primary Outcome: Recurrent Falls

The number of falls in which the participant had landed on the floor or ground in the past 12 months was self-reported by participants and assessed annually for 5 years from the 48-month visit through the 96-month visit. Our primary outcome was repeated recurrent falls, defined as reporting two or more falls in a 12-month reporting period.

10.4.4 Covariates

Participants were assessed annually at clinic visits, and detailed self-reported questionnaires (e.g., demographics, health status/behaviors), clinical and physiological measurements, and measures of progression of knee OA were collected.

Demographic and lifestyle variables were collected at in-person clinic assessments through self-report and included age, sex, race, education, self-reported physical activity (Physical Activity Scale for the Elderly; (PASE)) [529], smoking status, alcohol intake, depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D)) [530], number of persons living in household, co-morbidities (Katz modification of the Charlson Comorbidity Index) [531], Knee Injury and Osteoarthritis Outcome Score symptom subscale (KOOS), knee confidence rating, and medication usage via 'brown bag' collection [532]. Higher scores on the KOOS indicate less

symptomology. Knee confidence was rated based on patient self-report to the question from the KOOS 'how much are you troubled with lack of confidence in your knees?'[502]. Lifestyle activity modification was also assessed using self-report to the question from the KOOS "have you modified your lifestyle to avoid potentially damaging activities to your knees". Standardized physical examination assessments were used to collect information on body mass index (BMI), knee range of motion, medial-lateral knee joint laxity, knee joint effusion, knee alignment (varus, valgus, neutral), and physical performance (chair stand pace). BMI was categorized into groups based on the Centers for Disease Control cut points. The clinical examination variables of knee range of motion, laxity, alignment, and effusion were categorized into person-level variables due to their high correlation between the right and left sides and worse score was used. Knee range of motion was categorized into a yes and no variable based on the presence of a flexion contracture. Knee joint laxity was categorized as yes for any level of laxity: mild and moderate/severe. Knee alignment was categorized as neither, varus, or valgus.

10.4.5 Statistical Analyses

Participants were classified based on their worst radiographic evidence of OA in both knees from baseline to the 36-month follow up visit. Those with no radiographic evidence of knee OA in either knee formed the referent group. Participant characteristics at baseline were summarized by worse OA status with appropriate descriptive statistics (mean, standard deviation (SD), frequency, and percentage). We used Pearson's chi-square tests for categorical variables. one-way analysis of variance for continuous measures with normality and Kruskal-Wallis tests for non-parametric continuous variables to compare characteristics across OA groups.

We used generalized estimating equations for repeated logistic regression to model the association between OA groups and the likelihood of experiencing recurrent falls. Base and adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated controlling for risk factors age, sex, race, and clinic site. To account for the time between the baseline assessment and our follow-up period, we created time-varying covariates in the model to account for changes in age, BMI, knee alignment, self-reported knee confidence, KOOS pain, PASE, chair stand pace, use of narcotics, and use of anti-depressants from baseline to the 36-month visit. Models were also adjusted for baseline, CESD score, smoking status, average alcohol consumed per week, co-morbidity score, and 30-month KOOS lifestyle modification, and education level. We conducted a sensitivity analysis where we excluded participants if they had a total knee arthroplasty. Analysis was completed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

10.5 Results

Overall, 3,972 OAI participants were included in our analysis. 1,118 (28%) participants had no radiographic evidence of KOA and formed the referent group; 601 (15%) participants have possible KOA; 1,212 (30%) had unilateral or bilateral mild radiographic KOA group; 733 (18%) participants had unilateral moderate to severe radiographic evidence of KOA and 308 (8%) had bilateral moderate to severe radiographic KOA. Baseline characteristics are summarized in **Table 1**. Participants in the referent group were more likely to be younger, white race, and have higher level of education in comparison to those with OA. Participants in the referent group were also less likely to have positive clinical signs of knee joint laxity or effusion in comparison to the other

OA groups, were more likely to report more confidence of no knee buckling and were less likely to report symptoms based on the KOOS. Self-reported physical activity was highest in those with no OA and decreased with greater severity of radiographic KOA. Participants in the reference group had higher physical function, measured by the rate of chair stands per second. This measure also demonstrated a negative trend in performance with higher levels of KOA. Participants in the unilateral moderate to severe OA and in the bilateral moderate to severe OA were similar across most study characteristics presented, except those in the bilateral moderate to severe OA group had a greater co-morbidities score (0.76 vs 0.61), higher percentage of African Americans (26.6% vs 17.3%), and had a greater BMI on average (31.3vs 30.1). Participants in the bilateral moderate to severe OA group were more likely to use strong pain medication in comparison to those with no or possible OA. A self-reported history of falls differed minimally between those with possible OA (227, 37.8%) and those with mild OA (416, 34.3%), unilateral moderate-severe (240, 32.7%), and bilateral moderate-severe (91, 29.4%). There was no difference in the depression scale and number of medications.

We found a significant interaction between age and KL severity in both knees p= 0.025. To account for this all the models were stratified by age (≥ 65 years of age and < 65 years of age). In base models adjusted for sex, race, and clinic site, adults ≥ 65 years of age, with unilateral or bilateral moderate to severe radiographic evidence of knee OA had increased likelihood of experiencing recurrent falls in comparison to those with no radiographic evidence of knee OA in either knee (unilateral KOA OR= 1.85, 95% CI 1.28-2.67; bilateral KOA OR= 1.88, 95% CI 1.23-2.87, respectively and referenced in **Table 2**). In models additionally adjusting for body mass index, knee symptoms and clinical factors (KOOS, knee confidence, lifestyle modification, range of motion, joint alignment, and effusion), physical activity and performance, medication usage,

depression, and life-style factors, adults ≥ 65 years old, all groups with radiographic knee OA had increased odds of recurrent falls in comparison to the referent group. Adults ≥ 65 years with possible OA in one or both knees had 2.23 times higher odds (95% CI=1.10-4.54), with mild OA in one or both knees had 2.48 times higher odds (95% CI=1.34-4.61), with unilateral moderate to severe radiographic knee OA had 2.93 times higher odds (95% CI= 1.52-5.63) and adults with bilateral moderate to severe knee OA had 2.52 times higher odds (95% CI = 1.16- 5.46) of recurrent falls in comparison to adults with no evidence of radiographic knee OA in either knee.

In base models for participants less than 65 years, those with possible knee OA in one or both knees had increased likelihood of falls in comparison to those without knee OA in either knee (OR=1.37, 95% CI=1.05-1.77). Results were similar after further adjustments (OR=1.68, 95% CI=1.01-2.79). Complete results are summarized in **Table 3**. In sensitivity analyses, removing 223 participants who had a total knee arthroplasty after the baseline visit, the results remained the same.

10.6 Discussion

We showed that adults ≥ 65 years of age with possible or definite radiographic tibiofemoral knee osteoarthritis have higher likelihood of experiencing recurrent falls in comparison to adults ≥ 65 years of age without radiographic evidence of OA independent of many known covariates, including symptoms of knee OA. Older adults with possible or definite radiographic evidence of knee OA are at risk for recurrent falls and should be targeted for fall prevention interventions.

This work builds on the existing research that adults with radiographic knee OA have an increased risk of falls in comparison to adults without knee OA. Smith et al reported that persons with incident radiographic unilateral knee OA had 54% greater likelihood of experiencing a fall in

the 12 months prior to the diagnosis compared to those without knee OA. [533] Barbour and Strotmeyer et al recently reported data from the Health, Aging, and Body Composition study demonstrating that men with symptomatic and radiographic knee OA have a 2.6 times hazard ratio for experiencing an injurious fall in comparison to men without pain or radiographic OA in either knee.[499] Our work, however, is distinct in that we were able to incorporate the severity of radiographic knee OA, including KL grade 1, for each knee joint while controlling for OA-related symptoms, detailed clinical examinations, and physical performance measures that are also associated with our outcome of recurrent falls.

For adults <65 years of age, only those with possible radiographic OA in one or both knees had increased likelihood of recurrent falls in comparison to those without OA. This finding is plausible given the group of younger adults with possible OA, had higher reports of a positive fall history. Possible explanations for why middle age adults with more advanced OA do not show increased likelihood of falls may reflect lifestyle modifications to reduce the risk, such as less frequent and less intense physical activity.

For adults ≥65 years of age, in base models those with moderate to severe radiographic OA did not demonstrate increased odds of recurrent falls. However, after accounting for other factors of disease progression, including changes in clinical symptoms, physical performance, changes in medication usage, and pain, in older adults with any stage of KOA (from possible to moderate-severe) an increased odds of recurrent falls was observed. Osteoarthritis has been associated with a decline in physical activity, physical function and increased reports of pain, which may lead to the increased likelihood of experiencing a fall.[534] Adults with OA, mild through severe KOA also demonstrate decreased physical performance on the chair stand test which may also contribute to their increased risk of falls. [498, 535, 536]. While radiographic features of OA may not always

correlate with symptoms of OA, the radiographic changes occurring may result in biomechanical changes that impact the center of balance, gait and may impact lower extremity strength in adults with various stages of KOA [153]. KOA may also be associated with changes in the joint range of motion and alignment that alter normal gait biomechanics, which may imply greater risk for falls [537, 538]. Additionally, confidence that the knee will not buckle during weight-bearing activities has been associated with poor future physical function and is also a factor to consider when assessing fall risk [539].

The results from this study suggest the need for intervention to prevent falls should be implemented at the early stage of radiographic evidence of KOA, given that those with possible (KL grade 1) and mild (KL grade 2) show an increased risk of recurrent falls in adults. Interventions should not be postponed until more severe joint symptoms appear. Intervention to manage and address these clinical features may be a target to reduce falls in this population. Rehabilitation to address lower extremity strength, physical function, range of motion, confidence with movement, balance, and pain are targets common in physical therapy treatments.

10.6.1 Strength and Limitations

Strengths of this study include the prospective design, detailed assessment of potential confounders, radiographically confirmed KOA in a large sample of community dwelling adults across the US. KOA was assessed at multiple time-points which allows for examination of disease and symptoms at multiple time points, by using x-ray grades from baseline through 36-month follow-up and time-varying clinical and self-reported symptoms, as well as extended follow-up time. Self-reported history of falls in the past year has been shown to be highly specific (91–95%) compared with results using more frequent assessment, however this tends to be an under-reported

event.[25] However, there are a number of limitations. OAI recruited adults at high risk for knee OA or who already have knee OA, limiting the generalizability. The knee joint is comprised of more than the tibiofemoral component, which is what we used to categorize knee OA.

10.6.2 Conclusion

In conclusion, older adults with radiographic evidence of knee OA, mild to severe KOA, have an increased likelihood of experiencing recurrent falls in comparison to those without KOA that is independent of known risk factors. The results from this study indicate that fall prevention efforts should focus on older adults with all stages of KOA from possible to moderate-severe.

Future work should consider the role of the patellofemoral joint as well as use of 'pre-clinical' features that can be detected with other imaging approaches. The mechanism of the recurrent falls is not documented and the circumstances surrounding the fall events in those with mild knee OA and those with moderate to severe bilateral knee OA may be very different. A more in-depth understanding of these associations would be warranted in future research.

10.7 Funding

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10.8 Tables and Figures

Table 17. (Table 1) Baseline Characteristics by Worst Severity of Knee OA from Baseline to 36 months

Variables	No OA (0/0) n= 1118	Possible OA (0/1), (1/1) n= 601	Mild OA (0/2), (1/2), (2/2) n= 1212	Unilateral Moderate-Severe (0/3), (1/3), (2/3), (0/4), (1/4), (2/4) n=733	Bilateral Moderate-Severe (3/3), (3/4), (4/4) n=308	p-value (p<0.05)
Age, n (yrs)	59.8 (0.11)	62.1 (0.15)	61.9 (0.10)	64.7 (0.13)	66.0 (0.20)	(0v1), (0v2), (0v3), (0v4), (1v3), (1v4), (2v3), (2v4), (3v4)
Female, n (%)	656 (58.7)	356 (59.2)	771 (63.6)	382 (52.1)	157 (50.9	(0v2), (0v3), (0v4), (1v2), (1v3), (1v4), (2v3), (2v4)
White, n (%)	944 (84.4)	507 (84.4)	920 (75.9)	594 (81.1%)	222 (72.1%)	(0v2), (0v3), (0v4), (1v2), (1v4), (2v3), (3v4)
Post College Education, n (%)	489 (43.7)	235 (39.2)	461 (38.2)	281 (38.3)	88 (28.7)	(0v2), (0v3), (0v4), (1v2), (1v3), (1v4) (2v4), (3v4)
Body mass index, n (kg/m^2)	27.2 (0.06)	28.37 (0.07)	29.96 (0.06)	30.10 (0.07)	31.29 (0.11)	(0v1), (0v2), (0v3), (0v4), (1v2), (1v3), (1v4), (2v4), (3v4)
Charlson Comorbidity Index, n (%)	0.50 (0.01)	0.59 (0.02)	0.57 (0.01)	0.61 (0.07)	0.76 (0.03)	(0v1), (0v2), (0v3), (0v4), (1v3), (1v4), (2v4), (3v4)
Number of medications, n (%)	4.9 (0.04)	4.9 (0.05)	5.2 (0.04)	4.9 (0.05)	4.9 (0.07)	------
Narcotics use, n (%)	31 (2.8)	11 (1.9)	41 (3.4)	29 (3.9)	22 (7.1)	(0v3), (0v4), (1v2), (1v3), (1v4)
Pain medication use (OTC), n (%)	395 (35.3%)	249 (41.5)	599 (49.4)	453 (61.8)	210 (68.1)	(0v1), (0v2), (0v3), (0v4), (1v2), (1v3), (1v4), (2v3), (2v4), (3v4)
KOOS, n (%)	88.4 (0.19)	87.2 (0.24)	82.7 (0.22)	78.9 (0.29)	77.5 (0.45)	(0v2), (0v3), (0v4), (1v2), (1v3), (1v4), (2v3), (2v4), (3v4)
Knee confidence, n (%)	655 (58.6)	326 (54.2)	519 (42.8)	229 (31.2)	94 (30.5)	(0v1), (0v2), (0v3), (0v4), (1v2), (1v3), (1v4), (2v3), (2v4)

(+) bulge sign, n (%)	97 (8.7)	83 (13.8)	200 (16.5)	155 (21.1)	64 (20.8)	(0v1), (0v2), (0v3), (0v4), (1v3), (1v4), (2v3) (2v4)
(-) laxity test, n (%)	792 (70.8)	418 (69.5)	800 (66.0)	449 (61.2)	164 (53.4)	(0v2) (0v3), (0v4), (1v2), (1v3), (1v4), (2v3), (2v4), (3v4)
Neutral alignment, n (%)	366 (32.7)	165 (27.5)	345 (28.5)	208 (28.4)	80 (26.1)	(0v2), (0v4), (1v4), (2v3), (2v4)
Alcoholic drinks/week	1.8 (0.02)	1.6 (0.02)	1.5 (0.02)	1.7 (0.02)	1.6 (0.03)	(0v1), (0v2), (0v3), (0v4), (1v2), (2v3), (2v4)
History of smoking n, (%)	178 (15.9)	87 (14.4)	194 (16.0)	65 (8.9)	37 (11.9)	(0v3), (1v3), (2v3)
CES-D, n (%)	6.8 (0.09)	7.4 (0.13)	7.7 (0.10)	7.0 (0.10)	7.3 (0.16)	------
Lives alone, n (%)	216 (19.3)	127 (21.1)	287 (23.7)	167 (22.8)	72 (23.3)	(0v1), (0v2), (0v3), (0v4), (1v2), (1v4)
PASE	159.0 (1.05)	155.7 (1.33)	151.0 (0.98)	148.1 (1.19)	138.9 (1.74)	(0v2), (0v3), (0v4), (1v2), (1v3), (1v4) (2v4), (3v4)
Chair stand pace, n (stand/sec)	0.53 (0.002)	0.52 (0.003)	0.47 (0.002)	0.47 (0.002)	0.45 (0.003)	(0v1), (0v2), (0v3), (0v4), (1v2), (1v3), (1v4), (2v4), (3v4)
Fall past year, n (%)	350 (31.3)	227 (37.8)	416 (34.3)	240 (32.7)	91(29.4)	(0v1), (0v2), (1v2), (1v3), (1v4), (2v4)

Adjustment made for multiple comparisons; presented as mean (standard deviation) unless otherwise noted; 0= no OA; 1= Possible OA; 2= Mild OA; 3= moderate-severe unilateral OA; 4= moderate-severe bilateral OA

Table 18. (Table 2) Base Model for Stage of OA and Recurrent Falls

Osteoarthritis (OA) Group	< 65 years OR 95% CI (n=2, 458)		≥ 65 years OR 95% CI (n= 1, 514)	
No OA (0/0)	1.0		1.0	
Possible OA (0/1, 1/1)	1.37	1.05-1.77*	1.47	0.97- 2.22
Mild OA (0/2, 1/2, 2/2)	1.20	0.96-1.50	1.39	0.96-2.02
Moderate-Severe OA Unilateral (0/3, 0/4, 1/3, 1/4, 2/3, 2/4)	1.04	0.80-1.35	1.85	1.28-2.67[a]
Moderate-Severe OA Bilateral (3/3, 3/4, 4/4)	1.06	0.74-1.50	1.88	1.23- 2.87[a]

Note: Worst OA severity from baseline to month 36; Adjusted for: clinic site, age, race, sex.

[a] Indicates statistical significance KL grade*age interaction p = 0.02

Table 19. (Table 3) Multivariable Model for Severity of OA and Recurrent Falls

Osteoarthritis (OA) Group	**< 65 years OR 95% CI (n=2,458)**		**≥ 65 years OR 95% CI (n= 1,514)**	
No OA (0/0)	1.0		1.0	
Possible OA (0/1, 1/1)	1.68	1.01-2.78[a]	2.22	1.09-4.52[a]
Mild OA (0/2, 1/2, 2/2)	1.22	0.79-1.88	2.48	1. 34-4.62[a]
Moderate-Severe OA Unilateral (0/3, 0/4, 1/3, 1/4, 2/3, 2/4)	1.03	0.62-1.72	2.84	1.47-5.50[a]
Moderate-Severe OA Bilateral (3/3, 3/4, 4/4)	0.94	0.45-1.95	2.52	1.13-5.62[a]

Note: Worst OA severity from baseline to month 36; MV model adjust for : clinic site, age, race, sex, age*KL grade, knee confidence, knee ROM, joint alignment, joint effusion, history of fall, knee symptoms (KOOS pain, knee confidence), chair stand pace, BMI, physical activity report (PASE), lifestyle activity modification, medication use (narcotic, opioids, anti-depressants), alcohol intake, smoking status, depressive symptoms (CESD), education level, number of comorbidities.

[a] Indicates statistical significance; KLgrade*age interaction p= 0.01

11.0 Associations between Knee OA and Mobility Limitations

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11.2 Abstract

Background: Knee osteoarthritis (KOA) is a major cause of disability. The World Health Organization (WHO) ranked OA as a top 10 contributor to years lived with disability from 1990-2013.[503] Over 43% of individuals with arthritis experience arthritis-attributable activity limitations. The purpose of the current analysis was to examine the cross-sectional and longitudinal associations between sub-groups of KOA (no KOA, symptoms only, radiographic KOA, and symptomatic KOA) and the likelihood of completing the 400-meter walk and the time to complete the walk.

Methods: An analytic sample of 4,725 participants were followed from baseline to 48-months. Participant characteristics were summarized by baseline knee OA group with appropriate

descriptive statistics. Cross-sectional analyses used logistic regression for likelihood to complete and linear regression for time to complete the 400-meter walk at baseline. We used generalized estimating equations for repeated logistical regression to model the association between KOA and the likelihood of completing the 400-meter walk over 4 years. We used generalized estimating equations for repeated ordinal regression to model the association between KOA and the likelihood of completing the 400-meter walk in the worst quartile of performance over 4 years. We used generalized linear models to model the time to complete the 400-meter walk over 4 years.

Results: In cross-sectional results for multivariate models at baseline, adults with no KOA were 31% less likely to perform in worst quartile of performance in comparison to adults with symptoms only (95% CI=0.48-0.91) and adults with symptoms only were 51% less likely to perform in the worst quartile compared to adults with symptomatic KOA (95%CI= 0.28-0.87). All associations were attenuated with adjustment for chair stand pace in longitudinal assessment for worst quartile of performance. The odds of completing the 400-meter walk test from baseline to 48-months of follow-up, in minimally adjusted models adults with no OA were more likely to complete the walk than adults with symptoms and adults with symptomatic KOA (OR=0.93, 95%CI= 0.91-0.96; OR=0.96, 95%CI=0.93-0.99) respectively.

Conclusions: Adults with symptoms only, radiographic KOA, and symptomatic OA, had the lowest likelihood of completing long distance walks in comparison to adults with no symptoms or radiographic KOA in cross-sectional findings. Adults with symptomatic KOA were more likely to be in the worst quartile of performance and may identify a group to target with therapeutic intervention to prevent mobility decline. Longitudinal associations between baseline KOA status and 400 m completion rates and times over the follow-up were attenuated by other measures of physical function and risk factors for performance declines

Key Words: Osteoarthritis, Physical function, Mobility Limitations

11.3 Introduction

Knee osteoarthritis (KOA) is a major cause of disability. The World Health Organization (WHO) ranked OA as a top 10 contributor to years lived with disability from 1990-2013.[503] Clinical treatment or recommendations for management of disability with KOA is challenging because these recommendations (exercise, consistent physical activity) are often difficult for persons with KOA to perform. Persons with KOA are often limited by their pain and other symptoms resulting in reduced capacity to participate in activity, which further perpetuates this cycle. Approximately 15.1 million persons in the US have symptomatic knee OA.[540] The OA-related cost at the population level is estimated to be close to $80 billion and Barbour et al found that over 43% of individuals with arthritis experience arthritis-attributable activity limitations.[503, 541]

The ability to walk a distance of 400-meters is associated with independence while walking in the community and is an indicator of aerobic fitness.[505, 506] The ability to walk 400-meters may be an assessment that can indicate future decline and disability in middle and older aged adults and may be an early sign of mobility limitation that may not be detected by other shorter performance tasks.[415, 416] Maintaining mobility independence is important on a personal level as well as on a population level. It may be beneficial to clinicians to assess changes in walking distance with patients with various types of KOA and those at risk for developing KOA in the

future to identify early time-points to intervene. Walking endurance, similar to walking speed, has been shown to be a predictor of health outcomes such as mobility limitations, disability, and death.[415] Understanding if any sub-group of KOA is at most risk for mobility limitations is of value to clinicians and their patients for prevention of disability.

The purpose of the current analysis was to examine the cross-sectional and longitudinal associations between sub-groups of KOA (no KOA, symptoms only, radiographic KOA, and symptomatic KOA) and the likelihood of completing the 400-meter walk and the time to complete the walk. We hypothesize that adults with symptomatic KOA will have the lowest odds of completing the 400-meter walk test in both cross-sectional and longitudinal analysis and will require the greatest amount of time to complete the walk across a 4-year follow-up.

11.4 Methods

11.4.1 Participants

The Osteoarthritis Initiative (OAI) is a multi-center, longitudinal, prospective observational study, with publicly available detailed protocols and data (https://nda.nih.gov/oai/). Individuals with or at risk for symptomatic KOA, ages 45-79, were recruited from five clinical centers and followed with comprehensive annual visits over nine years. All participants provided informed consent and institutional review boards at each center approved the study. Participants enrolled in OAI either had symptomatic OA in at least 1 knee or risk factors for developing knee OA, including being overweight or obese, knee symptoms, history of knee injury, history of

surgery, history of repetitive knee bending, family history of knee replacement, or the presence of Heberden's nodes. Persons with rheumatoid or inflammatory arthritis were excluded from the OAI study. Additional reasons for exclusion included: findings of severe joint space narrowing in both knees on baseline knee radiographs, unilateral total knee arthroplasty and severe joint space narrowing in the other knee, bilateral total knee arthroplasties, plans to have bilateral knee arthroplasties in the next 3 years, inability to undergo a 3.0T magnetic resonance imaging of the knee due to contraindications, positive pregnancy test, inability to provide a blood sample, use of ambulatory aids other than a single straight cane for 50% of the time during ambulation, co-morbid conditions that may interfere with the ability to participate in a 4 year study, or current participation in a double-blind randomized trial.

11.4.2 Independent Variable: 400-meter Walk Test

The 400-m walk test at usual pace represents a less-intensive, practical, objective examination of mobility that is closer to the walking activity of an older person's daily life.[443] Participants were not medically eligible to attempt the 400-m walk if they did not complete the 20-m walk, had a heart rate ≥ 110 beats per minute, had a systolic or diastolic blood pressure exceeding 180 mm Hg or 100 mm Hg, respectively, required a walker or quad cane to ambulate, called a doctor within the past 3 months for worsening chest pain or shortness of breath, were hospitalized in the past 3 months, or did not feel safe to perform the test. The test was conducted on a 20-meter course. Participants were instructed to walk 10 laps, with standard encouragement provided with each lap. Study participants could take as many breaks as needed, up to 60 seconds per break. Participants received a maximum of 15 min in which to complete the task. We defined mobility limitation as not completing the 400-m walk at any of the clinic assessments.[416]

11.4.3 Covariates

Demographic and lifestyle variables were collected at in-person clinic assessments through self-report and included age, sex, race, education, self-reported physical activity (Physical Activity Scale for the Elderly; PASE [529]), smoking status, alcohol intake, depressive symptoms (Center for Epidemiologic Studies Depression Scale; CES-D [530]), co-morbidities (Katz modification of the Charlson Comorbidity Index [531]), knee confidence rating, and medication usage via 'brown bag' collection[532]. Knee confidence was rated based on patient self-report to the question from the Knee Injury and Osteoarthritis Outcome Score symptom subscale (KOOS) 'how much are you troubled with lack of confidence in your knees?'.[502] Lifestyle activity modification was also assessed using self-report to the question from the KOOS "have you modified your lifestyle to avoid potentially damaging activities to your knees". Standardized physical examination assessments were used to collect information on body mass index (BMI), knee alignment (varus, valgus, neutral), and physical performance (20-meter walk pace, chair stand pace). BMI was categorized into groups based on the Centers for Disease Control cut points. The clinical examination variable alignment was categorized into a person-level variable due to their high correlation between the right and left sides and worse score was used. Knee alignment was categorized as neither, varus, or valgus.

11.4.4 Statistical Analyses

Participant characteristics at baseline were summarized by OA status with appropriate descriptive statistics (mean, standard deviation (SD), frequency, and percentage). We used Pearson's chi-square tests for categorical variables, one-way analysis of variance for continuous

measures with normality and Kruskal-Wallis tests for non-parametric continuous variables to compare characteristics across groups. 71 participants were missing either radiographic or symptom information at baseline and 80 participants were missing data from the 400-meter walk test at baseline and were excluded from the analysis leaving an analytic sample of 4,725.

We used logistic regression to model the association between baseline OA groups and completion of the 400-meter walk test cross-sectionally at baseline. We used generalized estimating equations for repeated logistic regression to model the association between OA groups and the likelihood of 400-meter walk completion longitudinally from baseline to the 48-month follow-up. Base and adjusted odds ratios (OR) with 95% Confidence Intervals (CI) were estimated controlling for risk factors age, sex, race, and clinic site (Model 1). Models were also adjusted for baseline covariates including body mass index, PASE, KOOS lifestyle modification, KOOS fear of knee buckling, co-morbidity score, number of medications, CESD score, smoking status, average alcohol consumed per week, history of a fall, and education level (Model 2). Models were further adjusted chair stand pace (Model 3). Models excluded participants who did not attempt the test.

We used repeated ordinal regression to model the association between OA groups and quartile of time to complete the 400m walk test from baseline to 48-month follow up. To account for failed completers, those who began the walk test but did not complete the full 400-meters, were assigned to the worst quartile of performance. Base and adjusted odds ratios (OR) with 95% Confidence Intervals (CI) were estimated controlling for risk factors age, sex, race, and clinic site. Models were also adjusted for baseline covariates including body mass index, PASE, KOOS lifestyle modification, KOOS fear of knee buckling, co-morbidity score, number of medications, CESD score, smoking status, average alcohol consumed per week, history of a fall, and education

level (Model 2). Models were further adjusted chair stand pace (Model 3). Analysis was completed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

11.5 Results

Overall, 4,725 participants were followed over 4 years for completion of the 400-meter walk test. The average age of the cohort was 60 years of age. Those with radiographic KOA only were older than those with no OA and those with symptoms. 59% of the cohort was female with no differences across the groups. 79% of the cohort was white, with a higher percentage of white in the no OA and radiographic KOA groups in comparison to those with symptoms only and those with symptomatic KOA. Adults with symptomatic KOA had a higher BMI (30.2 kg/m^2) compared to those with radiographic only (28.8 kg/m^2), symptoms only (28.0 kg/m^2), and no OA (26.9 kg/m^2). Those with no OA (0.29) had a lower co-morbidity index score in comparison to those with symptoms only (0.40), radiographic KOA only (0.37), and those with both (0.49). There was no difference between number of medications, pain medication, and narcotic use across the groups. Adults with symptomatic KOA were more likely to report modifying activities in their lifestyle due to knee pain. Adults with symptoms of knee OA were more likely to be current smokers in comparison to those with no OA or radiographic KOA only. Adults with symptomatic KOA were more likely to report depressive symptoms than adults with radiographic KOA only (7.7 versus 5.7) and no OA (7.7 versus 5.5). Adults with symptoms of OA reported similar scores on the CES-D as those with symptomatic KOA (7.6 vs 7.7). Physical activity based on the PASE was higher for adults with no OA and symptoms only versus those with radiographic only and symptomatic KOA. Adults with radiographic KOA, with and without symptoms had a slower chair stand pace

(0.46 and 0.52 respectively) in comparison to adults with no OA and no symptoms (0.54). Adults with no OA and no symptoms demonstrated a faster walking speed 1.37 meters per second in comparison to adults with symptoms (1.33 m/s), radiographic only (1.33 m/s), and symptomatic KOA (1.27 m/s) over a 20-meter walking course. Adults with no KOA were less likely to report history of a fall at baseline in comparison to those with symptoms and those with radiographic KOA. Results are summarized in Table 1.

11.5.1 Cross-Sectional Results

In models examining the association of knee OA status and odds of completing the 400-meter walk at baseline, base models (model 1), adults with no KOA were more likely to complete the 400-meter walk than adults with symptoms only and symptomatic KOA (Table 2). There was no statistical difference between adults with radiographic KOA and adults with no KOA. In multivariate models, all associations were attenuated (Model 2) when adjusting for report of activity modification.

In models examining the association between knee OA status and odds of completing the 400-meter walk in the worst quartile of performance, base models (model 1), adults with no KOA were less likely to have worst performance compared to adults with symptoms only (OR=0.54 95%CI=0.45-0.64), radiographic KOA (OR=0.71, 95%CI= 0.60 – 0.84), and symptomatic KOA (OR=0.43, 95%CI= 0.37 – 0.50) (Supplemental Table 2). Adults with symptoms only were less likely to perform in the worst quartile compared to adults with radiographic KOA and adults with symptomatic KOA by 62% (95%CI=0.29-0.51) and 77% (95%CI= 0.17-0.31) respectively. Adults with radiographic KOA were 69% less likely to perform in the worst quartile of performance

compared to adults with symptomatic KOA. (Supplemental Table 2). In multivariate models (model 2), adults with no KOA were 31% less likely to perform in worst quartile of performance in comparison to adults with symptoms only (95% CI=0.48-0.91) and adults with symptoms only were 51% less likely to perform in the worst quartile compared to adults with symptomatic KOA (95%CI= 0.28-0.87).

Mean time to complete the 400-meter walk at baseline was different amongst KOA status. Adults with no KOA were able to complete the walk in a faster time at each time-point (Table 4), 295 seconds, 298 seconds, and 302 seconds.

At each time point (baseline, 24-month, 48-month), adults with symptomatic KOA had the highest percent of participants medically excluded from attempting the 400-meter walk test. At baseline 3.4% of symptomatic KOA participants were medically excluded compared to 1.2% of participants with no KOA. At 48-months, 12.5% of adults with symptomatic KOA were medically excluded compared to 6.5% of adults with no KOA. Full results are summarized in supplemental table 1.

11.5.2 Longitudinal Results

The odds of completing the 400-meter walk test from baseline to 48-months of follow-up, in minimally adjusted models (model 1) adults with no OA were more likely to complete the walk than adults with symptoms and adults with symptomatic KOA (OR=0.93, 95%CI= 0.91-0.96; OR=0.96, 95%CI=0.93-0.99) respectively (Table 3). Adults with symptoms only were 10% more likely to complete the 400-meter walk over the 4 year follow up than adults with radiographic or symptomatic KOA. Adults with radiographic KOA were 6 times more likely to complete the walk

than adults with symptomatic KOA as well. Results are summarized in Table 3. In multivariate models (Model 2), all associations were attenuated.

Adults with no KOA were less likely to perform in the worst quartile of 400-meter walk performance from baseline to 48-months of follow-up in minimally adjusted models (Model 1) than all other groups. Adults with symptoms only were less likely to perform in the worst quartile compared to adults with radiographic and symptomatic KOA. Adults with radiographic KOA were less likely to perform in the worst quartile compared to adults with symptomatic KOA in minimally adjusted models as well. In multivariate model (Model 2), adults with no KOA were 19% less likely than adults with symptoms only to perform in the worst quartile over follow-up. Adults with symptoms only were 23% less likely and 30% less likely to perform in the worst quartile compared to adults with radiographic and symptomatic KOA respectively. Results are summarized in Table 4. All associations were attenuated with adjustment for chair stand pace.

11.6 Discussion

We found that middle and older aged adults with no signs or symptoms of knee OA were more likely to complete the 400-meter walking test in comparison to those with symptoms, radiographic KOA and symptomatic KOA in minimally adjusted models. We found that adults with no KOA were 31% less likely than adults with symptoms only and adults with symptoms only were 51% less likely than adults with symptomatic KOA to perform in the worst quartile of performance at baseline. In multivariate models, we found adults with no KOA were less likely to perform in the worst quartile compared to adults with symptoms only and adults with symptoms only were less likely to perform in the worst quartile compared to adults with radiographic and

symptomatic KOA. In fully adjusted models we did not find significant associations with longitudinal assessments of the association between KOA status and the 400-meter walk test.

Consistent with previous literature, adults experiencing no signs or symptoms of this chronic disease were less likely to show signs of mobility limitations or disability. Adults who experienced symptoms, with and without radiographic disease, were the least likely to complete the 400-meter walk, suggesting that this group is most susceptible to mobility disability and should be a group targeted for intervention to prevent this functional decline. Adults no KOA or symptoms were 31% less likely to have the worst performance compared to adults with symptoms only, in models accounting for known covariates. While adults with symptoms only were less likely to perform in the worst quartile compared to adults with radiographic and symptomatic KOA. Our results suggest that symptoms associated with KOA and radiographic KOA may play an important role in mobility. This is consistent with work from the Women's Health and Aging Study II that showed that women with symptomatic KOA were more likely to have worse performance and less strength than women who were symptomatic or intermittently symptomatic. [542] Reports from the CDC estimate 44% of adults with OA report activity limitations, with walking ¼ mile as one of the top 9 activities that are limited.[504, 543]

The mean time to complete the walk at baseline is clinically different between those with symptomatic KOA and those with no KOA (20-30 seconds).[544] Our results continue to suggest that adults with symptoms of KOA may also be at risk for worst performance on longer distance walks and may be groups provide intervention. Our results are consistent with results from Davison et al that found that adults from OAI with pain symptoms had worse performance on the 400-meter walk at baseline compared to those with no OA[545]. This is also consistent with work from Oiestad et al who showed that adults with symptomatic incident KOA experienced a decline in

physical function (20-meter walk) over 3 years of follow-up[546]. Our work is the first to report the odds of completing the 400-meter walk and time to complete the walk over a 4-year follow up period. Future work may warrant a more in-depth assessment of which symptoms have the largest influence and the impact these may have on mechanics, strength, and psychosocial factors may be of importance to develop preventative measures.

The longitudinal association between baseline KOA status and the likelihood of completing the walking task 4 years later showed that the symptomatic groups were less likely to complete the walk in minimally adjusted models. These associations were attenuated when accounting for factors that influence walking performance. In those with symptoms, but not radiographic KOA, adjusting for physical function (chair stands), attenuated that association. Chair stand pace also attenuated all associations between knee OA status and performance in the worst quartile longitudinally. Chair stand performance may reflect knee extensor strength and power and the observed attenuation suggests that lower extremity strength and power are modifiable factors that may play an important role in maintaining mobility in adults with KOA symptoms.[107, 547, 548]

In those with symptomatic KOA, accounting for body mass index, physical activity, confidence of no knee buckling, and activity modifications, attenuated the association. It is possible that symptoms, such as pain, play a role with inhibiting muscle contraction, resulting in experiences of buckling or almost buckling at the knee which may result in fear avoidance of certain activities. A recent systematic review found that duration of symptoms, slower walking speed, higher co-morbidity count, and radiographic KOA were associated with deterioration of performance-based measures of function.[549] The lack of longitudinal associations in our study may also reflect changes in performance due to age-related decline or it may be possible that adults with symptomatic KOA have developed coping strategies to manage their disease, activity

modifications.[550] In a healthy cohort of older adults, Lange-Maia et al found that the rate of decline in performance over a 7-year follow-up was similar across participants regardless of their physical activity status. [550] Adults with symptomatic KOA in our analyses had higher co-morbidity index scores and the impact of other chronic conditions may also be important factors to consider in the longitudinal assessment of this type of aerobic test.

11.6.1 Strength and Limitations

Limitations of this current study include use of baseline radiographic and symptomology to determine KOA; Knee OA may have progressed over the course of the 4 year follow up. We utilized radiographic images to assess stage of knee OA and there may be important factors early signs not distinguished on radiographic images as compared to MRI. By the 48-month visit, a higher percentage of those with symptomatic KOA were excluded from the 400 m walk test, which may exclude those already experiencing mobility limitations. The OAI cohort recruited community-dwelling middle and older aged adults in the US and is not a population-based study so it is unclear if the results are broadly generalizable. The OAI cohort used imaging to assess tibiofemoral knee OA and cannot report on findings from patella-femoral knee OA. Strengths of this analysis include use of a well characterized cohort in the US with detailed and consistent assessments and extended time periods of follow-up. We were able to adjust for important confounding variables.

11.6.2 Conclusions

Adults with symptoms only, radiographic KOA, and symptomatic OA, had the lowest likelihood of completing long distance walks in comparison to adults with no symptoms or radiographic KOA in cross-sectional findings. Adults with symptomatic KOA were more likely to be in the worst quartile of performance and may identify a group to target with therapeutic intervention to prevent mobility decline. Longitudinal associations between baseline KOA status and 400 m completion rates and times over the follow-up were attenuated by other measures of physical function and risk factors for performance declines

11.7 Funding

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11.8 Tables and Figures

Table 20. (Table 1) Baseline Characteristics by Baseline Knee OA status

Variable	No KOA (Group 0) n= 1152	Symptoms Only (Group 1) n= 937	Radiographic KOA (Group 2) n= 1268	Symptomatic KOA (Group 3) n=1368	p-value
Age (years)	60.4 (0.11)	58.4 (0.15)	63.5 (0.10)	61.3 (0.13)	(0v1), (0v2), (0v3), (1v2), (1v3), (2v3),
Female n, (%)	662 (57.5%)	564 (60.2%)	758 (59.8%)	778 (56.9%)	
Race: White n, (%)	985 (85.5%)	694 (74.4%)	1095 (86.4%)	960 (70.2%)	(0v1), (0v3), (1v2), (2v3)
Education: Post College Education n, (%)	434 (37.9%)	290 (31.3%)	370 (29.3%)	325 (24.1%)	(0v1), (0v2), (1v3), (2v3)
BMI (kg/m^2)	26.97 (0.06)	27.99 (0.07)	28.83 (0.06)	30.20 (0.07)	(0v1), (0v3), (1v2), (1v3), (2v3),
Charlson Comorbidity Index	0.29 (0.01)	0.40 (0.02)	0.37 (0.01)	0.49 (0.07)	(0v1), (0v3), (2v3)
Number of medications	4.9 (0.04)	4.9 (0.05)	5.2 (0.04)	4.9 (0.05)	
Narcotics Use n, (%)	31 (2.8)	11 (1.9)	41 (3.4)	29 (3.9)	
KOOS	88.4 (0.19)	87.2 (0.24)	82.7 (0.22)	78.9 (0.29)	

Knee Confidence (no fear of buckling) n, (%)	795 (69.1)	325 (35.4)	730 (57.7)	302 (22.1)	(0v1), (0v2), (0v3), (1v2), (1v3), (2v3)
Self- report using no activity modification n (%)	691 (60.0)	288 (30.7)	608 (48.0)	272 (19.9)	(0v1), (0v2), (0v3), (1v2), (1v3), (2v3)
Neutral Alignment n, (%)	366 (32.7)	165 (27.5)	345 (28.5)	208 (28.4)	
Alcoholic drinks/week	1.8 (0.02)	1.6 (0.02)	1.8 (0.02)	1.7 (0.02)	(0v1), (0v3), (1v2), (2v3),
Current Smokers n, (%)	56 (10.9)	96 (20.6)	66 (11.4)	104 (16.4)	(0v1), (0v3), (1v2),
CES-D	5.5 (0.09)	7.6 (0.13)	5.7 (0.10)	7.7 (0.10)	(0v1), (0v3), (1v2), (2v3)
PASE	168.4 (1.05)	168.8 (1.33)	153.2 (0.98)	158.0 (1.19)	(0v2), (0v3), (1v2), (1v3)
Chair stand pace (stand/second)	0.54 (0.002)	0.49 (0.003)	0.52 (0.002)	0.46 (0.002)	(0v1), (0v2), (0v3), (1v2), (1v3), (2v3),
20-m gait speed (m/s)	1.37	1.33	1.33	1.27	(0v1), (0v2), (0v3), (1v3), (2v3)

400-meter walk test completion (baseline) n (%)	1043 (98.6)	894 (95.5)	1226 (96.8)	1290 (94.4)	(0v1) (0v3) (2v3)
Fall past year n, (%)	345 (30.5)	320 (34.9)	412 (33.0)	465 (34.5)	(0v1), (0v2),

P-value <0.05; Adjustment made for multiple comparisons; presented as mean (standard deviation) unless otherwise noted; 0= no KOA, referent group; 1= symptoms only; 2= radiographic KOA; 3= symptomatic KOA

Table 21. (Table 2) Odds of Completing 400-meter Walk Test at Baseline (OR, 95%CI)

	Model 1	Model 2
No KOA	Ref	Ref
Symptoms Only	0.37 (0.21 – 0.64) *	0.82 (0.36 – 1.54)
Radiographic KOA	0.57 (0.33 – 1.00)	0.75 (0.34 – 1.63)
Symptomatic KOA	0.38 (0.23 – 0.63) *	1.01 (0.48 – 2.46)

Model 1-adjusted for knee group status, age, gender, race, clinic; Model 2- adjusted for model 1 plus BMI, co-morbidity score, confidence of no knee buckling, activity modification, CESD score, fall history, smoking status, alcoholic drinks/week, education level; * indicates statistical significance

Table 22. (Table 3) Odds of Completing the 400-meter Walk Test from Baseline to 48-month follow-up (OR, 95% CI)

	Model 1	Model 2
No KOA, No Symptoms	1.0	1.0
Symptoms Only	0.93 (0.91 – 0.96)*	1.01 (0.96 – 1.07)
Radiographic KOA	0.97 (0.94 – 1.00)	1.01 (0.96 – 1.05)
Symptomatic KOA	0.96 (0.93 – 0.99)*	1.01 (0.95 – 1.06)

Model 1 adjusted for knee group status, age, gender, race, clinic; Model 2- adjusted for model 1 + plus BMI, co-morbidity score, knee buckling, activity modification, CESD score, education level, fall history; * indicates statistical significance (p<0.05)

Table 23. (Table 4.) Odds of Completing 400-meter walk in Worst Quartile of Performance (>335 seconds) from Baseline to 48-months follow up

	Model 1	Model 2
No KOA, No Symptoms	1.0	1.0
Symptoms Only	0.68 (0.59 – 0.77) *	0.84 (0.70 – 0.96) *
Radiographic KOA	0.77 (0.68 – 0.87) *	0.95 (0.82 – 1.08)
Symptomatic KOA	0.53 (0.47 – 0.60) *	0.87 (0.75 – 1. 01)

Non-completers included as worst quartile of performance; Model 1 adjusted for knee group status, age, gender, race, clinic; Model 2 adjusted for base model + plus BMI, PASE, co-morbidity score, knee buckling, activity modification, CESD score, smoking status, alcoholic drinks per week, education level, fall history* indicates statistical significance ($p<0.05$)

Table 24. (Table 5) Mean Time to Complete 400-meter walk at each follow-up time point

	Baseline	24 months	48 months
No OA	295.21 (2.35)	298.19 (2.44)	301.99 (2.75)
Symptoms Only	304.74 (2.45)	308.68 (2.56)	305.15 (2.94)
Radiographic KOA	305.63 (2.25)	303.93 (2.34)	309.92 (2.66)
Symptomatic KOA	318.09 (1.56)	319.86 (1.66)	317.67 (1.89)

Time in seconds, mean (standard deviation); F-test significant at each time point ($p<0.05$)

Table 25. (Supplemental Table 1.) Non-Attempters with OA groups: Medical Exclusion

	Baseline	24 Months	48 Months
Referent	13 (1.2%)	42 (4.7%)	55 (6.5%)
Symptoms Only	31 (3.3%)	51 (6.7%)	62 (8.9%)
Radiographic KOA	32 (2.5%)	93 (8.6%)	98 (9.8%)
Symptomatic KOA	46 (3.4%)	103 (9.5%)	125 (12.5%)

Table 26. (Supplemental Table 2.) Odds of completing 400-meter walk in Worst Quartile of Performance at Baseline

	Baseline	
	Model 1	Model 2
No KOA	Ref	Ref
Symptoms Only	1.78 (1.52 – 2.09)*	1.43 (1.10 – 1.85)*
Radiographic KOA	1.31 (1.12 – 1.52)*	0.86 (0.68 – 1.09)
Symptomatic KOA	2.26 (1.94 – 2.62)*	1.25 (0.94 – 1.58)

Non-completers included as worst quartile of performance; Model 1 adjusted for age, gender, race, and clinic site; Model 2 adjusted for model 1, plus BMI, co-morbidity score, knee buckling, activity modification, CESD score, smoking status, alcoholic drinks per week, education level, fall history; *indicates statistical significance

12.0 Association between the Components of Sarcopenia and Incident Fractures

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12.2 Abstract

Background: The association between the components of sarcopenia definitions have not been clearly elucidated and has hindered the development of appropriate therapeutic interventions. Our aim was to evaluate the associations between the individual components of sarcopenia, specifically lean mass, strength, and physical performance and fracture (any fracture, hip fracture, and major osteoporotic fracture) in the Osteoporotic Fractures in Men (MrOS) study.

Methods: The Osteoporotic Fractures in Men study (MrOS) recruited 5,994 men ≥ 65 years of age. We measured appendicular lean mass (ALM) by dual-energy x-ray absorptiometry (low as residual value <20th percentile for the cohort), walking speed (fastest trial of usual pace, values <0.8 m/s were low), and grip strength (max score of 2 trials, values <30 kg were low). Information on fractures was assessed tri-annually over an average follow-up of 12 years and centrally adjudicated. Cox proportional hazards models estimated the hazard ratio (HR) (95% Confidence Intervals) for slow walking speed, low grip strength and low lean mass.

Results: Overall, 1,413 men had a fracture during follow-up. Slow walking speed was associated with an increased risk for any HR=1.39, 1.05-1.84; hip HR= 2.37, 1.54-3.63; and major osteoporotic, HR= 1.89, 1.34-2.67 in multi-variate adjusted models. Low lean mass and low grip strength were not significantly associated with fracture.

Conclusions: In this cohort of older adult men, the risk of experiencing any, hip, or a major osteoporotic fracture is greater in men with slow walking speed in comparison to men with normal walking speed, but low grip strength and low lean mass were not associated with fracture.

12.3 Introduction

The lack of a consensus definition of sarcopenia has limited its use clinically and has hindered the development of appropriate therapeutic interventions.[71] Sarcopenia was initially defined as the loss of lean mass associated with aging.[507] Lean mass, measured by dual energy x-ray absorptiometry (DXA), has variable associations with adverse health outcomes including fractures. [74, 508-510]Current definitions of sarcopenia include varying cut-points for body composition, strength, and functional performance further creating challenges for clinical utility. [71, 511] It is not clear whether all the components of sarcopenia definitions (slow walking speed, low lean mass and low grip strength) each individually predict adverse outcomes, particularly fractures, in older adults. Disentangling which components are meaningful predictors of outcomes will elucidate which of these measures should be included in a composite definition.

Previous work in MrOS has demonstrated that once BMD is accounted for, appendicular lean mass divided by height square (ALM/ht^2) mass is not an independent risk factor for fracture. However, whether an alternative measure of lean mass, which accounts for body fat mass in addition to height and has shown a stronger association with lower function in older adults is unknown. Worse performance on functional measures and weakness has been associated with increased risk of fracture and are recommended components of sarcopenia definitions by the Sarcopenia Definitions and Outcomes Consortium. [71, 72, 512, 513] The association between this alternative measure to assess low lean mass and various fracture types has not been explored in MrOS.

Therefore, we evaluated the associations between the individual components, low lean mass, low strength, and low gait speed using 3 fracture outcomes (any fracture, hip fracture, and major osteoporotic fracture) in the Osteoporotic Fractures in Men (MrOS) study.

12.4 Methods

12.4.1 Participants

The Osteoporotic Fractures in Men study (MrOS) is a multicenter prospective study of aging with a focus on risk factors for fractures. The design, measures, and recruitment have been previously described.[551] In brief, from March 2000- April 2002, 5,995 men ≥ 65 years of age were recruited and enrolled from 6 centers across the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California.[551] Men were excluded from the study if they could not walk without the assistance of another or had bilateral hip replacement. Approval of the conduct of MrOS was obtained from institutional review boards of participating institutions, and written informed consent was obtained from all participants before data collection.[551, 552]

12.4.2 Independent Variables: Any Clinical, Hip, Major Osteoporotic Fracture

Men were followed for incident fractures by completing and returning a questionnaire every 4 months that was administered by mail or telephone; >95% complete follow-up over a mean of 12 years.[553] Fractures were verified by centralized physician adjudication of the medical records. Pathological fractures were excluded. Exclusion of fractures resulting from excess trauma underestimates the contribution of osteoporosis to fractures, we included fractures regardless of trauma level.[554, 555]

12.4.3 Primary Predictors: Components of Sarcopenia Definition

12.4.3.1 Body Composition

Whole body lean mass, including appendicular lean mass, and total body fat were obtained using Hologic QDR 4500 dual energy x-ray absorptiometry machines. Central training, quality control, and standardized procedures were used to insure reproducibility of measurements. Appendicular lean mass (ALM) was calculated as the sum of soft-tissue lean mass in the arms and legs. Men were considered to have low lean mass if their ALM was below the 20^{th} percentile of the regression residuals derived from the cohort (Newman definition). The Newman residuals method to define low lean mass regresses both height and fat mass on total ALM and has been shown to be a strong predictor of physical function [509] (aLM (kg) = -23.53 + 25.34 x height (m) + 0.17 total fat mass (kg), 20^{th} percentile cut point = -2.17).

12.4.3.2 Gait Speed

Gait speed was assessed by usual gait speed over a 6-meter course. Two trials were performed, and the fastest value was used in this analysis. Slow gait speed was defined as usual walking speed < 0.8 m/s. This cut-point has been used in definitions of sarcopenia (European Working Group on Sarcopenia and the Foundation for NIH Sarcopenia Project) and shown to be associated with physical performance and clinical relevance. [556-558]

12.4.3.3 Weakness

Grip strength was measured using a Jamar hand dynamometer with adjustable handgrip. Two trials were performed on each hand with highest value used in the analysis. Weakness was

defined as grip strength <30 kg which is used in definitions of sarcopenia [556, 558, 559] and shown to be associated with increased risk of non-spine fractures in men. [560]

12.4.4 Covariates

12.4.4.1 Bone Mineral Density

Total body, lumbar spine (L1-L4), and total hip areal BMD were measured at baseline using dual-energy x-ray absorptiometry (DXA). The same scanner model was used at all 6 sites (QDR 4500 W, Hologic Inc.; Bedford, MA, USA). Standardized procedures for positioning and san analysis were followed for all scans. All DXA operators were centrally certified based on an evaluation of scanning and analysis techniques.

12.4.4.2 Other Covariates

At baseline, information regarding demographic, anthropometric, personal and family medical history, lifestyle, functional status, visual acuity, and cognitive data were obtained through self-report, interview, or examination by trained and certified staff. [551] Data on age and race were collected at baseline. Physical activity was assessed with the Physical Activity Scale for the Elderly (PASE).[561] Additional questions included self-report for physician diagnosis of specific common medical conditions. Participants were asked about falls over the previous 12 months. General health status was self-rated and categorized as either excellent/good versus fair/poor. Mood was assessed using the Geriatric Depression Scale. [562]

Body weight (kg, indoor clothing without shoes) was recorded with a calibrated balance beam or electronic scale. Height (cm) was measured using a wall mounted Harpenden stadiometer (DyFed). Body mass index was calculated by dividing weight by height squared (kg/m^2).[563]

Participants were asked to bring in all prescription and non-prescription medications taken regularly during the previous 30 days to their clinic visit. All medications were recorded by the clinics were stored in an electronic medication inventory database (San Francisco Coordinating Center, San Francisco, CA, USA). Each medication was matched to its ingredients based on the Iowa Drug Information Services Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA). [564]

12.4.5 Statistical Analyses

Participant characteristics were summarized using means and standard deviation, median and interquartile range, or frequencies and percentages as appropriate. Baseline characteristics of the cohort were assessed as a whole cohort and based on fracture status. To test for differences across groups, analysis of variance was used for continuous variables and chi square tests for categorical variables.

Separate Cox proportional hazards models were used to estimate the risk of incident fracture by low lean mass, slow walking speed, and weakness as independent variables, hazard ratios (HR) and 95% confidence intervals (CI) were calculated per standard deviation (SD). All models were adjusted for age and clinic site. To construct multi-variable models, additional variables were selected for inclusion in the model based on identification from previous literature as a risk factor for fracture, including each of the independent variables low lean mass, slow walking speed, and weakness. These variables include age, race, history of diabetes, fall, and arthritis, health rating, physical activity, smoking status, alcohol consumption, education, symptoms of depression. Interaction between independent variables, low lean mass, slow walking

speed, and grip strength were assessed in each model. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

12.5 Results

The average age of the cohort was 74 years, Table 1. Men who experienced any clinical fracture were older than those who did not experience a fracture over follow-up. Low lean mass was defined using the Newman residuals method, therefore 20% of the cohort was defined as low lean mass. Slow walking speed and weak grip strength did not differ by fracture status. Those who experienced a fracture were more likely to have a history of falls in comparison to men with no fracture. Men who experienced a fracture in this cohort were more likely to self-rate their health as fair to poor versus good or excellent. No differences were seen in physical activity, smoking status, alcohol intake, and living alone across the groups.

In minimally adjusted models, low lean mass was associated with 25% increased risk of any fracture and 35% increased risk of major osteoporotic fracture (table 2) but not hip fracture. These associations were attenuated and no longer significant after adjustment for covariates including BMD

In minimally adjusted models, weakness was only associated with any fracture (but not hip or major osteoporotic fracture). In fully adjusted models, weakness was no longer significantly associated with any fracture, hip or major osteoporotic fracture.

Slow walking speed was associated with all fracture outcomes. Although the association was attenuated in the fully adjustment models, the relationship between slow walking speed and fracture remained strong, particularly for hip fractures. Slow walking speed showed a 39%

increased risk for any clinical fracture, 89% increased risk for osteoporotic fracture and 137% increased risk for hip fracture in our multivariate adjusted models.

No interaction terms between low lean mass, slow walking speed, and weakness were significant in any of the models.

12.6 Discussion

In this cohort of older adult men, the risk of experiencing any, hip, or a major osteoporotic fracture was greater in men with slow walking speed in comparison to men with normal walking speed independent of many covariates, such as bone mineral density, low lean mass, grip strength, physical activity and lifestyle variables. In contrast there was no association of grip strength or lean mass with any fracture outcome after accounting for multiple confounding variables.

Low lean mass, when defined by the Newman-residuals methods, was associated with an increased risk of any fracture and major osteoporotic fractures in minimally adjusted models, but this association was attenuated after adjustment for BMD. This finding is in line with the previous literature that demonstrates no association between DXA ALM/ht^2 and fracture after accounting for BMD. These results are also consistent with the updated guidelines from the Sarcopenia Definition and Outcomes Consortium (SDOC) that lean mass measured by DXA is not a strong predictor of adverse health outcomes, including fracture. [71]

Weakness, measured by grip strength, was not an independent risk factor for fracture in this cohort. While weakness measured using the maximum score on a handheld dynamometer is easy and reliable. [565, 566], it may not be the most robust measure of function to assess in terms of fracture risk. Although grip strength has been shown to be cross-sectionally associated with

lower-extremity strength, [565] assessment of lower extremity power may be a stronger predictor of fracture. [107, 559, 567, 568] Our results vary from other analyses within the MrOS cohort. Harvey et al reported using the MrOS cohorts from US, Sweden, and Hong Kong that physical performance, including grip strength, is an independent risk factor for incident factures over 9 years of follow-up above BMD, prior falls, and Fracture Risk Assessment Tool (FRAX) probability. In fact, previous work in MrOS has demonstrated that a measure of lower extremity function – chair stands performance – is strongly related to hip fractures and varies greatly from grip strength assessments. [512, 569] Chair stands are a weight bearing activity that stand as a proxy for power however, to be consistent with clinical definitions of sarcopenia we opted to assess grip strength. Another potential limitation of grip strength is that other factors may also have impacted the measurement including arthritis, pain, depression, and motivation.

Walking speed has become a vital measure across many clinical areas as it can provide insight into an older person's health A gait speed less than 0.8 m/s has been consistently used in definitions of sarcopenia and has been associated with independent community ambulation. [71, 570] Gait speed is a task that combines the effort of numerous body systems neuromuscular, vestibular, cardiopulmonary, and musculoskeletal. In this analysis, gait speed itself was an independent predictor of any fracture, hip fracture, and major osteoporotic fractures in this cohort. Routine measurement of gait speed and identifying the cause of slow gait speed would be important to consider with clinical care for this risk factor, given it may be addressed in rehabilitative treatment by addressing lower extremity strength and power, efficiency of gait, and biomechanical factors. [571-573].

12.6.1 Strength and Limitations

Limitations of this study include the limited generalizability of the cohort, given it is predominately white race and limitation to men only. Strengths of this study include use of a well characterized cohort of community dwelling older men who are at risk for adverse health outcomes, with ascertainment of fractures over an extended follow up time and use of a clinical definition of sarcopenia.

12.6.2 Conclusion

Overall, slow walking speed was associated with an increased the risk of all fracture types in older men. In contrast there was no association with grip strength or appendicular lean mass. Thus, the all components within definitions of sarcopenia do not similarly increase the risk of fracture. Our findings suggest that a simpler definition of sarcopenia to identify those at risk of poor outcomes (e.g., just slowness) may be most appropriate in the context of fracture risk consideration in addition to the Fracture Risk Assessment (FRAX) tool.

12.7 Funding

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12.8 Tables and Figures

Table 27. (Table 1) Baseline Characteristics of the MrOS Cohort

	Whole Cohort (N= 5994)	No Fracture (n= 4581)	Fracture (n=1413)	p-value
Age ($\bar{x}\pm\sigma$)	73.7 ± 5.9	73.5 ± 5.9	74.2 ± 5.9	<0.0001
Caucasian (n, %)	5362 (89.5)	4047 (88.0)	1315 (22.6)	<0.0001
Low Lean Mass (n, %)	1191 (20)	1191 (20)	315 (22.6)	0.0063
Slow Walking Speed <0.8 m/s (n, %)	273 (4.6)	208 (4.5)	65 (4.6)	0.92
Grip Strength <30 kg (n, %)	380 (6.4)	208 (4.5)	65 (4.6)	0.84
BMD T-score	-0.62 ± 1.07	-0.51 ± 1.06	-0.96 ± 1.01	<0.0001
History of Diabetes (n, %)	653 (10.9)	504 (11.0)	149 (10.5)	0.63
History of Arthritis/gout (n, %)	2847 (47.5)	2183 (47.7)	664 (47.0)	0.66
History of a fall (n, %)	1268 (21.2)	908 (19.8)	360 (25.5)	<0.0001
Good/Excellent Health Rating (n, %)	5135 (85.7)	3896 (85.1)	1239 (87.7)	0.0146
Use of Benzodiazepine (n, %)	205 (3.6)	157 (3.6)	48 (3.6)	0.99
Use of Selective Serotonin Reuptake Inhibitors (n, %)	163 (2.8)	117 (2.7)	46 (3.4)	0.15
Visual Acuity 20/50 (n, %)	114 (1.9)	91 (2.0)	23 (1.6)	0.39
3MS ($\bar{x}\pm\sigma$)	93.3 ± 5.9	93.1 ± 6.1	93.7 ± 5.1	0.0007
College Education (n, %)	3188 (53.2)	2378 (51.9)	810 (57.3)	0.0004
Depressive feelings (n, %)	178 (3.0)	130 (2.8)	48 (3.4)	0.28
PASE score (median + IQR)	142 (100 – 186.1)	142.1 (101- 185.9)	141.2 (95.7 – 189.7)	0.63

Current Smoker (n, %)	206 (3.4)	153 (3.3)	53 (3.8)	0.46
Zero Alcoholic Drinks per week (n, %)	2121 (35.4)	1639 (35.8)	482 (34.2)	0.42
Live Alone (n, %)	840 (14.0)	642 (14.0)	198 (14.0)	0.99

*Low Lean Mass defined by the Newman Residual Method; p-scores indicate difference between no fracture and fracture groups

Table 28. (Table 2.) Association between Low Lean Mass, Slow Walking Speed, and Weakness with Any Fracture, Hip Fracture, and Major Osteoporotic Fractures

	Any Fracture HR (95% CI)		Hip Fracture HR (95% CI)		Major Osteoporotic Fracture HR (95% CI)	
	Base	Full	Base	Full	Base	Full
Low Lean Mass	*1.25 (1.10 –1.42) **	1.10 (0.96 –1.26)	1.23 (0.95 – 1.59)	0.91 (0.69 – 1.20)	*1.35 (1.12 – 1.62) **	1.16 (0.95 – 1.40)
Slow Walking Speed	*1.70 (1.32 – 2.20) **	1.39 (1.05 – 1.84) *	3.44 (2.33 – 5.07) *	2.37 (1.54 – 3.63) *	*2.39 (1.73 – 3.29) **	1.89 (1.34– 2.67) *
Weakness	*1.31 (1.06 – 1.63) **	1.20 (0.96 – 1.50)	1.01 (0.65 – 1.57)	0.81 (0.51 – 1.30)	1.12 (0.82 – 1.55)	0.97 (0.70 – 1.35)

*indicates statistical significance

13.0 Discussion

13.1 Summary of Findings

The overall objective of this dissertation was to investigate the associations between chronic conditions and mobility disability, recurrent falls, and fractures in adults. These associations represent various sub-populations that would benefit from preventative measures to reduce functional decline and morbidity. Within the International Classification of Function (ICF) model, impairments within body structures (e.g. radiographic knee OA, sarcopenia) may lead to limitations in activity (e.g. walking) and in combination, contribute to disability in participation (e.g. unable to walk in a grocery store) in physical and social roles. These impairments may be targeted at different levels, as secondary prevention, to reduce the likelihood of experiencing disability and compress the morbidity commonly associated with chronic medical conditions.

The Osteoarthritis Initiative (OAI) is a multi-center longitudinal prospective observational study with the goals to improve understanding of the natural history of knee osteoarthritis and to identify risk factors for the development and or progression of knee osteoarthritis. This cohort recruited 4,796 participants between 45-79 years of age at the time of enrollment. We examined the association between severity of knee OA and recurrent falls over a 4 year follow up time period. Severity of knee OA and the risk of recurrent falls in the OAI study revealed that older adults (age >65 years) with all levels of radiographic knee OA were more likely to experience recurrent falls than their counterparts without radiographic knee OA. While radiographic knee OA may not mirror symptoms throughout the progression of the disease, there are alterations that commonly occur in the biomechanics of mobility and other functional tasks. Alterations in range of motion

and muscle inhibition due to pain and other symptoms can have an impact on function, lower extremity strength and confidence performing those tasks as well. These changes may increase the likelihood of experiencing a fall. Dore et al found an association between older adults with symptomatic knee OA and falls but was limited to a single follow-up while other longitudinal studies have found a null association. [402] To our knowledge, this was the first study to examine how the *severity* of radiographic knee OA impacts recurrent falls. Previous work in falls and knee OA reported that adults with symptomatic knee OA or incident knee OA have increased risk of falls. [407, 497, 499] Our results extend these earlier findings to include examination of the severity of KOA. Adults age $\geq$ 65 years with possible OA in one or both knees had 2.2 times higher odds (95% CI=1.10-4.54), with mild OA in one or both knees had 2.5 times higher odds (95% CI=1.34-4.61), with unilateral moderate to severe radiographic knee OA had 2.9 times higher odds (95% CI= 1.52-5.63) and adults with bilateral moderate to severe knee OA had 2.5 times higher odds (95% CI = 1.16- 5.46) of recurrent falls in comparison to adults with no evidence of radiographic knee OA in either knee. We were able to account for symptoms associated with knee OA as well as clinical variables that are common to OA. Given the high prevalence of knee OA, our results suggest that prevention of KOA could reduce the risk of falls and the potential for fall-related injuries. Older adults who experience recurrent falls are more likely to experience a fall injury as well. Our results identify a sub-group of the population that should be targeted with intervention to prevent recurrent fall events and possible subsequent functional decline. [574-576]

In the OAI study, we examined adults with knee OA and the likelihood to complete the 400-meter walk, likelihood to complete the walk in the worst quartile of performance and the time to complete at baseline and 4-years of follow up. Cross-section results from our work show that adults with symptomatic knee OA and adults with symptoms of pain and stiffness have a decreased

likelihood of completing the 400-meter walk and may be more likely to experience mobility limitations than adults without knee OA. Longitudinal associations of the likelihood of completing were attenuated with adjustment for body mass index for adults with radiographic KOA and lifestyle variables of smoking status and alcohol consumption for adults with symptoms. At enrollment, the referent group required on average 295 seconds to complete the 400-meter walk test in comparison to adults with symptomatic KOA, who on average required 318 seconds to complete the task. In the Health Aging and Body Composition study, the time to complete the 400-meter walk test increased over time across those who exercised and those who did not over 8 years of follow up. The Health ABC study also demonstrated that taking >362 seconds to complete the walk test were at highest risk for cardiovascular events, mobility disability, and mortality. [415] In our OAI cohort, adults with symptomatic KOA were most likely to have worst performance, taking >362 seconds to complete. [550, 577] In this analysis, adults with symptomology were more likely to complete the test in the worst quartile of performance in cross-sectional and longitudinal analyses. The role of pain and stiffness vary throughout the course of knee OA and a baseline assessment of symptoms may not reflect future symptoms and may limit the strength of our longitudinal analyses. Work from White et al demonstrated that adults with symptoms of knee OA were 4.5 times more likely and adults with symptomatic knee OA were 8.9 times more likely to experience fast decline (2.75%/year) in gait speed over 4 years of follow-up. [578] While this difference was measured in a shorter length walk, the impact of pain and the ability to manage the pain while performing tasks varies across individuals, it may likely contribute to decline in mobility. The lack of associations longitudinally, in likelihood to complete and time to complete, may be due to the higher percentage of persons not attempting the 400-meter walk in subsequent clinic visits. Refusal to attempt the test, missing the in-person clinic visit, and medical restrictions

to qualify to attempt the longer distance walking test likely eliminate adults who are experiencing greater morbidity and functional limitations. Work from Master et al in the OAI cohort, reported that adults with radiographic and symptomatic OA who take less than 6000 steps/day, viewed as those with less physical activity, have worse performance on the 400-meter walk test.[579] Impairments in cardiorespiratory fitness can limit daily walking and endurance activity, as can symptoms of knee OA, which may be associated with low levels of physical activity.[415, 506, 550] It is not clear if one impairment causes another, but the cycle of reduced physical activity is perpetuated by both impairments and both can lead to further functional decline, mobility disability and higher risk for adverse health outcomes.

The Osteoporotic Fractures in Men Study (MrOS) is a prospective cohort study examining fracture risk and its association to bone mass, bone geometry, lifestyle, neuromuscular and anthropometric measure, fall propensity and how fractures affect quality of life in men. MrOS enrolled 5,994 men with a mean age of 73.5 (± 5.9 years). [580] We examined in the MrOS study the association between the components of sarcopenia definitions and risk of fracture in older adult men. The Sarcopenia Definition and Outcomes Consortium (SDOC) committee determined that grip strength and gait speed should be components of a standard definition of sarcopenia, however a true consensus definition of sarcopenia has not been established. [71] Both weak grip strength and slow gait speed have been associated with adverse health outcomes. [72, 511, 581] The Newman-residuals definition of sarcopenia, defines sarcopenia by regressing height and fat mass on the total appendicular lean mass and using the 20^{th} percentile as a cut-point. This definition of sarcopenia has been shown to have a strong association with physical function. [509] Examination of this definition with the proposed measures of strength and mobility and the association with fractures has not been explored. Results from this analysis showed that older men with slow

walking speed (≤0.8m/s) have higher risk of any, hip, and major osteoporotic fracture in comparison to men with normal walking speed. Weakness (grip strength <30 kg) and low lean mass (20^{th} percentile cut point = -2.17 kg) did not have an association with fracture (any, hip, or major osteoporotic). Our results vary from other analyses within the MrOS cohort. Harvey et al reported using the MrOS cohorts from US, Sweden, and Hong Kong that physical performance, including grip strength, is an independent risk factor for incident factures over 9 years of follow-up above BMD, prior falls, and Fracture Risk Assessment Tool (FRAX) probability. [582] Our results may vary as we utilized a cut-point of <30 kg to define weakness, as suggested by the SDOC, versus use of grip strength as a continuous measure and only included results from the US cohort. Grip strength may not be the most robust measure of muscle function to assess in terms of fracture risk. In fact, previous work in MrOS has demonstrated that a measure of lower extremity function – chair stands performance – is strongly related to hip fractures and this measurement captures different information regarding strength and function in comparison to grip strength assessments. [512, 569] The findings from our analyses are important as they demonstrate that assessment of usual gait speed is a strong risk factor for fracture risk in older men. Assessment of usual gait speed can be implemented in clinical settings without increased time and effort and may allow ease in identifying those in the population who would benefit from intervention to reduce risk of adverse health outcomes.

13.2 Strength & Limitations

A major strength of each study in our research is that we have included detailed data and follow-up from well-characterized cohort studies. In the OAI study, we included imaging variables with rigorous radiographic readings and assessment from multiple time points. These carefully ascertained variables provide confidence that we were able to correctly characterize participants in our analyses. In our studies within OAI, we were able to include detailed clinical examinations to assess for joint alignment, laxity, range of motion, and joint effusion which are not readily available within most cohort studies. We accounted for these clinical signs in our analyses examining fall risk and mobility disability. We were also able to account for many other important covariates including physical activity, KOOS scores (pain, symptoms of knee buckling, activity modifications), medication usage, co-morbidities, and detailed questionnaires about mood and lifestyle. There are however several limitations to the OAI study. Although, OAI recruited across numerous races, the overall cohort is still largely white and limits the generalizability of our findings. Assessment of falls occurred on an annual basis, which may have biased our results to the null as recall of a fall, particularly a non-injurious fall may have forgotten over that time period. A more detailed assessment of fall events, including injurious falls would be a warranted in future research. Our assessment of the 400-meter walk was limited longitudinally as greater than 12% of the study population did not attempt the walk by the 4-year follow-up clinic visit, though our results were similar at shorter follow-up time periods. We may have excluded some adults who were experiencing mobility limitations with this specific longer distance walk. We additionally accounted for symptoms at baseline, which may not accurately reflect symptoms at the other follow-up time periods. Future work in this research may need to examine if there is a more

appropriate endurance assessment for this population with symptomatic knee OA and accounting for the variation that commonly occurs with symptoms and pain in knee OA.

The MrOS cohort has numerous strengths. In our study within the MrOS cohort, we were able to include adjudicated outcome assessment of various fracture types including any, hip, and major osteoporotic fractures. We included detailed assessment of lean mass from DXA, which is the current gold standard for body composition assessment. In addition, the assessment of fracture events occurred in tri-annual assessments. If participants were not able to attend a clinic visit or return the follow-up post card, study staff called participants to complete the follow-up; thus, reduce the missing data and loss of follow-up. This allowed us to include all subjects irrespective of completing follow-up clinic visits. We were able to include men who were frail and experienced difficulty attending clinic visits. We were also able to utilize numerous years of follow-up within our analyses. The detailed assessments within the study allowed us to account for many covariates including medical conditions, vision, reliable strength and performance measures, and detailed questionnaires. We were also able to utilize a standard and clinically relevant definition of sarcopenia. We are limited in generalizing our findings to men and are also limited across race as this is a mostly white cohort with few men experiencing weakness by grip strength and slow walking speed.

13.3 Public Health Significance

The prevalence of disability increases with age, with 42% of those ≥ 65 years of age reporting any type of disability and approximately 27% of adults ≥ 65 years of age report mobility disability.[583] Given current demographic shifts to an aging society, this is a major public health

concern. Nearly 44% of adults with arthritis reported activity limitations. [584] Identifying targets for intervening, such as adults who experience symptoms of pain and stiffness in their knees on most days, is important to identify those who may be at higher risk of developing mobility limitation and falls. Within the ICF model, targeting interventions to improve body function & structure as well as activity may prevent this decline at a participation or societal level.

A single fall event is self-reported by 20-35% older adults each year. [516] The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study, found that 19% of their community dwelling older adults experience recurrent falls over 18-months. [585] Reported fall rates vary but it has been estimated between one and two thirds of adults who fall experience a recurrent fall within a year. [586, 587] Falls are a leading cause of disability and mortality in older adults, as well as a costly event to manage within our healthcare system. Recurrent fallers are more likely to experience an injury from repeated occurrences. [588] Knee OA is the most common form of arthritis and is a leading contributor to functional decline and disability. [589, 590] Men and women age ≥ 65 with radiographic knee OA irrespective of their symptoms were more likely to experience recurrent falls and have greater risk of functional decline in their activity and participation. [591-593] Providing preventative measures, which may include community-based physical activity programs or rehab specific interventions to improve mobility safety and skill as well as lower extremity strength and balance for this population may improve their risk for falls and reduce the subsequent public health burden.

1 in 5 men over 50 years of age will experience an osteoporotic fracture in their lifetime. [594, 595] The global number of hip fractures alone is expected to increase from 1.3 million in 1990 to 4.5 million by 2050. [596] Slow gait speed, in older men, has been shown in our research to be a risk factor for any, hip, and major osteoporotic fractures. Slow gait speed has been

associated with other adverse health outcomes including falls, hospitalization, and mortality. [107, 567, 568] Identification of adult men with slow gait speed for interventions to improve their gait, (e.g. leg strength and power) and activity (e.g. timing and coordination of gait) may reduce fractures.

Within the ICF model, there are multiple levels in which targeted interventions can be enacted to prevent future functional decline and disability. In this research, we focused on impairment and limitations that occur on a person-level and would identify potential targets to address within a person's body function, activity, and participation level. With increasing numbers of aging adults and increasing challenges to maintain strength and function, targeting the modifiable factors to prevent decline is a significant public health concern.

13.4 Conclusion

In order to reduce the incidence and prevalence of functional disability in older adults, we need to better understand early impairments within body systems that are associated with fractures, falls, and mobility limitations. Identifying these changes in body structure and resulting impairments as targets for intervention is crucial to reduce the potential burden arising from the growing population of older adults. Functional measures, such as usual gait speed, may be simple efficient measures that can be employed in clinical settings to identify older adults who may be at risk for fractures, which may lead to subsequent disability and adverse health outcomes. Understanding the role that knee osteoarthritis radiographic severity has with fall risk and recurrent fall events in middle and older aged adults is important to be able to specifically target groups to prevent this costly adverse health outcome. Intervention to target KOA or fall prevention efforts

within KOA severity groups are potential targets. These interventions may include physical activity programs to help older adults meet the established guidelines (including both the goal to do at least 150 minutes of moderate intensity multi-component activity and the goal to move more, any amount of physical activity is better than none), rehab interventions to improve mobility, lower extremity strength and balance and education about ways to reduce fall risk are options to prevent this potential decline in function. Longer distance walking tests, such as the 400-meter walk, may not be as feasible to employ in many clinical settings. These challenging walks may be important in early identification of adults with radiographic and symptomatic subtypes of knee osteoarthritis, who may be at risk for mobility limitations but may not be scalable across within clinical settings though self-reported questions on the ease of walking several blocks in the community could identify those older adults at risk. The public health significance of these findings is that early identification of older adults who are at increased risk of mobility limitations, recurrent falls and fractures may best inform where preventative measures should be utilized to reduce future disability in older adults.

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