PHYSICAL ACTIVITY, BODY COMPOSITION, THIGH COMPOSITION AND STRUCTURAL CHANGES IN THE KNEES OF OLDER ADULTS

by

Tomoko Fujii

MD in Medicine, Chiba University, Japan, 1998

MPH in Global Epidemiology, Emory University, 2011

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This dissertation was presented

by

Tomoko Fujii

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and approved by

Dissertation Advisor:
Robert M. Boudreau, PhD
Assistant Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Iva Miljkovic, MD PhD
Assistant Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Elsa S. Strotmeyer, PhD MPH
Associate Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Jennifer Brach, PhD PT
Associate Professor, Department of Physical Therapy,
School of Health and Rehabilitation Sciences, University of Pittsburgh

Kent C. Kwoh, MD
Professor, Medicine and Medical Imaging
University of Arizona

Robert M. Boudreau, PhD

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ABSTRACT

Osteoarthritis of the knee (knee OA) is a major cause of disability. The effect of physical activity and sedentary time on knee structural changes in older adults has not been established. Recent studies highlight the metabolic aspect of knee OA, but whether higher weight or metabolic mechanisms are more important is unknown. First, physical activity level was defined based on subjectively measured energy expenditure in total and for exercise in the Health, Aging and Body Composition Study. In older adults without knee pain, being lifestyle active or an exerciser was associated with two times higher odds of severe cartilage damage in the medial tibiofemoral joint compared with being inactive, suggesting vulnerability of knee cartilage to higher physical activity levels. In older adults with knee pain, those watching TV for ≥7 hours/week had over two times higher odds of bone marrow lesion (BML) in the whole knee, and ≥14 hours/week with 2.6 times higher odds of severe cartilage damage in the medial compartment compared with <7 hours/week. Next, body composition from DXA, and abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) areas on CT were examined. Higher appendicular lean mass rather than total body fat mass was associated with knee structural changes. Greater VAT area per weight was not positively associated with knee outcomes. Significant associations between greater SAT area and higher odds of knee structural changes found only in women were not explained by inflammatory markers, adipokines, or cardiometabolic risk factors. Lastly, thigh fat composition on CT and knee extensor strength were examined. Higher thigh density reflecting lower intramuscular fat, specifically quadriceps in men and hamstring in women, and higher knee extensor strength per quadriceps area in women were associated with lower odds of structural changes. Generally, no association with structural change was found for thigh intermuscular adipose tissue area or thigh SAT area. These findings support the importance of mechanical mechanisms rather than metabolic mechanisms. This dissertation has the important public health implication that weight control, good muscle quality and proper levels of physical activity are recommended for knee OA prevention and control in older adults.

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PREFACE

I was able to complete my dissertation thanks to the support of many people. I would like to thank my committee members, all of whom provided expertise in their fields for my dissertation. I would like to thank Dr. Boudreau, who not only served as my primary advisor but also gave me my start at the Pivotal Osteoarthritis Initiative Magnetic Resonance Imaging Analyses (POMA), where my interest in knee osteoarthritis study began. I would especially like to thank Dr. Kwoh, who is a great mentor in knee osteoarthritis research and who provided his support even after he moved to Arizona. I am also thankful for the training in the Center for Aging and Population Health (CAPH). Past teachers, in particular, Dr. Kleinbaum, who is an enthusiastic educator of biostatistics, and Dr. Howards, who is a great Epidemiology methods teacher, both motivated me to seek my doctoral education. Without the support of friends in the US and in Japan, I would not have been able to complete my dissertation. My parents have always encouraged my education and given me their support. Finally, I would like to acknowledge the assistance in writing in English from Emily Riley and the instructors at the University of Pittsburgh Writing Center.

1.0 INTRODUCTION

Osteoarthritis of the knee (knee OA) is a common disorder in older adults. It causes pain and functional limitation and results in disability [1]. Because obesity is a risk factor for knee OA, the burden of knee OA would increase in aging populations with high prevalence of obesity. There are no approved disease modifying OA drugs which slow or reverse the progression of knee OA. Damages in knee joint cartilage and meniscus are essentially irreversible. The current therapy for knee OA is mainly symptom control or joint replacement surgery in severe cases.

There are only a few established risk factors for knee OA, such as female gender, obesity, knee injury, hand OA, and some occupational physical activities. Physical activity and obesity are modifiable lifestyle risk factors for knee OA. Regular physical activity is associated with lower risk of chronic diseases and obesity, and physical activity is recommended for all adults including older adults [2]. However, weight-bearing physical activity may have an adverse impact on weight bearing joints such as the knee. A number of studies have examined the association between physical activity and knee OA, predominantly using radiography, but results are inconclusive. Magnetic resonance imaging (MRI) enables direct evaluation of the structural changes in the knee joint. Hence, MRI is more sensitive to detect early changes in the knee compared with radiography. Some of the recent studies using MRI suggest beneficial effects of physical activity on knee cartilage, but studied populations were mainly people at higher risk of knee OA and/or middle age people. Consequently, the effects of physical activity on knee tissues in older adults are not well established. Older adults spend substantial time in sedentary behavior[3]. The effects of sedentary lifestyle on knee joints are also unknown.

Obesity is an established risk factor for knee OA [4]. Other than the mechanical mechanism through greater joint overload, recent studies suggest the metabolic mechanism [5-7]. However, it is not established which mechanism is more important. Examining the body composition, fat distribution and structural changes in the knee would inform the mechanism that mediates an increased risk of knee OA by obesity. Central adiposity, especially visceral adipose tissue and ectopic fat are associated with insulin resistance and cardiovascular disease [8-10], whereas peripheral adipose tissue is protective [11,12]. Fat infiltration in muscle is associated with lower muscle strength and incident mobility limitation in older adults. However, only a few published studies examined the associations between fat distribution and structural changes in the knee.

This dissertation study will add information on the effects of physical activity and sedentary behavior on tissues in knees of older adults, which will be useful in recommending appropriate amounts of physical activity to older adults. This study will fill some of the gaps in the literature on the potential mechanisms of increased risk of knee OA by obesity, which will be informative in determining the focus of knee OA prevention/control strategies in older adults. Ultimately, this dissertation will contribute to reducing the burden of knee OA. Figure 1 shows the conceptual frame work of obesity, body composition, fat distribution, and physical activity in relation to structural changes in the knee.

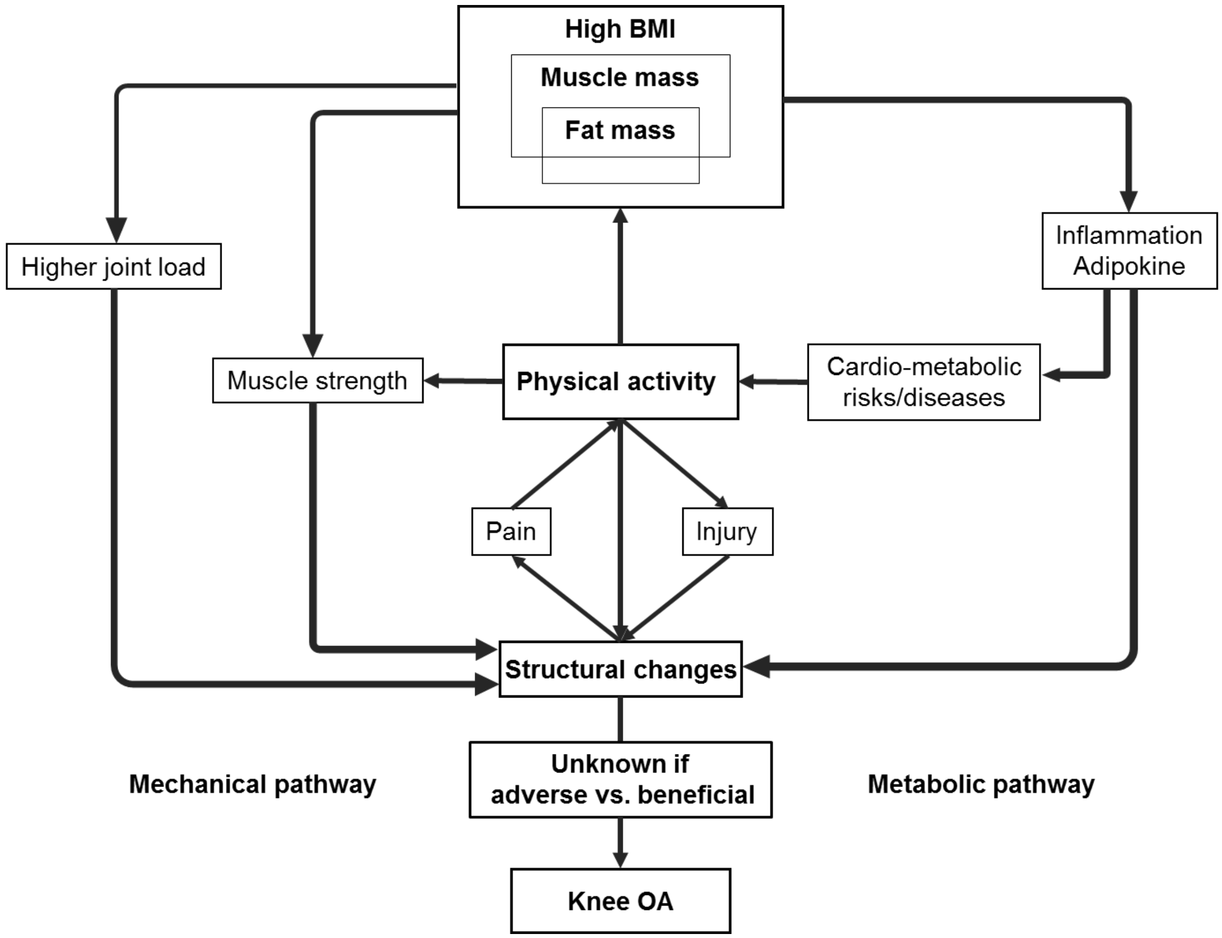

Figure 1. Conceptual framework of the study

1.1 EPIDEMIOLOGY

1.1.1 Epidemiology of Osteoarthritis of the Knee

Osteoarthritis of the knee (knee OA) is a common joint disorder among older adults. In the United States, 9 million (9,267,000) adults were estimated to have symptomatic knee OA in 2005 based on the Framingham OA Study[13]. Very recent data on the prevalence of knee OA is not available, but the estimated prevalence of radiographic knee OA (ROA) was 37 %, and that of symptomatic knee OA was 12% among people aged 60 years or older in the US based on the third National Health and Nutrition Examination Survey (NHANES) 1991-94 [1]. The Median age at knee OA diagnosis is 55 years, and the prevalence of knee OA steadily increases after age 55 based on the 2007-8 National Health Interview Survey [14]. The prevalence and slope are greater in obese people. The incidence data are also limited. The age- and sex-standardized incidence rate for symptomatic knee OA was 240/100,000 person-years (95% confidence interval CI [218, 262]) based on data from members of a health maintenance organization in central Massachusetts between 1988 and 1992 [15]. The incidence was higher in women, especially after age 50. The incidence rate increased with age, but leveled off at age 80 [15]. Lifetime risk of diagnosed symptomatic knee OA after age 25 was estimated to be 13.83% [14].

1.1.2 Public Health Significance

Consequences of symptomatic knee OA include pain, functional limitation, and disability [1]. Knee OA is one of the major contributors to physical limitation in the US among chronic diseases. Fifteen to sixteen percent of disability in walking, stair climbing, carrying, and housekeeping was attributed to knee OA, while 2-13% was attributed to heart disease [16]. OA was the third highest cause of Years Lost to Disability (YLD) in the US [17]. Hip and Knee OA was ranked as the 11th highest contributor to global disability in 2010 [18]. However, currently there is no approved therapy which reverses degenerative changes in the knee or delays progression of the disease. Damage in joint cartilage and meniscus is essentially irreversible. The treatment for knee OA is mainly symptom control or knee replacement in severe cases. Regarding the cost for OA, a study from Canada reported that total (direct and indirect) annual cost for OA (including knee, hip, hand, and spine) was US $5,700 per patient [19]. Because obesity is a risk factor for knee

OA, the burden of knee OA would increase in aging populations with high prevalence of obesity. Therefore, knee OA is a significant public health issue.

1.1.3 Established Risk Factors for Knee OA

Only a few risk factors have been identified that consistently show increased risk of knee OA incidence. In a systematic review of various risk factors for the onset of knee OA in people aged 50 years or older, meta-analysis was available for body mass index (BMI), previous knee injury, smoking, gender, and hand OA/Heberden's nodes [4]. All but smoking was consistently associated with higher risk of knee OA both in case-control studies and cohort studies. The summary odds ratio (OR) for obesity was 2.63 [2.28, 3.05]. Previous knee injury had the largest effect size among these five factors (summary OR=3.86 [2.61, 5.70]). Female gender and hand OA/Heberden's node were associated with the moderately increased risk of knee OA (summary OR=1.84 [1.32, 2.55] for gender, summary OR=1.49 [1.05, 2.10] for hand OA/Heberden's nodes). Current smoking compared to never smoking was protective in case-control studies (summary OR=0.60 [0.51, 0.71]) but did not have a significant association in cohort studies (summary OR=0.97 [0.88, 1.07]). Evidence is limited on the association between female hormonal aspects and incidence of knee OA [20]. There is some evidence that valgus malalignment (>3 º) is a risk factor for incident joint space narrowing in the lateral compartment [21]. Twin studies and family studies suggested that the heritability of knee OA would be 37-39% [22-24].

Regarding race/ethnicity, studies reported higher prevalence of knee OA in African Americans than in whites. The prevalence of ROA was higher in Non-Hispanic blacks than in whites or Mexican Americans in NHANES III [1]. The difference between Non-Hispanic blacks and Non-Hispanic whites was significant, adjusting for age, sex, BMI, occupation, smoking status, education, and income (OR=1.97 [1.51, 2.56] for ROA, OR=2.54 [1.64, 3.95] for symptomatic OA). In the Southeast Michigan cohort, which consisted of middle-aged female participants in the Michigan site of the Study of Women's Health Across the Nation (SWAN) study and the Michigan Bone Health Study (MBHS), the prevalence of knee OA was significantly higher in black females than white females adjusting for age, BMI, previous knee injury, and smoking [25]. The Johnston County Osteoarthritis Project, a population-based prospective cohort study in North Carolina, reported that African Americans had a similar incidence of radiographic knee OA (OR=0.80 [0.53, 1.22]) but a significantly higher risk of progression of knee OA (OR=1.67 [1.05, 2.67]) than whites adjusting for age, sex, BMI, and education [26]. The prevalence of ROA and symptomatic OA was 1.4 times higher in Chinese women in Beijing compared with the white women in the Framingham study, even though Chinese women were thinner than women in the Framingham study [27]. The prevalence of knee OA in Chinese men was similar to that in US men in that study.

Two recent systematic reviews of risk factors for progression of knee OA found strong evidence that age, BMI, alignment, presence of OA in multiple joints, and radiographic features were predictors of knee OA progression in people with established knee OA [28,29].

1.2 ASSESSMENT OF KNEE JOINTS

Knee OA is characterized by joint cartilage loss in the knee, but the disease involves multiple tissues, such as joint cartilage, meniscus, subarticular bone, synovium, ligaments, and peri-articular muscles. Knee OA is currently diagnosed based on knee radiography and symptoms in clinical settings. In research, various outcomes have been used to represent OA changes of the knee, which include radiographic knee OA, symptomatic knee OA, clinical knee OA, self-reported physician diagnosis of knee OA, knee arthroplasty, and changes in the knee tissues assessed using magnetic resonance imaging (MRI).

1.2.1 Definition of Knee OA

Radiographs of joints are often assessed using the Kellgren-Lawrence (KL) grade, which is a grading system for OA changes of joints based on joint space narrowing (JSN), osteophyte formation, bone sclerosis, and deformity [30]. Radiographic knee OA (ROA) is defined as knees with KL grade ≥ 2, which is characterized by definite osteophytes and possible joint space narrowing. To assess individual radiographic features of knee OA, such as osteophytes, JSN, tibial attrition, and bone sclerosis, an atlas by the Osteoarthritis Research Society International (OARSI) is used [31]. Osteophyte and JSN are graded as normal, 1+, 2+, and 3+ changes, and attrition and sclerosis as absent/present according to the images in the OARSI atlas. Symptomatic knee OA is defined as ROA with frequent knee symptoms. The typical definition of frequent knee symptoms in epidemiologic studies is pain, aching or stiffness in or around the knee on most days for at least one month [32,33]. The American College of Rheumatology (ACR) classification criteria are often used to define clinical knee OA, which are based on knee pain, age >50, stiffness <30min, crepitus, bony tenderness, bony enlargement, joint warmth, and osteophytes [34].

1.2.2 Assessment of Knee Joint Using MRI

Radiography shows changes of bone shape and bone sclerosis. It is an indirect measure of cartilage pathology in the knee. Radiography based knee OA is probably a blunt definition of this disease. A study suggested that early radiographic knee OA was associated with substantial cartilage loss assessed using MRI [35]. MRI can identify changes of tissues in the knee that are relevant to knee OA, such as cartilage, meniscus, subarticular bone and synovium. MRI can identify early degenerative changes in the knee, as well as the continuum of disease progression.

There are several techniques to assess knee MRI images. Currently, it is not established which tissue change(s) in which assessment(s) best predicts knee OA development, progression and knee symptoms. Imaging markers of knee OA have being studied in the Osteoarthritis Initiative (OAI) which is a large prospective cohort study funded by the National Institutes of Health [36].

1.2.2.1 Semiquantitative MRI Assessment of Structural Changes

Several scoring systems to systematically assess knee MRI images using a semiquantitative approach have been proposed [37-39]. Whole-Organ Magnetic Resonance Imaging Score (**WORMS**) of the knee is a method to score 14 features in the knee which include cartilage pathology, meniscus integrity, subarticular bone marrow abnormality and joint effusion. Knee joint surfaces and tissues are divided into sub-regions, and each feature is scored by sub-region[37]. WORMS was used in the knee OA substudy in the Health, Aging and Body Composition (Health ABC) Study. Inter-rater agreement (ICC) for each feature by compartment was 0.73-1.0 in WORMS except for bone attrition which was very rare (ICC=0.61) [37]. An another scoring system is Boston Leeds Osteoarthritis Knee Score (**BLOKS**) which is similar to WORMS, but it scores bone marrow lesion (BML) size, BML percentage surface area, and BML percentage lesion separately [39]. Weighted kappa for inter-rater reliability for each feature was 0.51-0.79 in BLOKS. In WORMS, meniscus tear, maceration, and dislocation are graded in one score. Thus, morphological changes and dislocation cannot be scored separately. BML scoring is complex in BLOKS. MRI Osteoarthritis Knee Score (MOAKS) was developed recently to overcome these limitations [38,40]. In MOAKS, the knee joint is separated into 14 sub-regions, and 10 features are graded. These 10 features are 1) size of cartilage loss, 2) depth of cartilage loss, 3) BML size, 4) BML size relative to associated bone cyst, 5) number of BMLs, 6) meniscus morphology, 7) meniscus extrusion, 8) osteophyte, 9) Hoffa-synovitis, and 10) effusion-synovitis. Inter-rater and intra-rater reliability of MOAKS was very good (weighted kappa = 0.61-0.8) or near perfect agreement (0.81-1.0) except for inter-rater reliability for tibial cartilage area, tibial osteophyte, and intercondylar synovitis (kappa = 0.36-0.49) and intra-rater reliability for tibial BML number, infrapatellar synovitis, and intercondylar synovitis (kappa = 0.42-0.57) [38].

Which features or how much abnormality is predictive for knee OA has not been fully established yet. Regarding knee symptoms, semi-quantitatively assessed BML was associated with knee pain in several studies [41]. In the Health ABC study participants who had knee pain only in one knee and had some features only in one knee, these features were more likely to occur in the painful knee [42]. However, the majority of these participants with pain in one knee had certain feature in both knees or did not have the feature in either knee. Thus, no individual feature added more predictive ability to distinguish painful knee and non-painful knee above KL grade.

Semi-quantitative MRI measures have been used as the outcome in several knee OA trials [41]. In the clinical trial of licoferone treatment, BML assessed by modified WORMS increased over 24 months in the licoferone group and the controls except for medial tibial plateau BML in the licoferone group [43]. In the clinical trial of chondroitin sulphate (CS) treatment, BML score in the lateral compartment at 12 months was significantly lower in the CS group [44]. However, there was no significant difference in reduction of symptoms between the treatment group and the controls in these trails. In the clinical trial which compared wedge insole and flat insole, changes in BML score, cartilage defect and pain were not different between the two groups [45]. In the small trial of intra-articular Hylan G-F 20 injection, worsening of cartilage defects in the medial tibia over 24 months as well as cartilage volume loss was smaller in the patients who received Hylan G-F 20 injection than those with usual treatments [46].

1.2.2.2 Quantitative MRI Measurement of Structural Changes

Cartilage volume, cartilage thickness, and bone area which is not covered with cartilage, can be measured quantitatively based on MRI images. Joint cartilage and bone area in the femur and the tibia are segmented manually. Eckstein et al. reported that cartilage loss in the central and total medial tibiofemoral compartment was significantly higher in OA knees that had knee replacement in four years than the controls in a nested case-control study [47]. The authors concluded that quantitative MRI-based measures of cartilage could be used as a marker for disease prognosis or efficacy in intervention trials.

1.2.2.3 Other MRI Assessment Measures

MRI Transverse Relaxation Time

MRI transverse relaxation time of articular cartilage, a quantitative tissue parameter, is another potential imaging marker. Articular cartilage is consisted of a matrix which contains type 2 collagen and proteoglycans. The proteoglycans include negatively charged glycosaminoglycan chains which help keep water in the cartilage. Higher MRI T2 relaxation time would reflect increased water mobility in the tissue due to early cartilage degeneration [48,49]. Dunn et al. compared the mean T2 relaxation time of cartilage in each of the four compartments in the knee (medial tibia, lateral tibia, medial femur, and lateral femur) between people with radiographic knee OA and controls [48]. The mean T2 relaxation time was significantly higher in the medial tibia and medial and lateral femur in people with radiographic OA compared with controls adjusting for age. In addition, T2 relaxation time was significantly correlated with cartilage thickness and cartilage volume as well as knee pain and knee functional scores.

T2 distribution of knee articular cartilage has a spatial pattern reflecting the regional variation in the collagen fiber anisotropy and water content. The signal in T2 weighted MRI is low near the bone and rises higher toward the articular surface [49]. The change in T2 variability may reflect cartilage damage. Urish et al. compared the baseline T2 texture index of cartilage (TIC) which reflects T2 heterogeneity in the whole knee cartilage between people who developed symptomatic knee OA in three years (cases) and those who did not (controls) [49]. The T2 TIC was significantly higher in cases than controls. The authors concluded that T2 TIC can predict development of symptomatic knee OA in a 3-year follow-up.

Bone Shape

Joint bone remodeling in knee OA has been suggested in MRI studies [50]. Therefore, bone shape of the knee joint could be a marker of knee OA. Neogi et al. used active appearance models (AAMs) and a linear discriminant analysis (LDA) to calculate a single scalar value (multiple of bone shape vector) which represents bone shape [51]. Bone shape vector was estimated for tibia, femur, patella or a combination of bones. The bone shape at the OAI baseline predicted incidence of radiographic knee OA during 24-48 months from baseline among knees with KL grade 0 at baseline. The OR of knee OA for the highest tertile of femur bone shape vector vs. the lowest tertile was 4.8 [1.5, 15.6].

1.3 PHYSICAL ACTIVITY

1.3.1 Benefit of Physical Activity

Regular physical activity is beneficial to prevent chronic diseases, such as cardiovascular disease, thromboembolic stroke, hypertension, type 2 diabetes mellitus, osteoporosis, obesity, colon cancer, breast cancer, anxiety, and depression [2]. Regular physical activity also has a therapeutic role for these chronic diseases. In addition, physical activity could be beneficial for cognitive function [52]. Higher physical activity level was associated with better physical function based on performance measures such as the Epidemiologic Studies of the Elderly (EPESE) battery and the Health ABC performance battery in older adults [53]. Thus, regular physical activity is recommended to older adults as well [2].

The American College of Sports Medicine and the American Heart Association published physical activity recommendation for older adults in 2007 [2]. It recommends moderate-intensity aerobic physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week. Older adults will benefit from muscle-strengthening activity on two or more nonconsecutive days per week. Flexibility activity and balance exercises are also recommended.

Some types of exercise help to control knee OA symptoms, although damage in joint cartilage and meniscus is essentially irreversible. A meta-analysis of clinical trials showed that aerobic, resistance and performance exercises reduced knee pain and disability [54]. Quadriceps specific exercise was especially beneficial. The guidelines by the Osteoarthritis Research Society International (OARSI) [55] and the American College of Rheumatology [56] recommend the following types of exercise for knee OA patients. Land-based exercise is beneficial for pain control and physical function. It includes strength training, active range of motion exercise, aerobic activity, and Tai chi. Water-based exercise is beneficial for function and quality of life but not for pain control. Strength training for lower limb muscle is especially beneficial for pain and physical function. The guidelines state that both weight-bearing and non-weight bearing are effective.

Older adults spend substantial time in sedentary behavior [3]. Based on the 2003-2004 NHANES data, 60 to 70% of waking hours were spent in sedentary behavior in older adults [3]. The time in sedentary behavior is associated with increased mortality even taking into account the time spent in moderate-vigorous physical activity [57]. Therefore, sedentary behavior seems to be independently associated with health outcomes.

1.3.2 Assessment of Physical Activity

Amount of physical activity can be assessed in terms of energy expenditure used for physical activity. Type, frequency, intensity, and duration of physical activity are assessed using direct or indirect measures of physical activity [58].

1.3.2.1 Energy Expenditure

For skeletal muscle contraction, metabolic energy is transferred, and a large amount of heat energy is produced. Therefore, energy expenditure due to physical activity can be directly quantified by measuring body heat. Direct calorimetry measures body heat production most precisely. The measurement is done under laboratory conditions, where an individual is confined in an airtight chamber. Using indirect measures, energy expenditure is estimated by measuring the fractional concentrations of expired carbon dioxide and oxygen. The indirect measures include whole room calorimeter, portable indirect calorimetry, and a measure using water labeled with a stable isotope (doubly labelled water). Direct calorimetry and whole room calorimetry are conducted under laboratory conditions, and are not practical for measuring various types of habitual physical activities in epidemiological studies. Portable indirect calorimetry is usually used to assess specific task activities such as treadmill walking/running, cycling or occupational activity. Doubly labelled water gives data on total activity related energy expenditures but not the type, duration, frequency or intensity. The cost and availability of isotopes limit the practicality of these measures in large population studies.

1.3.2.2 Objective Measures of Physical Activity

Physical activity can be measured objectively by direct observation or using activity monitors. In direct observation, physical activity is observed during a certain time period. It provides information on factors which influence physical activity such as presence of others and barriers to physical activity, but does not provide information on activity performed outside the observation.

Activity monitors include the pedometer and accelerometer. A pedometer measures steps taken. It has reasonable precision when walking is a predominant activity. Pedometers are usually cheaper than accelerometers. However, it does not provide information on type, intensity or duration of physical activity. The accuracy may be less when the individual walks slowly. Accelerometers measure body movement in single or multiple planes. It measures the absolute value and frequency of acceleration force over a defined period and output as an activity count per minute. It provides information on frequency, intensity, duration, and patterns of physical activity, and has been used to validate physical activity questionnaires. Accelerometers cannot capture physical activity without acceleration or physical activity in water. There is also the issue of substantially higher costs for accelerometers. Analysis of the data is not very easy. In addition, there are differences in sensitivity by accelerometer model and setting. For example, the ActiGraph is a commonly used brand, but there are differences in sensitivity for each activity intensity category between the older (7164) and the newer (GT3X+) model [59]. The newer model with normal filter outputs more minutes/day for sedentary activity but less time for light and moderate activities. Using the low frequency extension with the newer model, the time for each intensity is more similar to the older model, but the average counts per day was significantly higher than the older model. Therefore, caution is needed to compare the results from the studies which used different accelerometers.

Physical fitness is a set of attributes which is related to the ability to perform physical activity. Because physical fitness is related to participation in physical activity, physical fitness is often used as a surrogate for physical activity level. These measures include maximum oxygen uptake and heart rate monitoring.

1.3.2.3 Subjective Measures of Physical Activity

Subjective measures include questionnaire and activity logs. Physical activity questionnaires are often used in epidemiological studies. Physical activity questionnaires are subject to imprecise recall and social desirability bias. Physical activity energy expenditure based on self-report can under or overestimate (-39% to 37%) energy expenditure from doubly labeled water or accelerometers in older adults. The correlation between subjective measures and objective measures were weak to high (-0.02 to 0.79) in older adults [60]. It is hard for older adults to recall sedentary behavior accurately. Comparing the data from two subjective measures (Yale Physical Activity Survey for Older Adults (YPAS) and Community Health Activities Model Program for Seniors (CHAMPS)) and accelerometer [61], the time in sedentary behavior estimated from the CHAMPS was shorter by 5.21 hours/day compared with the accelerometer, and YPAS also underestimated sedentary behavior. Therefore, predominant physical activities, the particular physical activity of research interest, and cognitive function of the population being studied must be considered when one chooses the measure of physical activity.

There seems no gold standard for the classification of physical activities particularly in older adults with chronic condition. For example, in the Health ABC study, Brach et al. proposed a classification of physical activity level based on two measures: the estimated total activity energy expenditure and exercise energy expenditure (kcal/week) derived from self-report [53]. In the Health ABC, at least 15 published studies examined physical activity as predictors or outcomes [62-76]. Three papers used Brach's physical activity type, and 12 studies examined various physical activity variables from self-reports and classification. Thus, classification of physical activities needs to be chosen based on the research question.

1.4 PHYSICAL ACTIVITY AND KNEE OA

Weight-bearing or certain types of physical activity may have adverse impacts on weight bearing joints. Some people consider knee OA to be a "wear and tear" disease. An in vitro study showed that static compression of cartilage leads to a suppression of metabolism. In contrast, cyclic loading with certain frequencies increases chondrocyte anabolism and synthesis of components of extracellular matrix of cartilage [77]. Animal studies show that changes in physical activity may lead to an anabolism or catabolism of cartilage depending on the intensity, duration and age. Moderate exercise induces anabolic changes. However, high intensity exercise or a sudden increase in exercise in older age leads to catabolism of cartilage. Severe inactivity also leads to catabolic changes in cartilage. In human, numerous epidemiological studies have examined the association between physical activity and knee OA. However, the results of these studies are inconsistent, and the effects of physical activity and inactivity on knee joints in middle-aged and older adults are not fully established yet.

1.4.1 Occupational Activities and Knee OA

Certain occupational physical activities are consistently associated with knee OA. A recent cohort study, a systematic review and a meta-analysis of occupational activities showed that heavy or manual work, elite sports, kneeling, squatting, lifting/carrying, climbing stairs, and knee bending/straining are risk factors for knee OA [78-80]. Standing was not a significant risk factor. Studies on symptomatic knee OA and ROA had similar results. Current, lifetime, longest occupation and occupation in early adulthood similarly increase the risk of knee OA.

1.4.2 Exercise/Sports and Knee OA

Early studies which compared current runners or former college runners and non-runners did not find any difference in radiographic OA grade, osteophytes, JSN or incident knee/hip pain between runners and non-runners [81-83]. However, the cross-sectional or retrospective nature of these studies prevents the drawing of sound causal inferences. A prospective cohort study by

Lane et al. which followed running club members and community controls who were 50-72 years old at baseline did not find differences in knee radiography between runners and non-runners at the end of 8 year follow-up adjusting for age, sex, BMI, knee injury, the initial radiography score, and the follow-up time [84-86]. Among the running members, 56% of them were still running at the follow-up. This study suggested no increased risk of knee OA in runners, but the sample size was relatively small (n=98).

Results of a retrospective study by Spector et al., which compared female former elite long-distance runners (national or international level) and tennis players with controls, were different from the above study [87]. With adjustment for age, height, and weight, the odds of osteophytes were significantly higher in former athletes. In this study, the prevalence of knee injury history was higher in the controls. Thus, the results would be conservative. The controls who participated in moderate or vigorous sports activity for a long period had increased osteophytes similar to ex-athletes, which supports the conclusion. This study suggests an increased risk of radiographic knee OA in elite level female athletes.

Two more recent case-control studies on ROA examined various sports as potential risk factors [88,89]. A study from Germany by Vrezas et al. reported that participation for longer hours cumulatively in cycling or ball games (handball, volleyball, and basketball) was associated with higher risk of knee OA in men [89]. Jogging, weight lifting, body building/strength training or swimming was not associated with knee OA. The results were not consistent for soccer. The results were adjusted for occupational physical activity but not for knee injury [89]. Based on these results, it is unknown whether the types of sports (e.g. weight-bearing or not) matter, or whether the increased injuries in certain sports are attributable for knee OA. In addition, inaccurate recall for sports activity history is possible, and recall bias is also possible with case-control designs in general. In a hospital based case-control study from Sweden by Thelin et al., soccer, ice hockey, and tennis were significantly associated with knee OA in the crude analysis [88]. However, these sports were not associated with knee OA with adjustment for knee injuries. The authors concluded that increased risk for knee OA was attributed to knee injuries [88].

Studies which examined knee-OA related hospital admission or knee replacement as the outcomes reported the association between sports participation and higher risk of knee OA [90-92]. A longitudinal study by Kujala et al., which followed male athletes who represented Finland and general Finnish men for 20 years, reported that the risk of hospital admission due to hip, knee or ankle OA was significantly higher in athletes who played endurance sports, power sports or mixed sports [90]. The strength of this study is the prospective design with a large sample size (n=2,046). The limitation is that occupation but not knee injury was adjusted. In addition, hospital admissions due to hip, knee, and ankle OA were not separated. Thus, it is hard to make a conclusion on risk of knee OA in former male athletes. A case-control study on knee replacement in Sweden by Sandmark et al. reported that high exposure to all sports (among men age <65), soccer, track and field, cross-country skiing (among men age <65) or ice hockey/bandy between age 15 and 50 years was associated with a higher risk of knee replacement in men [91]. Exposure to all sports and cross-country skiing between age 15 and 50 years was not associated with knee replacement in men at age ≥65. In women, sports activity was not associated with knee replacement. This study suggests effect modification by age and sex. In this study sports activity from age 15 to 50 years were asked retrospectively. Therefore, inaccurate recall and recall bias are possible. The analyses were adjusted for physical load in occupation, housework, and leisure time but not for knee injury. Thus, again, higher risk could be attributed to knee injury. A prospective study in Sweden by Michaelsson followed participants in the 90 km long distance cross-country ski race for an average of 10 years (range 0-16) [92]. It reported that completing more races during that time was associated with a higher risk of knee arthroplasty (knee replacement or tibial osteotomy) due to knee OA, adjusting for knee injury and occupation. The strengths of this study are a large sample size and prospective design. However, the results may not be generalizable, because individuals who participated in the 90 km long distance cross-country ski race would be very different from a general population. These studies suggested an increased risk of severe knee OA due to certain sports participation. However, caution is needed to interpret these studies, because behavior for seeking medical treatment or expectation for the treatment could be different based on patients' activity level.

Some sports are associated with higher risk of knee injury. A study in Switzerland examined causes of knee injuries treated in a clinic during a 10 year period [93]. Two common causes were soccer (35% of all knee injuries) and skiing (26%). Taking into account the number of members in sport clubs of each sports, the risk was also higher in squash and American football. Sports injury data in US high school students have been collected. The data showed that the incidence rate for knee injury was high in football, girls' soccer, girls' gymnastics, wrestling and girls' basketball. The risk was lower in swimming, diving and boys' volleyball [94]. For US college sports, causes of anterior cruciate ligament (ACL) injury have been published [95]. Incident rates were higher in men's football, women's gymnastics, women's soccer, and women's basketball. The incidence was lower in men's baseball. Although popular sports are different across countries, these studies show that a risk of knee injury is higher in football, female soccer, female gymnastics, female basketball, and skiing, whereas the risk is lower in swimming. Therefore, higher risk for knee OA in some sports reported in the above studies, such as soccer, basketball, and skiing could be attributed to knee injuries.

Summarizing studies on sports activity, running does not seem to be associated with knee OA except at the elite level. Some sports activities, especially at the elite level, may be associated with knee OA, but the associations could differ by age and/or sex. The types of sports that confer increased risk of knee OA, such as weight-bearing or not, are not well-established based on these studies. These studies are heterogeneous in terms of adjustment for occupational physical load and knee injury, which possibly influenced the results. Knee injury could be attributable for higher risks in athletes, and without adjustment for knee injury, the results could be overestimated. Recall bias and misclassification are probable for physical activity assessed subjectively decades later in the case-control studies. Studies which examined exercise/sports and knee OA are summarized in table 1.

1.4.3 Physical Activity Levels and Knee OA

More recent studies examined overall physical activity level or overall leisure time physical activity as a potential risk factor for knee OA. Several cohort (longitudinal) studies examined the association between physical activity and radiographic knee OA (Table 2). In the Melbourne Women's Midlife Health Project, a population-based prospective study, 224 middle-aged women (45-55 at baseline) underwent knee radiography at year 11 [96,97]. More frequent physical activity for fitness or recreational purposes at age 20-29 was associated with higher prevalence of ROA at year 11 (p-value for trend=0.03) [96]. Further, higher frequency of physical activity averaged over 11 years was associated with higher prevalence of JSN in the patellofemoral joint (p=0.02). There was a trend that higher physical activity over 11 years was related to higher prevalence of osteophytes in the tibiofemoral joint (p=0.08) [96]. The limitation of this study is that the results were adjusted for age, BMI, hormone therapy, and smoking status but not for knee injury.

The Framingham OA Study, a substudy of the Framingham Heart Study, followed participants who completed knee radiography at examination 18 (1983-1985) [98-100]. The physical activity level was measured using the Framingham Physical Activity Index which was based on a weighted sum of various physical activities in a 24 hour time periods. At baseline, the average of physical activity level at exam 4 (1954-57) and 12 (1971-73) were not associated with prevalent knee OA at exam 18 in 1,404 participants, whose mean age was 73 years (range 63-93) [98]. By exam 22 (1992-1993) 8.8% of the 940 knees developed ROA. The higher physical activity index scores at exam 20 were associated with a higher incidence of ROA between exam 18 and exam 22 [99]. However, physical activity level at exam 4 or exam 12 was not associated with incident ROA, which suggests that the recent physical activity level is more important than activities decades ago. When hours spent for physical activity at exam 20 were categorized by intensity of physical activity (heavy, moderate, and light), longer hours of heavy activity were associated with a higher incidence of ROA (odds ratio OR=7.2 [2.5, 21] for ≥ 4 hours vs. 0 hour, trend p<.0001) in 470 participants [100]. Hours of heavy activity were also associated with incident symptomatic knee OA. These analyses were adjusted for knee injury. Hours spent for moderate or light activity were not associated with an incidence of knee OA. The longer distance walked and more flights of stairs climbed were associated with a non-significant moderately increased risk of knee OA incidence (OR=1.6 [0.4, 5.7] for walking ≥ 3 blocks vs. none, OR=1.9 [0.9, 4.0] for ≥ 4 flights of stairs vs. none). The strength of this study is a large sample size and the classification of physical activity by intensity.

In the Framingham Offspring Cohort, physical activity was assessed based on the following questions: distance walked for exercise per week, frequency of intense physical activity per week which was enough to work up a sweat, and how the participant would compare his/her activity level to others in the same age [101]. Between exam 5 and 2002-2005 (about 9 years apart), 9.5% of the 2,259 eligible knees developed ROA. No association was found between the above physical activity variables at exam 5 (1993-1994) and the incidence of ROA, symptomatic knee OA or JSN in the 1,279 participants. The mean age at baseline (exam 5) was 53.2 (range 26-81). History of knee injury was adjusted in the analysis. Because physical activity level was assessed globally, and the age range of participants was different, the results cannot be compared directly with the above Framingham Heart study.

In the Chingford study middle-aged women (mean age 54.1 ± 5.9) underwent knee radiography at baseline and 4 years later. The study reported that walking, job physical activity or sport was not associated with the incidence of osteophyte formation in the 715 women or that of JSN in the 644 women adjusted for knee injury [102]. However, the definition of physical activity was unclear in this paper. Thus, caution is needed for interpretation.

In a population cohort study in Bristol, England by Cooper et al., 354 people with knee pain and without knee pain underwent knee radiography at baseline and 5 years later [103]. The median age at follow-up was 75.8 years. When knee OA was defined as KL ≥ 1, participation in sports at least weekly for a decade or longer after leaving school was associated with a higher risk of incident knee OA (OR=3.2 [1.1, 9.1]) adjusting for knee pain. However, if knee OA was defined as KL ≥ 2, sports participation was not associated with development of knee OA. Knee injury was not adjusted, which was the limitation of this study. Sports participation was not associated with knee OA progression regardless of the KL grade cut-off point. This study suggests that the definition of incident OA influenced the study results, which is worth consideration.

The following recent longitudinal studies used different validated subjective measures to assess physical activity. The Johnston County Osteoarthritis project, a population based cohort study in North Carolina, used the Minnesota Leisure Time Physical Activity Questionnaire [104] to measure physical activity [32]. The mean age at baseline was 59.8 ± 0.3. Participants who completed assessment at baseline and at follow-up were included in the analysis, and the median follow-up period was 6.5 years (range 4-10.2). Physical activity level at baseline was categorized in two ways: 1) whether it met the Department of Health and Human Services (HHS) guidelines of ≥150 minutes of moderate equivalent physical activity per week, and 2) what category it fell in the four health benefit levels from the 2008 HHS Physical Activity Guidelines for Americans (inactive: 0 to <10 min/w, low: 10 to <150 min/w, medium: 150 to <300 min/w, high: ≥300 min/w). Neither of the physical activity variables was significantly associated with incident ROA or incident symptomatic knee OA. However, meeting the guidelines or the high health benefit level was associated with a higher risk of incident JSN, adjusting for occupational activity and history of knee injury (Hazard ratio HR=1.42 [1.10, 1.82] for met vs. not meet, HR= 1.97 [1.20, 3.26] for high vs. inactive). The strengths of this study were that physical activity was assessed using a validated tool and categorized using clinically relevant cut-offs.

The Multicenter Osteoarthritis (MOST) and Osteoarthritis Initiative (OAI) are cohort studies on OA, and participants of the two studies are people with or at higher risk of knee OA. Both studies use the Physical Activity Scale for the Elderly (PASE) to assess physical activity[105]. Analysis was done combining 30 months follow-up data in MOST and 48 months follow-up data in OAI [106]. Participants who had prior knee injury were excluded from this analysis. Mean age of the included participants was 61.2 ± 8.4 years. Physical activity in the highest quartile (upper 25%) compared with lower levels (lower 75%) was not associated with joint space loss (OR=0.9

[0.5, 1.5]). In people with knee malalignment (varus ≤ -2.0º or valgus ≥2.0º), the highest physical activity level was not associated with incident symptomatic knee OA (OR=0.9 [0.2, 3.4]). In people without knee malalignment there was a non-significant trend that the highest physical activity level was associated with a lower risk of incident symptomatic knee OA compared with lower physical activity levels (OR=0.3 [0.1, 1.2], p=0.09). The analysis was adjusted for knee pain but not for incident knee injury. This study suggests that higher overall physical activity levels may not increase the risk of symptomatic knee OA in people at risk of knee OA. The strengths of this study were the large sample size (n=2,073 subjects, 3,542 knees), the validated physical activity assessment tool, and the stratified analysis by knee malalignment. The results on the risk of joint space loss conflicted with the Johnston County Osteoarthritis project, but these studies may not be comparable because the participants in MOST and OAI had risk factors for knee OA.

These longitudinal (cohort) studies are less prone to recall bias for physical activity assessment compared with case-control studies. The results were taking into account knee injury, and most studies took into account knee pain, so they would be less prone to confounding by knee injury or reverse causation through knee pain. However, results were not consistent. The Framingham OA study found that the amount of high intensity activity was associated with a higher risk of OA, but the Framingham offspring study found no association. The MOST and OAI studies found a trend for higher overall physical activity and lower risk of symptomatic ROA in people with risk factors for knee OA. The follow-up periods and the assessments of physical activity (time of physical activity, timing of assessment, classification of physical activity) were heterogeneous among these studies. Because all studies assessed physical activity subjectively, misclassification may be an issue and could be one of the reasons for inconsistent results. Thus, it is hard to make conclusions on the direction of the association between physical activity and knee OA risk. The types of physical activity which are associated with an increased risk of knee OA is also unclear based on these studies.

1.4.4 Physical Activity Type and Clinical Knee OA

Some studies used clinical knee OA based on symptoms or (self-reported) physician diagnosis of knee OA as the outcomes and tried to examine the risk of knee OA by the type of physical activities [107-111].

In the Longitudinal Aging Study Amsterdam (LASA) by Verweij et al., participants aged 55-85 years were followed every 3 years for 12 years [108]. Frequency and duration of walking, bicycling, light and heavy household work and two sports activities were assessed using the LASA Physical Activity Questionnaire which was validated against diaries and pedometer. For each physical activity, intensity score (2.5-6.0 METS, e.g., fishing=2.5, tennis=6.0), mechanical strain score (1-4 METS, e.g., bicycling=1, volleyball=4), turning actions score (1-3 METS, e.g., walking=1, dancing=3) and muscle strength score (1-4 METS, e.g., fishing=1, heavy household work=4) were calculated. Mean scores over all activities for each component were estimated for each participant. The mean scores were categorized into three levels, and the middle group was a reference. Low muscle strength score and high mechanical strain score were associated with a higher risk of incident self-reported or physician reported clinical knee OA (HR=1.30 [1.01, 1.68] for muscle strength low vs. medium, HR=1.43 [1.15, 1.77] for high mechanical strain vs. medium). Intensity and turning actions scores were not significantly associated with risk of knee OA. This suggests that the effects on knee OA may differ by activity type. The analyses were adjusted for lifetime physical work demand and lifetime general physical activity but not for history of knee injury, which is a limitation.

Another study followed adults who were examined at the Cooper Clinic by mail every 5 years and asked if they were diagnosed with hip or knee OA [109-111]. When physical activity level was defined only by distance of walking and running, higher activity levels at baseline were associated with a higher risk of hip/knee OA in 10 years in men age < 50 years but not in men age ≥ 50 or in women in any age [109]. When overall joint stress was estimated based on the type of each physical activity, moderate/high level of joint stress was associated with lower odds of hip/knee OA compared with no joint stress in men (OR=0.62 [0.43, 0.89]) [110]. In women, both moderate/high level and low level of joint stress were associated with lower odds of hip/knee OA compared with no joint stress (OR=0.24 [0.11, 0.52] for moderate/high vs. none, OR=0.58 [0.34, 0.99] for low vs. none). These results suggest having no stress could be harmful for knee/hip joints. In the third analysis, the joint stress activity score (JSPAS) was estimated based on the frequency and the duration of each session for 9 types of physical activity (walking, running, bicycling, swimming, racquet sports etc.) [111]. JSPAS was not associated with risk of hip/knee OA. In the latter two analyses, previous joint injury was adjusted. The limitation of this study is that hip OA and knee OA were not asked separately. Because the risk factors for knee OA and hip OA may differ, caution is needed to interpret these studies.

Because the outcomes of these studies were self-reported or physician reported diagnosis, knee OA was likely to be symptomatic. Thus, the results could be different for radiographic OA. These studies suggest that the impact on knee OA development may differ by the type of physical activity. The LASA study suggests that mechanical strain is harmful, but intensity or turning may not be associated with knee OA. In the latter study, it is unclear whether joint stress is harmful or beneficial for hip/knee OA or if there is no association. In summary, there has not been enough evidence on the specific types of activity which increase the risk of knee OA.

The results from studies which examined knee arthroplasty were mixed. The case-control study in Finland by Manninen et al. reported that higher cumulative hours of regular physical exercise during lifetime were associated with lower odds of knee arthroplasty compared with those without regular exercise adjusting for age, BMI, physical work stress, knee injury, and smoking, although the association was statistically significant only in men [112]. The limitation of this study was a case-control design. Recall bias was possible, although physical activity was associated with a lower risk in men. The longitudinal study from Australia by Wang et al. with average follow-up of 4.8 years reported that higher total physical activity levels were associated with a significantly higher risk of primary knee replacement (trend p=0.003) adjusting for age, sex, BMI, county of birth, occupational physical activity, and education level [113]. In particular, higher frequency of vigorous activity was associated with a higher risk of knee replacement. However, no association was found for the frequency of less vigorous activity or walking. The strength of this study is the prospective design, which is less prone to recall bias. The limitation is that there was no adjustment for knee injury. The other longitudinal study with 11 year follow-up from Sweden by Ageberg et al. reported a non-significant trend that higher leisure physical activity levels were related with a higher risk of knee arthroplasty adjusting for age, sex, BMI, education, smoking and marital status (OR=1.27 [0.97,1.66], p=0.087) [114]. The strength of this study is a large population cohort (n=27,813) followed prospectively over 11 years through the Swedish hospital discharge register and the Swedish cause of death register.

In summary, the study by Manninen which adjusted for knee injury found a lower risk of knee replacement in the higher physical activity group, and the latter two studies without adjustment for knee injury found a higher risk of knee replacement. However, caution is needed to interpret the studies on knee arthroplasty, because physical activity level may affect the decision of medical treatment [115] along with the pain and disability due to knee OA.

1.4.5 Physical Activity and Structural Changes in the Knee

Knee OA is currently diagnosed based on knee radiography and symptoms. While radiography is used as an indirect measure of cartilage pathology in the knee, degenerative changes in the knee, such as cartilage damage can only be directly observed using MRI. In addition, a study suggested that early radiographic knee OA was associated with substantial cartilage loss assessed using MRI [35]. MRI can identify early degenerative changes in the knee, as well as along the continuum of the disease progression, which is important because the factors associated with early changes could be causally associated with disease development.

1.4.5.1 Physical Activity and Prevalent Structural Changes in the Knee

The results of cross-sectional studies which examined the association between physical activity and knee structural changes on MRI are mixed (Table 3). The Melbourne Collaborative Cohort Study (MCCS) by Racunica et al. suggested the beneficial effects of vigorous activity on cartilage volume [116]. Frequency of vigorous activity, less vigorous activity at home and work, and walking during a 6 month period was assessed in 1990-1994. Physical activity during a 7 day period was again assessed in 2003-2004. MRI of the dominant knee was obtained in 2003-2004. People with diagnosed knee OA, knee pain or previous knee injury were excluded. The mean age of the 297 participants was 58.0 ± 5.5 years at follow-up. Participation in vigorous activity at baseline and follow-up were correlated. Cartilage volume was measured quantitatively, and cartilage defects were assessed semiquantitatively by using Ding's grading (grade 0=normal cartilage, grade 1 = focal blistering and intracartilaginous low-signal intensity area with an intact surface and bottom, grade 2 = irregularities on the surface or bottom and loss of thickness of < 50%, grade 3 = deep ulceration with loss of thickness of > 50%, grade 4 = full-thickness cartilage wear with exposure of subchondral bone) [117]. Coefficients of variation for cartilage area were 2.3% for the medial tibia and 2.4% for the lateral tibia. ICC for cartilage defect was 0.85 - 0.90. More frequent (never, 1 - 2 times, ≥ 3 times) vigorous physical activity for at least 20 min at baseline was associated with higher tibial cartilage volume. Longer duration (< 1 year, 1 - 5 years, > 5 years) of regular vigorous physical activity at least three times a week at baseline was also associated with higher tibial cartilage volume (p=0.01). No association was found between vigorous physical activity and prevalent tibial cartilage defect or BMLs in the tibia or femur. Frequency of less vigorous physical activity or frequency of walking at baseline was not associated with cartilage volume or defect. However, frequency of walking was associated with lower prevalence of BMLs (OR=0.6 [0.3, 0.98]). Participation in vigorous physical activity at follow-up was associated with higher cartilage volume (p=0.02) and lower odds of cartilage defect (OR=0.5 [0.3, 0.9]) [116]. This study suggests that vigorous activity is beneficial for knee cartilage. Less vigorous activity was not associated with cartilage, but walking could be beneficial for BMLs. The strength of this study was that individuals with knee pain or injury were excluded, so it would be less prone to bias and reverse causation. Another strength is that physical activity was assessed at baseline and in 2003-4.

Several other studies reported the association between higher physical activity levels and knee structural changes in people with risk factors for knee OA. Stehling et al. examined the cross-sectional association between the PASE score and the WORMS score of the right knee at the baseline visit in 236 participants of OAI who were 45-55 years old, not obese, without knee OA, without knee pain but with risk factors for knee OA. Higher PASE groups had higher WORMS summation scores and WORMS maximum scores (higher scores mean more abnormalities) for cartilage adjusted for age, gender, BMI, KL grade, knee injury, knee surgery, family history of knee replacement, and Heberden's nodes. In the middle and high PASE groups compared with the low PASE group, the prevalence of a structural abnormality was significantly higher for cartilage, meniscus, ligament, bone marrow edema, and joint effusion [118]. The same group of researchers assessed the WORMS score as well as T2 relaxation time in 128 participants who met the above criteria and in 33 people who did not have risk factors for knee OA (super controls) in OAI. In this analysis, no association was found between PASE scores and WORMS cartilage grades both in people at risk and in the controls. However, the T2 value in the lateral tibia was higher in the low and high PASE groups than the middle group in people at risk, which suggests a U-shape association. The significant association between PASE and T2 value was not found in the medial tibia, femur or patella [119], although when PASE was classified into two levels, the T2 value in the patella was higher in the high PASE group than the low PASE group [120] . Kretzschmar et al. recently reported the cross-sectional associations between the time spent in moderate to vigorous activity assessed by accelerometers and knee structural changes in the OAI participants with no or mild OA symptoms and without ROA [121]. This study found that higher quartile groups of activity had significantly higher maximum WORMS scores for meniscus damage (p trend=0.0087) and BMLs (p=0.0089). Especially, higher activity levels were associated with higher sum scores for medial meniscus damage (p=0.0017). Physical activity was not associated with cartilage damage. The authors also assessed T2 of cartilage. The T2 values tended to be higher in higher activity groups, but the differences were small and non-significant. The authors discussed that higher levels of physical activity may have both beneficial and detrimental effects on knee joints. These studies suggest that higher physical activity levels could be associated with more severe tissue abnormalities in the knee. The lowest activity level might have an adverse effect compared with the middle level. The effects of activity could be different by compartment. However, causation is unknown with the cross-sectional design.

Kumar et al. examined T1 rho and T2 in superficial and deep cartilage of the medial tibia and medial femur in 3T MRI images in 41 knee OA cases and 110 controls [122]. The mean age was 58 years in cases and 50 years in controls. Total physical activity (MET min/week) was assessed using the International Physical Activity Questionnaire. Total physical activity level was not different between cases and controls. T1 rho in the superficial medial femur, T1 rho in the deep medial tibia, and T2 in the superficial medial femur were significantly higher in cases than controls. In the linear regression models, higher total physical activity was associated with significantly higher values of these parameters adjusting for age, BMI, KL grade and knee alignment. This study suggests that higher levels of total physical activity are associated with cartilage degeneration in the medial femur and tibia in middle-aged people with and without knee OA.

Some studies focused on the patellar cartilage. Hanna et al. examined 176 women, aged 40 - 67 (mean 52.3) without significant knee pain or knee injury in the past 5 years. Cartilage defect was assessed using Ding's grading [117]. Participation in light exercise in past 2 weeks was not associated with cartilage volume or cartilage defect in the patella. There was a trend that participation in strenuous exercise was associated with higher prevalence of cartilage defects in the patella (OR=2.3 [0.9, 6.0]). Strenuous exercise was not associated with patella cartilage volume [123]. Because only the patella cartilage was assessed, the clinical significance of the results is unknown.

Overall, there have not been many cross-sectional studies which used MRI to assess structural changes in the knee. The participants were middle-aged people in three cohorts, and the sample sizes were moderate (n=120-297). The directions of the associations were different between the community-based cohort and people with risk factors for knee OA. Causality was indeterminate with the cross-sectional design.

1.4.5.2 Knee MRI Longitudinal Studies

There have not been many longitudinal studies which examined physical activity and structural changes in the tibiofemoral (TF) joint using MRI (Table 4). These studies suggest that physical activity could be beneficial in some populations but could have adverse effects in people with existing tissue damage. Hanna et al. followed a convenient sample of 28 healthy white men whose mean age was 51.9 years for two years [124]. The study did not find any association between physical activity and change in the tibial cartilage volume. The focus of this study was sex hormones, and the definition of physical activity was not reported [124]. The small convenience sample is a limitation of this study. An observational study by Foley et al. followed adult children of people who had knee replacement and randomly selected controls (total 325 participants) [125]. Mean age of these participants was 45 years (26 - 61) at baseline. Participants were asked the number of days with strenuous or light leisure time activity for more than 20 min in the past 2 weeks. Cartilage in the tibia and patella were examined using MRI at baseline and follow-up (mean follow-up length was 2.3 years). Cartilage defect was assessed using Ding's grading [117]. More days of strenuous exercise were associated with lower odds of cartilage defect progression in the lateral TF (OR=0.73, p=0.039) adjusted for age, sex, BMI, offspring status and baseline cartilage score and volume. There was also a similar trend in the medial TF (OR=0.86, p=0.24). The results were independent of knee pain or injury. The focus of this study was physical fitness and muscle strength. Physical fitness change was positively associated with cartilage volume change in the medial, lateral and total knee. Higher muscle strength in the lower limbs at baseline was positively associated with annual total cartilage volume change. This was probably the first longitudinal MRI study with a moderate sample size, and it suggested a beneficial effect of strenuous activity on knee cartilage.

The Tasmanian Older Adult Cohort study by Dore et al., reported the effect modification by existing structural damage. In this study 405 participants aged 50-80 underwent knee MRI at baseline and at follow-up (mean 2.7 years) [126]. Physical activity at baseline was examined using pedometers for 7 days, 2 times a year. Meniscus pathology, BML, cartilage defect, and cartilage volume were assessed by using Ding's grading [117]. For change in meniscus pathology, a significant interaction between physical activity and baseline meniscus pathology was found. In participants with worse meniscus scores at baseline, higher physical activity was associated with worsening of meniscus pathology (RR=2.49 [1.05, 3.93]). If meniscus score was low (better) at baseline, physical activity was not associated with changes in meniscus pathology. For cartilage defect, there was an interaction of baseline BMLs. In participants with prevalent BMLs at baseline, higher physical activity was associated with worsening of cartilage defect. In those without BML at baseline, activity level was not associated with cartilage defect worsening. For cartilage volume, there was an interaction between physical activity and baseline cartilage volume. In people with the lowest and middle baseline cartilage volume, cartilage volume loss was higher in people with higher physical activity levels. To the contrary, in people with the highest cartilage volume at baseline, cartilage volume loss was smaller in people with higher physical activity levels. This is the first longitudinal MRI study that assessed physical activity objectively, which is the strength. This study suggests that higher physical activity levels have adverse effects on knee joints if there is existing tissue damage at baseline, whereas physical activity could be beneficial for knee cartilage if the cartilage volume is high at baseline.

Two studies focused on the patellar cartilage. Both of these studies suggested beneficial effects of physical activity on the patellar cartilage. A study in Australia with 148 women by Wijayarantne et al. reported a trend that participation in exercise that increased heart rate and respiratory rate for at least 20 min in the past 2 weeks at baseline was associated with smaller annual cartilage loss (p=0.09) [127]. Individuals with knee injury were excluded. In the Melbourne Collaborative Cohort Study (MCCS), 271 subjects completed knee MRI in 2003-2004 and 2006-2007 [128]. Individuals with knee pain or knee injury were excluded. Physical activity in the previous 7 days was assessed in 2003-2004. Annual loss of patella cartilage volume was smaller in those who participated in vigorous physical activity (p=0.02). There was a trend that participation in vigorous activity was associated with lower odds of cartilage defect worsening (OR=0.4 [0.2, 1.1], p=0.07). Both studies suggest that high intensity activity is beneficial for the patellar cartilage. However, the clinical significance of the patellar cartilage for knee OA is unknown. Line et al. reported a U shape association between the PASE score and T2 progression in the medial and lateral tibia in OAI participants without knee OA [129]. The clinical implication of T2 time is unknown.

1.4.5.3 Summary of Physical Activity and MRI-Assessed Structural Changes in the Knee

In cross-sectional studies vigorous activity was associated with higher cartilage volume and fewer cartilage defects in the tibia in the community-based cohort. Higher physical activity was associated with prevalent abnormalities in knees in people with risk factors for knee OA such as hand OA and family history of knee replacement. Prospective studies suggest that physical activity could have beneficial effects on cartilage volume and/or cartilage defects in people without baseline abnormality, whereas physical activity have adverse effects on the knee joints with existing structural damage. The impact of physical activity on the knee may differ by knee compartment (tibiofemoral vs. patellofemoral), and/or age. The number of available studies is too limited to make definitive conclusions about the effects of physical activity on each of joint tissues. Whether physical activity has beneficial or adverse impact on knee joints in community-dwelling older adults is not established.

1.4.6 Physical Inactivity and Knee OA

The amount of time spent in sedentary behavior is associated with increased mortality taking into account for the time spent in moderate-vigorous physical activity [57]. Physical inactivity may also have an adverse impact on the knee joints. The effects of decreased loading and motion in the knee joint due to spinal cord injury (SCI) have been reported. Cartilage volume was measured in 9 men (age 17 - 65) with traumatic complete SCI just after injury, 6 months and 12 months of post injury [130]. These men received standardized physical therapies such as passive range of motion exercises, hydrotherapy, and cardiovascular training. Cartilage volume in the whole knee declined 7% at 6 months and 10% at 12 months. In rats, knee cartilage thickness after SCI was lower in the tibia and the posterior femoral region but higher in the anterior femoral region compared with controls without SCI [131]. The number of chondrocytes decreased in the anterior region of tibia and femur, and cartilage matrix staining decreased in the tibia. These two studies suggest that decreased physical activity or motion of knee joints may have an adverse impact on knee cartilage.

Most of the studies mentioned earlier did not focus on sedentary behavior as a risk factor for knee OA. However, some of them suggested that physical inactivity or lack of loading on the knee joints could be associated with a higher risk of knee OA. The study from the Cooper clinic reported that incident self-reported hip/knee OA cases were more likely to be sedentary at the previous assessment compared with people who did not report hip/knee OA (OR for moderate/high vs. sedentary=0.62 [0.43, 0.89] in men, 0.24 [0.11, 0.52] in women) [110]. There was a trend that annual cartilage loss in the patella was smaller in middle aged women who participated in exercise which increased heart and respiratory rate for at least 20 min in two weeks compared with those who did not participate (p=0.09) [127]. Higher frequency of walking in a week was associated with lower prevalence of BMLs [116]. A recent paper reported that T2 relaxation time in the medial tibia which would reflect cartilage degeneration was higher in the lowest physical activity level and in the highest physical activity level than in the middle level[129]. However, none of these studies examined sedentary behavior specifically. Future studies are needed to examine whether sedentary behavior has an adverse impact on knee tissues independently from moderate or high intensity activities.

Table 1. Studies on Exercise/Sports and Knee Osteoarthritis

Author	Design	N	Mean age (range)	Physical activity (assessment)	Outcome	Injury adjusted	Direction of association
Sohn[81]	Retrospective	791	57	Former runners vs. swimmers	Knee or hip pain	N	-
Panush[82]	Cross-sectional	35	56&61	Runners vs. non-runners	Xp	N	-
Konradsen[83]	Cross-sectional	54	58&57	Runners vs. controls	Xp	N	-
Chakravarty[86]	Longitudinal	98	58	Running club members vs. controls	Xp	Y	-
Spector[87]	Retrospective cohort	1,058	52&54	Elite female runners, tennis players vs. controls	Xp	Y	**↑**
Thelin[88]	Case-control	1,473	63	Questionnaire	Hospital TF OA case	Y	-
Vrezas[89]	Case-control	622	(25-70)	Questionnaire	OA diagnosis	N	**↑(cycling, soccer, ball games)**
Sandmark[91]	Case-control	1,183	(53-70)	Questionnaire	KR	N	**↑ men - women**
Michaelson[92]	Longitudinal	53,983	38	Long distance cross-country ski race participants	Knee arthroplasty	Y	**↑**
Kujala[90]	Longitudinal	4,113 men	44&45	Elite male athletes vs. controls	Hospital admission due to OA	N	**↑**

Xp radiography, KR knee replacement,
↑ activity was harmful, - no association, ↓ activity was protective

Table 2. Cohort and Longitudinal Studies on Physical Activity and Radiographic Knee OA

Author	**Study**	**N**	**Mean age (range)**	**Physical activity assessment**	**Outcome**	**Injury adjusted**	**Direction of association**
McAlindon[100]	Framingham	470	70	Framingham Physical activity Index	ROA sROA	Y	**↑ heavy PA** **- light/moderate PA**
Hart[132]	Chingford	715 women	54	Not reported	Xp	Y	**-**
Cooper[103]		354	(≥55)	Questionnaire	ROA	N	**↑**
Felson[101]	Framingham offspring	1,279	53	Questionnaire	ROA sROA	Y	**-**
Felson[106]	MOST+OAI	2,073	61	PASE	sROA JSN	Excluded	**↓(trend) sROA neutral knees** **-sROA malaligned knees** **-JSN**
Barbour[32]	Johnston County Osteoarthritis Project	1,114	60	Minnesota Leisure Time Physical Activity Questionnaire	ROA JSN	Y	**-ROA** **↑JSN**

MOST Multicenter Osteoarthritis Study, OAI osteoarthritis initiative, Xp radiography, ROA radiographic knee OA, sROA symptomatic radiographic knee OA, JSN joint space narrowing, PA physical activity,
↑ activity was harmful, - no association, ↓activity was protective

Table 3. Cross Sectional Studies on Physical Activity and Knee MRI Outcomes

Author	Study	N	Mean age	Physical activity assessment	Outcome	Injury adjusted	Direction of association
Racunica[116]	MCCS	297	58	Questionnaire	Cartilage defect (Ding), volume, BMLs	Excluded	**↓defect & vigorous PA ↑volume & vigorous PA ↓BMLs&walking -less vigorous PA**
Sterling[118]	OAI	236	51	PASE	Cartilage, meniscus, BMLs, effusion (WORMS)	Y	**↑**
Hovis[119]	OAI	161	50	PASE	WORMS T2	N	**U T2 lateral tibia ↑women T2 TF -WORMS**
Kretzschmar[121]	OAI	274	59	Accelerometer	WORMS T2	Y	**↑Meniscus ↑BMLs -Cartilage**
Kumar[122]		151	58&50	International Physical Activity Questionnaire	Tibia and femur cartilage laminar T1 rho T2	Y	**↑**
Hanna[123]		176 women	52	Questionnaire	Patella cartilage (Ding)	Excluded	**-**
Stehling[120]	OAI	120	51	PASE	Patella WORMS T2	Y	**↑**

OAI osteoarthritis initiative, MCCS Melbourne Collaborative Cohort Study
PASE Physical activity scale for elderly, WORMS Whole-Organ Magnetic Resonance Imaging Score
BML bone marrow lesion, PA physical activity, TF tibiofemoral joint
↑positive association, - no association, ↓inverse association, U U shape association
for cartilage volume, ↑means higher activity is associated with higher volume or increase of cartilage volume (beneficial)

Table 4. Longitudinal Studies on Physical Activity and Knee MRI Outcomes

Author	Study	N	Mean age (range)	Physical activity assessment	Outcome	Injury adjusted	Direction of association
Hanna[124]		28	52	Not reported	Tibia cartilage volume change	Excluded	-
Foley[125]	Southern Tasmania	325	45	Questionnaire	Tibia and patella cartilage defect worsening (Ding)	Y	**- medial ↓lateral**
Dore[126]	Tasmanian Older Adult Cohort	405	64&61 (50-80)	Pedometer	Cartilage defect (Ding), Meniscus, BMLs worsening, cartilage volume change	Y	**↑BML ↑meniscus, defect with existing damage ↓volume with low baseline cartilage ↑volume with high baseline cartilage**
Lin[129]	OAI	205	53	PASE	Cartilage (T2)	N	**U in tibia**
Davies-Tuck [133]		117	64 (OA patients)	No detail	Cartilage defect worsening	?	-
Wijayarantne [127]		148 women	53	Questionnaire	**Patella** cartilage volume change	Excluded	**↑**
Teichitahl[134]	MCCS	271	58	Questionnaire	**Patella** cartilage defect, volume change	Excluded	**↓defect ↑volume without baseline defect -defect & -volume with baseline defect**

PASE Physical activity scale for elderly, OAI osteoarthritis initiative,
MCCS Melbourne Collaborative Cohort Study,
↑positive association, - no association, ↓inverse association, U U shape association
for cartilage volume, ↑means higher activity is associated with higher volume or increase of cartilage volume (beneficial)

1.5 BODY COMPOSITION, FAT DISTRIBUTION AND KNEE OA

1.5.1 Obesity and Knee OA

Obesity or high BMI is one of the few established risk factors for the development of knee OA [4,135]. A mechanical mechanism (e.g. increased joint overload) is one possibility. The reported associations between cardiometabolic risk factors and knee OA suggests the metabolic mechanism as another possibility [136,137]. Physical activity could be related to both mechanisms: the metabolic mechanism through an individual's adiposity as well as the mechanical mechanism through joint load and muscle strength. It is not established whether a mechanical or metabolic mechanism is more important for knee OA development. BMI by itself cannot distinguish between fat mass and muscle mass. Some studies have reported an association between knee OA and measures of obesity other than BMI, such as body composition, fat distribution, and adipokines. Studying these measures would inform the mechanisms which mediate the association between knee OA and obesity.

1.5.2 Body Fat Distribution and Health Outcomes

About 80-90% of total body fat is stored in subcutaneous adipose tissue (SAT) mainly in abdominal, subscapular, and thigh area [138]. Intra-abdominal fat includes visceral adipose tissue (VAT). VAT stores about 6-20% of total body fat [138]. Women have more SAT in the abdominal and gluteofemoral area than men, and men have higher VAT than women [138]. Asian women have higher VAT than Caucasian women, but still lower VAT than Asian men [139]. Black women have VAT comparable to men and larger abdominal SAT than black men [140]. Central obesity is associated with an increased risk of cardiovascular disease and cardiovascular disease mortality[8,9]. Both VAT and abdominal SAT are associated with metabolic risk factors [10], whereas gluteofemoral adipose tissue is protective for cardiovascular disease and metabolic risk[11,12]. Gluteofemoral adipose tissue secrets more beneficial adipokines such as leptin and adiponectin compared with abdominal fat [11]. Ectopic fat refers to lipid deposits within and around non adipose tissues and organs such as liver, pancreas, and skeletal muscle [141]. Ectopic fat in liver and muscle are associated with insulin resistance, diabetes, hypertension, and cardiovascular disease [142-146]. Fat in the skeletal muscle includes two fat depots: inter-muscular adipose tissue (IMAT, visible fat beneath the fascia lata) and intra-muscular adipose tissue (fat between muscle fibers, extra- myocellular fat, and intra-myocellular (IMCL) fat) [144]. IMCL in soleus was increased in Type 1 diabetes patients (T1DM), type 2 DM, and offspring of T2DM compared with healthy controls in the study from Italy [147]. Higher IMCL was associated with insulin resistance in European Americans but not in African Americans adjusting for BMI [148]. In the Framingham Heart study, lower muscle attenuation, which reflects higher intramuscular adipose tissue, was associated with insulin resistance, but the association was reversed when VAT was further adjusted [149]. A study showed that offspring of long-lived nonagenarians in the Netherlands had significantly lower levels of IMCL than their partners [150]. Age associated increase in IMAT regardless of weight change in the Health ABC participants was reported [151]. Fat infiltration in muscle was associated with decreased muscle strength [152] and with incident mobility limitation independent of total body fat, muscle area, and muscle strength in white and black older participants in the Health ABC [153].

Fat distribution varies by race/ethnicity [11]. Asian women had greater VAT than Caucasian and African American women adjusting for total body fat [154,155]. African Americans have lower VAT than whites adjusting for total body fat [156]. Femoral-gluteal IMAT was greater in African Americans than Caucasians in both men and women, and Asian men had greater femoral-gluteal IMAT than Caucasian [155]. Lastly, a study reported that Hispanic adolescents had significantly higher IMCL than Caucasian and African American [157].

1.5.3 Assessment of Body Composition

Body can be characterized in 5 levels: atomic, molecular, cellular, tissue-organ and whole body. There are several methods to assess body composition of living humans, and each quantifies body composition in one of the 5 levels. In epidemiological studies, bioelectrical impedance analysis (BIA) and dual energy X-ray absorptiometry (DXA) have been often used to assess body composition. DXA is generally considered a gold standard. Computed tomography (CT) and MRI can quantify body composition at the organ and tissue level, such as SAT, VAT, IMAT, and visible intramuscular adipose tissue. Muscle density on CT reflects fat infiltration in muscle such as intra-muscular adipose tissue [158]. Skeletal muscle attenuation determined by CT was associated with skeletal muscle lipid content in biopsy specimens [158]. Magnetic resonance spectroscopy (MRS) can measure lipid content of skeletal muscles. Using volume localized MRS, intra-myocellular and extra-myocellular lipid deposits can be distinguished [159]. Radiation exposure in CT and high cost for CT and MRI are disadvantages for these imaging modalities. Other measures include skin fold thickness, underwater weighing, air displacement plethysmography, dilution techniques, and three-dimensional body scanning [159,160].

1.5.4 Cardio-Metabolic Risks and Knee OA

Osteoarthritis may be a component of metabolic syndrome [161]. Higher prevalence of cardio-metabolic risks in OA patients has been observed. Among US adults age 35 or older, the prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and renal impairment was higher in people with self-reported OA than in those without based on the NHANES III data [162]. In middle-aged women in the Chingford study, higher blood glucose (≥5 mmol/L, OR=1.95 [1.08, 3.59]) or moderately elevated serum cholesterol (6.0-7.1 mmol/L, OR=2.06 [1.06, 3.98]) was associated with having OA at least in one knee adjusting for age and BMI. Being ever treated for hypertension was associated with bilateral knee OA (OR=3.02 [1.51, 6.06]) [163].

Other cross-sectional studies reported the associations between metabolic risk factors and knee OA. Sowers et al. assessed obesity (BMI ≥ 30) and cardio-metabolic risks such as diabetes mellitus (DM, self-reports, medication and/or glucose (Glu) > 126 mg/dl), C-reactive protein (CRP) ≥ 2mg/L, dyslipidemia (high-density lipoprotein (HDL) ≤ 45 mg/dl or low-density lipoprotein (LDL) > 160 mg/dl), triglyceride (TG) ≥ 200 mg/dl, waist-to-hip-ratio (WHR) ≥ 0.81 and hypertension (HT, systolic blood pressure (SBP) > 135 mmHg, diastolic blood pressure (DBP) > 85 mmHg, and/or medication) in 664 women in Michigan [136]. In obese women, having 2 or more cardio-metabolic risk factors was associated with higher prevalence of ROA (OR=6.20 [2.93, 13.07] for ≥ 2 factors and obese, OR=3.00 [1.03, 8.71] for < 2 factors and obese, reference group was non obese women with < 2 factors). No difference in prevalence of ROA was found between non-obese women with cardio-metabolic risk clustering and the reference. Yoshimura et al. (2011) reported similar results in Japanese people [164]. Four metabolic risk factors were examined such as overweight (BMI > 25), HT (SBP > 130 mmHg, DBP > 85 mmHg and/or medication), dyslipidemia (HDL< 40 and/or medication) and impaired glucose tolerance (IGT, HbA1c $\geq$ 5.5 and/or medication). Prevalence of ROA was higher in people with two or more risk factors than those with no risk factor adjusting for age, sex, residence region, smoking, alcohol use, physical activity, exercise, and knee injury (OR=2.72 [1.77, 4.18]).

The association between metabolic risk and knee OA may differ by sex. Han et al. examined the association between metabolic syndrome (MetS) and self-reported knee OA in Koreans who were age 40 or older [165]. MetS was associated with prevalent knee OA only in women in the crude model (OR=1.80 [1.39, 2.32]), but the association did not persist after adjusting for exercise, alcohol intake, and smoking (OR=1.12 [0.81, 1.55]). Among the MetS components, only high waist circumference (WC) was associated with knee OA in women (OR=1.84 [1.31, 2.58]). Karvonen-Gutierrez et al. examined the association between the cardio-metabolic risk factors and knee OA using NHANES III data [137]. Sex differences were more apparent in this study. Higher insulin resistance (HOMA-IR) was associated with higher prevalence of ROA in men and non-obese women but with lower prevalence of knee OA in obese women. Higher LDL was associated with higher prevalence of knee OA in men but lower prevalence in obese women. Higher SBP was associated with lower prevalence of knee OA in men but with higher prevalence in women.

These studies suggest cross-sectional associations between knee OA and metabolic risks especially in women. However, it is unknown whether knee OA shares the same mechanisms with cardio-metabolic diseases, or whether the symptoms of knee OA and/or knee OA treatment modify the cardio-metabolic risk profile.

Several recent studies examined the association between MetS or components of MetS and knee OA prospectively. Yoshimura et al. (2012) examined the same four metabolic risks in the above study (Yoshimura et al. 2011) and incidence or progression of radiographic knee OA in the same Japanese cohort [5]. When assessed separately, continuous BMI, SBP, and HDL were each significantly associated with knee OA incidence. When examined together in the same model, only BMI was associated with incident knee OA (OR per unit =1.18 [1.07, 1.30]). If predictors were dichotomized as in the above mentioned study (Yoshimura et al. 2011), HT (OR=2.74 [1.30, 5.78]) and IGT (OR=1.94 [1.05, 3.59]) were associated with knee OA incidence in the mutual model. However, if continuous BMI rather than overweight was included in the model, IGT was not significant. For knee OA progression, continuous BMI and HDL were associated with progression. In the mutual model, only BMI had the significant association (OR=1.11 [1.06, 1.17]). With dichotomous predictors, overweight (OR=1.66 [1.21, 2.29]) and HT (OR=1.54 [1.10, 2.17]) were associated with knee OA progression. Having greater number of metabolic risks was associated with higher odds of knee OA incidence (OR=2.82 [1.05, 7.54] for 2 vs. 0, OR=9.83 [3.57, 27.1] for +3 vs. 0) and progression (OR=2.29 [1.49, 3.54] for 2 vs. 0, OR=2.80 [1.68, 4.67] for +3 vs. 0). Engstrom et al. reported the association between MetS and risk of knee arthroplasty in a middle-aged Sweden cohort [6]. MetS was defined as having ≥ 3 of high WC, low HDL, HT, high glucose, and high TG. MetS was associated with knee OA adjusting for age, sex, smoking, CRP, and physical activity only in women (OR=2.5 [1.5, 4.4]). The association was attenuated with BMI adjustment (OR=1.4 [0.8, 2.6]). Among the components of MetS in the separate models, only WC was associated with knee OA adjusting for BMI and other covariates (OR=2.2 [1.2, 4.0]). CRP was not associated with knee OA.

The association between metabolic risk factors and knee structural changes assessed using MRI has also been reported. Two studies reported the association between serum lipid and MRI outcomes. Davies-Tuck et al. (2009) examined the association between dyslipidemia and changes in knee cartilage volume and BML over 2 years in 148 middle-aged women [166]. Total cholesterol, TG, HDL, LDL or total cholesterol /HDL ratio were not associated with baseline BML. Total cholesterol (OR=1.84 [1.01, 3.36] per 1 unit of log cholesterol) and TG (OR=8.4 [1.63, 43.43] per unit) were associated with BML incidence adjusting for age and BMI. HDL and LDL were not associated with BML incidence. Lipid profiles were not associated with annual change of cartilage volume. Dore et al. examined the association between dietary factors, serum lipids and longitudinal changes of structural abnormalities in knees in 2.7 years in the Tasmanian Older Cohort study [167]. The mean age of the 394 participants was 63 years at baseline. Dietary information was collected using 74-item food-frequency questionnaire. Dietary factors and serum lipids were not associated with baseline BMLs. Baseline higher HDL cholesterol was associated with lower odds of incident BMLs (OR=0.34 [0.14, 0.78] per 1SD) adjusting for age, sex, BMI, ROA, and statin use. No association with BMLs was found for total cholesterol, TG or LDL cholesterol. HDL cholesterol was associated with resolving of BMLs (OR=2.00, p=0.027) with adjustment for the same covariates. Total fat intake and saturated fat intake were protective for incidence of BMLs (OR=0.32 [0.12, 0.86] for total fat, OR=0.24[0.08, 0.72] for saturated fat) adjusting for same covariates. Energy intake, carbohydrate intake, and sugar intake were significantly associated with increase in BML size (p=0.028 for energy intake, p=0.004 for carbohydrate, p=0.008 for sugars). Dietary factors and serum lipids were not associated with cartilage lesions or meniscus tear/extrusion at baseline or changes of them.

Davies-Tuck et al. (2011) examined the association between serum glucose level and changes in cartilage volume and BML over 2 years in 179 participants without clinical knee OA or clinical diabetes in the Melbourne Collaborative Cohort Study [168]. Serum glucose was not associated with baseline cartilage volume in either women or men. Glucose was positively associated with annual loss of cartilage volume over 2 years in women (β=44.2mm^3 [4.6, 83.8]) but not in men (β=6.0mm^3[-68.5, 80.6]). Serum glucose was not associated with baseline BML in both sexes. Serum glucose was associated with incidence of BML in women (OR=5.76 [1.06, 31.21]) but not in men (OR=0.11[0.01, 1.79]). Age, BMI change, and bone area (for cartilage volume) were adjusted for.

Jungmann et al. examined metabolic risks and change in T2 in knee MRI over 2 years in people age 45 - 60 without symptomatic knee OA or knee pain in the OAI participants [169]. WC (> 102 cm in men, > 88 cm in women), HT (SBP > 130 mmHg or SBP > 85 mmHg), self-reported DM and high fat consumption (≥ 78 gm/day from food frequency questionnaire) were assessed. When each component was examined separately, only DM was significantly associated with baseline T2 (β=1.6 [0.0, 3.1]) adjusting for covariates and BMI. In the mutual model with four components, WC (β=1.2 [0.7, 1.7]) and DM (β=1.8 [0.2, 2.4]) were significantly associated with baseline T2. Having greater number of components was associated with higher baseline T2 adjusting for BMI (trend p=0.032, ≥ 3 factors vs. ≤ 2 factors β=1.2 [0.3, 2.1]). None of the individual factors or the number of factors was associated with longitudinal change of T2.

Atherosclerosis may play a role in the metabolic aspect of knee OA. Kornaat et al. compared the vessel wall thickness of the popliteal artery in knee MRI between people with generalized OA (OA in at least 2 joints in hands, spine, knee or hip) and those without [7]. OA cases had higher average vessel wall thickness than controls (CI 0.9, 2.2) with adjustment for sex, age, and BMI, although the vessel wall thickness of popliteal artery is not a conventional measure for atherosclerosis. Hoeven et al. examined the association between atherosclerosis and OA in the Rotterdam Study cohort (mean age 68) [170]. Participants were followed after 6.6 years and 10 years. Intima media thickness (IMT) and presence of plaques in carotid artery were examined by ultrasonography. IMT was associated with prevalent knee OA only in women

(OR=1.7 [1.10, 2.73]) adjusting for age, BMI, total cholesterol /HDL, current smoking, DM, and arterial HT. Plaque was not associated with knee OA. Neither of IMT or plaque was associated with knee OA progression in women or in men.

These prospective studies suggest that accumulation of metabolic risks or metabolic syndrome would be associated with knee OA development or progression especially in women. Atherosclerosis could be mediating the association. High BMI or waist circumference would be the greatest contributor among these metabolic risks. There is some evidence that HT, lipid profile, and serum glucose could be independently associated with structural changes in the knee, but the number of prospective studies is still small.

1.5.5 Potential Mechanisms which Mediate Obesity and Knee OA Metabolically

Results of other studies suggest that inflammation and adipokines may play a role in the metabolic pathway between obesity and knee OA. Central adiposity is associated with higher metabolic risk [138] and inflammation [171]. Proinflammatory cytokine Interleukin-6 (IL-6) was shown to predict knee OA [172]. Fat tissue produces adipokines, such as leptin, resistin, and adiponectin. Leptin levels in serum and synovial fluid were correlated with BMI in OA patients [173,174]. Leptin expression was higher in osteoarthritic cartilage than normal cartilage [174]. In addition, leptin mRNA expression level was higher in cartilage from patients with higher BMI [174]. Leptin treatment reduced chondrocyte proliferation and induced IL-1β, Matrix metallopeptidase-9 (MMP-9) and MMP-13 production by chondrocytes, which suggested a pro-inflammatory and catabolic effect of leptin [174]. In rats, intraarticular leptin injection increased proteoglycan synthesis and the expression of Insulin-like growth factor 1 (IGF-1), transforming growth factor beta 1 (TGFβ1), and leptin mRNA in cartilage [173].

Observational studies also suggest the involvement of adipokines. Most studies have focused on leptin so far. The data from NHANES III reported that serum leptin level was positively associated with prevalent knee OA in women but negatively in men [137]. In the Michigan SWAN study, higher serum leptin levels at baseline were associated with a significantly higher knee OA prevalence (OR=1.38 [1.26, 1.52] per 5 ng/ml increase) and a higher incidence of knee OA in 2 years (OR=1.31[1.21, 1.41] per 5 ng/ml increase) adjusting for age, BMI residuals, race, and smoking status [175]. In the same cohort, baseline serum leptin level was associated with more severe tissue abnormalities at follow-up visit 11 adjusting for age, race, menopause status, smoking status, and BMI residuals: cartilage defect (OR=1.15 [1.08, 1.22]), BML (OR=1.13 [1.06, 1.20]), osteophyte (OR=1.24 [1.17, 1.32]), meniscus abnormality (OR=1.10 [1.04, 1.16]), synovitis (OR=1.19 [1.11, 1.27]), and effusion (OR=1.23 [1.15, 1.32]) (all ORs are per 5 ng/ml increase) [176]. Ding et al. reported that the association between percentage of trunk fat or total fat and cartilage volume was mediated by serum leptin level [177]. Berry et al. reported that higher serum soluble leptin receptor levels at baseline were significantly associated with cartilage defect score worsening (p=0.03) in two years [178]. In this study there was a trend that higher serum soluble leptin receptor levels (p=0.05) and higher adiponectin levels (p=0.08) were associated with greater cartilage volume loss over 2 years. Serum leptin and resistin were not associated with cartilage defect or volume change. These studies suggest that adipokines may play some roles in structural change in the knee. Much work has not been done on metabolites in relation to knee OA. An untargeted metabolomics analysis was conducted in knee OA patients and healthy controls in China [179]. The study found 14 metabolites which were significantly different between OA patients and controls. These metabolites were involved in the metabolism of amino acids, purine, energy, glycolysis, sphingolipid, fatty acid, and lipid.

There are few studies on myokines in knee OA. Irisin is a myokine which is induced with exercise. Elevated level of irisin increases energy expenditure and reverses obesity in mice. A cross-sectional study in China found that serum irisin level was lower in knee OA patients compared with age-, sex-, and BMI-matched healthy controls [180]. In addition, serum and synovial fluid irisin level was lower in severe knee OA patients than less severe patients. This study suggests that myokine could be another mediator between obesity and knee OA, but further studies are needed on the potential role of myokines in knee OA.

1.5.6 Body Composition and Radiographic Knee OA

Studies on body composition and knee OA are summarized in table 5. Several studies reported the association between higher body fat and knee OA. Hochberg et al. reported that higher percentage of body fat from skin fold measurement was significantly associated with prevalent ROA only in women (OR= 3.27 [1.39, 7.67]) in Caucasian participants of the Baltimore Longitudinal Study of Aging (mean age 65) [181]. In the Johnston County Osteoarthritis Project, fat mass and lean mass were measured using DXA [182]. Abbate et al. reported that higher percentage of fat mass and lower percentage of lean mass were significantly associated with prevalent ROA (OR=3.84 [2.26, 6.54] for % fat mass highest quartile vs. lowest, OR=0.20 [0.11, 0.35] for % lean mass) in middle-aged women (n=799) [182]. This study included 27% of African Americans, but all participants were female. In these two studies, these associations did not persist with adjustment for BMI, which suggests that percentage of body fat and/or lean mass do not add more information in predicting prevalent KOA beyond BMI.

Other studies examined fat mass and lean mass simultaneously in the same regression models. Sowers et al. reported that log of higher fat mass and skeletal muscle mass in the same model were both associated with a significantly higher risk of ROA in four years in 483 middle-aged women in the Michigan Bone Health Study (MBHS) [183]. In addition, this multiple model had a better fit than the one with BMI instead of body composition measures. Body composition was assessed by the bioelectrical impedance analysis, which is not a gold standard. This study suggests that fat mass and lean mass together better predict the incidence of ROA than BMI. In the Chingford study, higher lean mass and higher fat mass in lower limbs and lower abdominal fat mass assessed using DXA were associated with significantly higher prevalence of ROA at baseline adjusting for BMI [184]. In addition, higher lean mass in lower limbs was associated with a significantly higher incidence of ROA in 10 years adjusting only for age. This is one of the few studies which separated fat mass into abdominal fat and lower limb fat. The inverse association between abdominal fat and ROA is different from the positive association between abdominal fat and higher metabolic risks. However, more evidence is needed on differential impacts of each fat depot on knee OA. These two studies found that both higher fat mass and higher lean mass in the whole body or lower limbs were associated with a higher risk of ROA adjusting for each other. The positive association between lean mass and ROA in these studies is inconsistent with the study by Abbate el al., which examined fat mass and lean mass in separate models. Therefore, careful model selection would be important when examining body composition measures which are correlated each other. The inverse association between abdominal fat mass and prevalent ROA in the Chingford study is counter intuitive given that cardiometabolic risk factors are associated with knee OA.

Lee et al. classified men and women who were 60 - 69 years old into four groups based on obesity and sarcopenia, which is the another way to examine adiposity and muscle simultaneously. Sarcopenic obesity was associated with higher prevalent ROA than normal body composition (OR=1.87 [1.10, 3.17]) [185]. In this study, the point estimate of odds ratio of ROA relative to normal body composition was higher in sarcopenic obesity than in non-sarcopenic obesity (OR=1.40 [1.02, 1.94]), but a direct comparison of these two groups were not reported. Therefore, it is unknown from this paper whether sarcopenia would have a further impact on knee OA beyond obesity.

In summary, studies have shown that higher fat mass in the whole body and in lower limbs is associated with higher prevalence of ROA. The association between lean mass and ROA is inconclusive. There has not been much evidence on the association between fat distribution and ROA.

1.5.7 Body Composition and MRI-Assessed Structural Changes in the Knee

1.5.7.1 Cross-Sectional Studies (Including Cohort Studies which Examined Prevalent Disease)

Recent studies examined the association between body composition and quantitative and semiquantitative knee MRI outcomes (Table 6). In the Tasmanian older adult study by Ding et al, body composition was assessed using DXA [177]. In the cross-sectional analysis of the 190 participants (mean age 63), higher total fat % and higher trunk fat % were associated with significantly lower knee cartilage volume. The associations were independent of BMI, which indicates body composition would be useful to predict knee cartilage volume beyond BMI. In addition, the study reported that this association between fat % and cartilage volume was mediated by serum leptin level, which suggests a possible underlying mechanism. The study did not find a significant association between percentage of fat and prevalent cartilage defects.

Berry et al. assessed body composition of younger subjects than the above study using DXA [186]. Cartilage defects were graded by using Ding's grading [187]. Higher skeletal muscle mass but not fat mass (total body, android, gynoid or trunk) was associated with significantly greater cartilage volume. Higher total fat mass and trunk fat mass but not skeletal muscle mass were associated with prevalent cartilage defects. Higher total fat mass was also associated with prevalent BMLs. These associations were independent of BMI. The strength of this study was looking at fat mass by location to examine the differential effects on knee tissues. The study did not find a significant association between android or gynoid fat and knee cartilage.

In the Melbourne Collaborative Cohort Study by Wang et al., body composition was estimated by the bioelectrical impedance analysis [188,189]. Cartilage defect was graded by using Ding's grading [187]. Higher fat free mass or increase in fat free mass was associated with significantly higher tibial cartilage volume independent of fat mass in the 297 participants (mean age 58). Higher fat mass was significantly associated with prevalent cartilage defects independent of fat free mass. Change in fat mass was not associated with prevalent cartilage defects. In the patella, higher fat mass was associated with prevalent cartilage defects independent of fat free mass. However, fat mass or fat free mass were not associated with patellar cartilage volume.

Recently, Visser et al. reported a large study in which structural OA was defined as knees with osteophyte and full thickness cartilage loss or either of them and at least of two of BML, cyst, meniscus damage or partial cartilage loss [190]. The data from 1,142 middle-aged people (mean age 56) were included in this analysis. In both men and women, higher percentage of body fat was associated with prevalent structural OA (OR=1.42 [1.01, 1.99] in men, OR=2.36 [1.23, 4.51] in women). Higher percentage of skeletal muscle was associated with lower odds of prevalent structural OA, but the association was only significant in women (OR=0.74 [0.50, 1.09] in men, OR=0.51 [0.29, 0.88] in women). Higher fat mass/skeletal muscle ratio was associated with prevalent structural OA, and again the association was only significant in women (OR=1.35 [0.99, 1.85] in men, OR=1.92 [1.23, 3.00] in women). However, if fat mass and skeletal muscle mass were examined in the same regression models, both higher fat and higher skeletal muscle mass were associated with higher odds of knee OA, although the association was statistically significant only in fat mass in women and skeletal muscle mass in men. This study suggests that careful model selection is important based on the research question. The associations between body composition and MRI assessed structural changes seem to be stronger in women, although it was not formally tested.

In summary, these cross-sectional MRI studies agree that higher skeletal muscle mass or fat free mass is associated with higher cartilage volume. In addition, lower total fat % and trunk fat % were also associated with higher cartilage volume. Higher total fat mass seems to be associated with cartilage defects and other abnormalities in the knee. These results may suggest that fat free mass and fat mass are related to knee OA development though different morphological mechanisms such as baseline cartilage volume and development of cartilage defects.

1.5.7.2 Longitudinal Studies

Studies that examined body composition and longitudinal changes of the knee joint tissues are still few. Cicuttini et al. examined body composition assessed by DXA and change in tibial cartilage volume over 2 years in 70 middle aged people [191]. Higher total body muscle mass and muscle mass in legs but not body fat were associated with significantly higher medial tibial cartilage volume at baseline independent of BMI, which is consistent with the study results mentioned above. In addition, higher total, limbs' and legs' muscle mass were associated with significantly smaller annual cartilage loss independent of BMI. Total body fat mass, fat mass in limbs, fat mass in legs or trunk fat were not associated with change in cartilage volume.

Ding et al. also examined the change in tibial cartilage volume over about 3 years in 395 participants of the Tasmania Older adult study [192]. In this study, higher total body fat, trunk fat, % total body fat and % trunk fat were associated with significantly greater loss of medial cartilage. Although total lean mass was not associated with change in the medial cartilage volume, higher percentage of lean mass was associated with an increase in the medial tibial cartilage volume.

Although the participants' ages were higher in the latter study, the results of these longitudinal studies suggest that muscle mass would be protective for cartilage loss. Summarizing cross-sectional and longitudinal MRI studies, higher lean mass is associated with greater cartilage volume and seems to be protective for cartilage volume loss. Cicuttini et al. pointed out the possible coinheritance between muscle mass and cartilage volume [191]. Higher fat mass could be associated with smaller cartilage volume and seems to be associated with cartilage defects. So far, cartilage volume and cartilage defects have been the primary focuses, and the effect of body composition on worsening of tissue abnormalities such as BMLs and meniscus damages has not been well-established. In these studies on body composition, muscle strength was not taken into account.

1.5.8 Central Adiposity and Knee OA

Some of the above studies also examined the association between central adiposity and knee OA by looking at waist circumference (WC) and/or waist-to-hip ratio (WHR). Higher WC was associated with significantly narrower joint width in the study by Sowers et al. [183] and significantly higher prevalence of ROA in Abbate's paper [182]. In the Melbourne Collaborative Cohort study by Wang et al. WC was associated with a significantly higher risk of TKR in 5 years [193]. Similarly, WHR was related with higher prevalence of ROA in Hochberg's paper [181] and in Abbate's paper [182], but the associations were not statistically significant. WHR was associated with a significantly higher risk of TKR in Wang's paper [193]. There is still a paucity of studies which assessed central obesity using imaging. In Blumenfeld's paper mentioned previously, higher abdominal fat mass was associated with significantly lower prevalence of ROA adjusting for age, BMI, fat mass and lean mass in lower limbs [184]. Body composition was assessed using DXA, but the assessment of abdominal fat mass was not explained in detail in this paper. In Berry's paper, both android fat and gynoid fat were related with higher odds of cartilage defects adjusting for BMI and other covariates, but the association was not significant (p=0.05 for android fat and p=0.10 for gynoid fat) [186]. In Cicuttini paper, neither of trunk fat or fat mass in limbs was significantly associated with tibial cartilage volume loss [191]. In Ding's paper, higher trunk fat was associated with greater cartilage loss, but the association with other fat depot was not reported [192]. Summarizing these studies, the association between trunk or abdominal fat and knee tissue damages has not been well-established. It is also unknown whether central adipose tissue has adverse impacts and whether peripheral adipose tissue is protective for the knee joints as for cardiovascular disease. There seems to be no study which reported the association between VAT or abdominal SAT and knee MRI outcomes.

Table 5. Studies on Body Composition and Knee OA

Author	Study	Design	N	Mean age	Body composition assessment	Outcome	Direction of association for fat	Direction of association for lean
Hochberg [181]	Baltimore Longitudinal Study of Aging	Cross	740	65&66	Skin fold	ROA	**↑women -men**	
Abbate[182]	Johnston County	Cross	799	65	DXA	ROA	**↑**	**↓**
Sower[183]	Michigan Bone Health	Long	485	43	Bioelectrical impedance	ROA	**↑**	**↑**
Blumenfeld [184]	Chingford	Long	773	54&58	DXA	ROA & ROA incidence	**↑limb ↓abdominal**	**↑limb ↑incidence**
Wang[193]	MCCS	Long	39,023	55&60	Bioelectrical impedance	KR	**↑%fat**	

Cross cross-sectional, Long longitudinal, DXA dual-energy X-ray absorptiometry, ROA radiographic knee OA, KR knee replacement, MCCS Melbourne Collaborative Cohort Study

↑positive association, - no association, ↓inverse association

Table 6. Studies on Body Composition and Knee MRI Outcomes

Author	Study	Design	N	Mean age	Body composition assessment	Outcome	Direction of association for fat	Direction of association for lean
Ding[177]	Tasmanian older adults	Cross	190	63	DXA	Cartilage defect (Ding), volume	**-defect** **↓volume**	
Berry[186]		Cross	153	47	DXA	Cartilage defect (Ding), volume BML	**↑defect** **-volume** **↑BML**	**-defect** **↑volume** **-BML**
Wang[188]	MCCS	Cohort (prevalent outcome)	297	58	Bioelectrical impedance	Cartilage (tibia, femur) defect (Ding), volume	**↑defect** **-volume**	**-defect** **↑volume**
Teichtahl[189]	MCCS	Cohort (prevalent outcome)	297	58	Bioelectrical impedance	Patellar cartilage defect, volume	**↑defect** **-volume**	**-defect** **-volume**
Visser[190]		Cross	5,284	56	Bioelectrical impedance	Structural OA based on several features	**-men** **↑women**	**↑men** **- women**
Cicuttini[191]		Long	70	53&58	DXA	Tibial cartilage volume & volume change	**-baseline** **-change**	**↑baseline** **↑change**
Ding[192]	Tasmanian Older Adult Cohort	Long	395	62	DXA	Tibial cartilage volume change	**↓**	**↑lean mass**

Cross cross-sectional, Long longitudinal, DXA dual-energy X-ray absorptiometry, BML bone marrow lesion, MCCS Melbourne Collaborative Cohort Study

↑ positive association, - no association, ↓ inverse association

for cartilage volume, ↑ means higher mass is associated with higher volume or increase of cartilage volume (beneficial)

1.6 MUSCLE COMPONENT AND KNEE OA

1.6.1 Muscle Strength, Power and Knee OA

Knee extensor muscle components seem to have some roles in knee OA. Knee OA patients often have weaker quadriceps strength. A systematic review suggested that the positive effects of exercise on knee OA symptoms would be mediated by an increase of knee extensor and flexor strength and a decrease of extension impairment along with improvement of proprioception [194]. Higher muscle strength is beneficial at least for controlling symptoms in people with structural damages in the knee, although damages in joint cartilage and meniscus are essentially irreversible [195].

Muscle power could be playing a role in knee OA. Muscle power is a product of muscle dynamic force and muscle contraction velocity. In knee OA patients, knee extensor muscle power was more strongly associated with symptoms and physical function than knee extensor strength. Higher knee extensor power was associated with the lower WOMAC pain scores and the higher physical component scores of the Short Form 36 (SF-36) in 190 knee OA patients [196]. Knee extensor strength was not significantly associated with pain or function. In another study knee extensor power at high velocities explained more variance of the WOMAC functional score than maximal isometric torque or power at low velocities in 40 knee OA patients [197]. Knee extensor power was also significantly associated with physical performance measures such as timed stair ascent, timed stair descent, and the Six-Minute Walk Test in 55 knee OA patients adjusting for age, BMI, and self-efficacy [198]. Knee extensor strength was not associated with these outcome measures. However, variance explained by knee extensor power was small (3-8 %) in this study. These studies were all cross-sectional in design. Thus, temporality is not known. There have been only small pilot trials which examined the effect of power training in knee OA patients [199,200]. In 17 women with knee OA who were recruited through newspaper advertisement, quadriceps muscle power and the Knee Injury Osteoarthritis Outcome Score (KOOS) improved significantly after an 8 week knee extensor muscle power training program[199]. There were no controls in this study, which is the limitation. In another study, 33 participants with knee OA were randomized into high speed power training, slow speed strength training and controls [200]. The participants in the control group as well as the two training groups performed stretching and warm-up exercises. After the 12 week intervention, leg press power was more improved in the power training group than the strength training, and leg press velocity improved only in the power training. However, changes in the WOMAC pain and functional scores, 400m walk test, and timed chair rise did not differ between three groups. Regarding extensor power and biomechanics in knee OA, higher extensor power was associated with higher knee adduction moment (KAM) which reflects higher medial compartment load in small cross-sectional studies [201,202]. Muscle strength was not associated with KAM. In these studies, KAM variance explained by muscle power was 7 % and 9 %. The above studies were all conducted in knee OA patients. There has been no study which examined the association between knee extensor power and knee OA incidence or structural changes in the knee. Thus, it is unknown whether knee extensor power is playing a role in knee OA development.

The association between muscle strength, muscle quality and radiographic knee outcomes has been examined. In a study by Slemenda et al. lower muscle strength was measured using KIN-COM and lower extremity lean tissue mass was measured using DXA in community-dwelling independent individuals aged > 65 years. At baseline greater knee extensor strength was associated with lower prevalence of ROA and symptomatic OA adjusting for age, sex, and body weight (OR=0.80 [0.71, 0.90] for ROA and OR=0.71 [0.59, 0.87] for symptomatic OA per 1 lb-ft muscle strength) [203]. At mean follow-up of 31.3 months, knee extensor strength did not differ between people who developed ROA and those who did not both in men and women. However, peak knee extensor strength per body weight and peak extensor strength per lower extremity muscle mass tended to be lower in women who developed knee OA compared with those who did not (p=0.053 for muscle strength per weight, p=0.085 for muscle strength per muscle mass)[204]. These differences were not found in men. This study suggests the possibility that muscle quality could be associated with knee OA development in women. Eckstein et al. conducted a case-control study in OAI participants with KL grade 0-3 at baseline [205]. Cases were 213 women who had reduction in the medial joint space which was larger than the smallest detectable change (-323µm) in three years. Controls were 588 women without joint space loss. The study did not find any difference in muscle strength at baseline, at year 2 or muscle strength loss between baseline and year 2 between cases and controls, adjusting for age, BMI, and knee pain. Segal el al. examined knee extensor strength, knee extensor strength per thigh muscle mass (specific strength), and hamstring-to-quadriceps muscle strength (H:Q) ratio in the MOST study participants with mean age of 61 - 62 years. Baseline knee extensor strength was not associated with incident ROA by 30 months. However, higher knee extensor strength was associated with lower risk of symptomatic OA adjusting for age, BMI, femoral neck bone mineral density (BMD), physical activity (PASE), and knee pain at baseline (OR per 1SD strength increase=0.7 [0.6, 0.9] both in men and women). H:Q ratio (whether ≥ 0.6 or not) was not associated with incident ROA or symptomatic knee OA [206]. Lower knee extensor strength at baseline was associated with higher risk of JSN worsening in the whole knee in 30 months only in women (OR=1.66 [1.26, 2.19] lowest tertile vs. highest tertile). H:Q ratio < 0.8 was associated with lower risk of JSN worsening only in women (OR=0.78 [0.62, 0.99]) [207]. Thigh muscle mass was not associated with risk of ROA or symptomatic knee OA. Specific muscle strength (strength/muscle mass) was not associated with risk of ROA. Higher specific muscle strength was associated with a significantly lower risk of symptomatic knee OA in women, and the same trend was found in men, adjusting for age, BMI and history of knee surgery (p trend <.0001 in women, 0.072 in men) [208]. These results suggest that muscle quality (strength per muscle mass) would be more useful for predicting development of symptomatic knee OA than muscle mass or muscle strength per se. In addition, muscle strength could be more important for knee symptom development rather than structural changes. This may suggest that higher muscle strength does not merely protect knee structure through mechanical stability, and some component of muscle quality could be important for onset of knee symptoms.

A few studies reported the association between muscle strength and structural changes in the knee. Ding et al. examined the association between lower limb muscle strength (quadriceps and hip flexors) and MRI-assessed femoral cartilage change in 252 people in Southern Tasmania [117]. Knee MRI was obtained at baseline and at follow-up (mean 2.3 years). Lower muscle strength at baseline was associated with greater annual cartilage volume loss in the femur (P<0.001) adjusting for age, gender, family history of OA, baseline cartilage volume, and ROA. Whether there was adjustment for BMI is unclear. Baseline muscle strength was not associated with presence or increase in cartilage defects. Amin et al. examined change in cartilage WORMS scores over 30 months in 265 subjects with knee OA in the Boston Osteoarthritis of the Knee Study [209]. Mean age of participants was 67 ± 9 years. Baseline peak torque of quadriceps (Nm) was corrected by body weight (kg), and participants were classified based on the sex specific tertiles of corrected muscle strength. No association between muscle strength (Nm/kg) and cartilage loss was found in the TF joint or the medial patellofemoral (PF) joint. However, the highest strength group had smaller cartilage loss in the lateral PF joint (OR=0.4 [0.2, 0.9] for highest vs. lowest) adjusting for baseline cartilage score, age, BMI, sex, and duration of the follow-up. In summary, there is some evidence that lower muscle strength is associated with greater knee cartilage loss in the femur and PF joint, but evidence is still scarce.

1.6.2 Muscle Area, Fat in Muscle and Knee OA

Other studies examined muscle area, inter- or intra-muscular fat and knee OA. Pan et al. measured vastus medialis (VM) and vastus lateralis (VL) cross-sectional area in thigh MRI in 174 OAI participants who did not have knee pain or knee OA at baseline and were 45-55 years old with BMI of 19-27 kg/m^2 [210]. Muscle cross-sectional areas (CSA) were corrected for body size by dividing by body surface area. Knee cartilage T2 mapping and the WORMS scores in the right knee were assessed. Participants were divided into the two groups based on the area of each muscle. Although the analyses were exploratory, the high VL/VM ratio group had lower T2 compared with the low VL/VM ratio group. No association was found between VL/VM ratios and the WORMS scores in men, but in women, the high VL/VM group had lower scores for meniscus and cartilage.

There have been a few studies on thigh muscle fat and radiographic knee OA. Beattie et al. compared the longitudinal changes in inter-muscular fat (IMF) volume (not including intra-muscular fat) in thigh and quadriceps muscle (QM) volume between 45 women with symptomatic ROA and 41 women without OA in OAI [211]. The mean age of these women was 63 years. There was no difference in QM or IMF between OA and non OA at baseline. In addition, longitudinal changes in QM or IMF in two years were not significantly different between OA and non OA adjusting for age. Kumar et al. compared 30 ROA cases and 66 controls. Mean age was 57.7 years in cases and 50.7 years in controls, and mean BMI was 26.9 kg/m^2 in cases and 24.1 kg/m^2 in controls [212]. Intra-muscular fat (intraMF) fraction, intraMF volume and lean anatomical cross-sectional area (ACSA, area of the muscle minus area of the intraMF) for quadriceps, hamstrings and other muscles were estimated using MRI. IntraMF fraction of quadriceps was significantly higher in cases than in controls. IntraMF fraction of hamstrings or remaining muscles was not significantly different. IntraMF volume, ACSA, intermuscular fat or subcutaneous adipose tissue volume was not different between cases and controls. Quadriceps intraMF fraction was significantly correlated with age, KL, total cartilage WORMS score, and total meniscus WORMS score. Conroy et al. compared 261 older adults with radiographic knee OA and 597 older adults without knee OA in the Health ABC study [213]. Muscle attenuation was significantly lower in those with knee OA than those without, adjusting for age, sex, race, anti-inflammatory drugs, and physical activity. The significant association did not persist with adjustment for BMI.

In summary, higher intramuscular fat or lower muscle attenuation could be associated with radiographic OA, but the studies are still scarce. The above mentioned studies were all case-control studies of ROA, and with my best knowledge, there is no published study which examined the association between inter or intra-muscular fat and MRI-assessed structural changes in the knee.

1.7 SPECIFIC AIMS

1.7.1 Physical Activity and Structural Changes in the Knee

Many studies examined the association between physical activity and knee OA. However, these studies have been heterogeneous, and the results have been inconsistent. It has not been clear what types and intensity of physical activities are associated with radiographic knee OA. Recent studies using MRI suggest that some physical activity could be beneficial for knee joint cartilage especially for people without baseline structural damage. MRI studies have been conducted mainly in middle-aged individuals and people at higher risk of knee OA. Whether physical activity has beneficial, adverse or no impact on tissues in the knees of community-dwelling older adults has not been established. Regular physical activity is beneficial to prevent and control chronic diseases and recommended for older adults. Thus, this information will be important in recommending and prescribing physical activity to older adults. Older adults spent a substantial time in sedentary behavior. It is also unknown whether sedentary behavior has adverse impacts on knee tissues in older adults. In the Health ABC study, physical activity was assessed subjectively at baseline and knee MRI images were obtained in the participants with or without knee pain at the year 2 visit.

Specific Aim 1A: To examine the association between overall physical activity level and MRI-assessed structural changes in the knee

Hypothesis 1A: Older adults with high activity levels have more structural changes than those with low physical activity level.

Specific Aim 1B: To examine the association between time in sedentary behavior and MRI-assessed structural changes in the knee

Hypothesis 1B: Older adults who spent more time in sedentary behavior have more structural changes than people who spent less time in sedentary behavior.

1.7.2 General and Central Adiposity and Structural Changes in the Knee

Obesity is an established and modifiable risk factor for knee OA. The mechanical mechanisms through increased joint load are assumed. The association between metabolic risk factors and knee OA suggests the metabolic mechanisms. However, it is not established which mechanisms are more important. Examining the association between body composition and structural changes in the knee would inform the underlining mechanisms of an increased risk of knee OA by obesity. Studies on body composition and structural changes in the knee have been conducted mainly in middle-aged or young old people. The longitudinal MRI studies have primarily focused on the changes in cartilage volume. The associations between body composition and structural changes such as BMLs, synovitis, and meniscus damages in older adults have not been established. Central adipose tissue, especially visceral fat and ectopic fat are associated with insulin resistance and cardiovascular disease, whereas peripheral adipose tissue is protective. However, it is unknown whether analogous associations exist for knee OA. If there are the analogous associations in knee OA, it would support the metabolic mechanisms. To date, there have been no studies on knee OA which assessed abdominal fat tissues using imaging.

Weight reduction in obese individuals is not easy. If the metabolic mechanisms have more impact on knee joints than the mechanical mechanisms, the targets for knee OA prevention would be more focused on the control of metabolic risk factors than weight control, or vice versa. Thus, exploring the underlining mechanisms is important. In the Health ABC study body composition was assessed using DXA and abdominal CT images were obtained at baseline.

Specific Aim 2A: To examine whether total fat mass and appendicular lean mass are associated with MRI-assessed structural changes in the knee

Hypothesis 2A: Higher total fat mass is associated with higher prevalence of structural changes in the knees taking into account appendicular lean mass in older adults.

Specific Aim 2B: To examine whether abdominal SAT and VAT are associated with MRI-assessed structural changes in the knee

Hypothesis 2B: Both higher abdominal SAT and VAT are associated with higher prevalence of structural changes in the knees of older adults.

1.7.3 Thigh Composition and Structural Changes in the Knee

Muscle strength and muscle quality could be also associated with the development of knee OA. However, previous studies have been inconclusive. Measurement of knee extensor strength could be influenced by knee pain or other knee symptoms due to structural changes not detected on knee radiographs. Thus, it is challenging to examine whether quadriceps strength is causally associated with the development of knee OA. Adiposity in thigh muscle seems to be associated with muscle strength and muscle quality in older adults. There is some evidence that quadriceps intra-muscular fat and thigh muscle density are associated with radiographic knee OA. However, these studies were case-control studies of ROA. It is unknown whether fat composition of thigh muscles is associated with structural changes in the knees of older adults. In the Health ABC, thigh CT images were obtained at baseline.

Specific Aim 3A: To examine the association between thigh muscle density and structural changes in the knee

Hypothesis 3A: Lower thigh muscle density is associated with higher prevalence of structural changes in the knees of older adults.

Specific Aim 3B: To examine the association between thigh IMAT and structural changes in the knee

Hypothesis 3B: *Higher IMAT is associated with higher prevalence of structural changes in the knees of older adults.*

Specific Aim 3C: To examine the association between thigh SAT and structural changes in the knee

Hypothesis 3C: Higher thigh SAT is associated with higher prevalence of structural changes in the knees of older adults.

Specific Aim 3D: To examine the association between quadriceps specific strength and structural changes in the knee

Hypothesis 3D: Higher quadriceps specific strength is associated with lower prevalence of structural changes in the knees of older adults.

2.0 PHYSICAL ACTIVITY AND MRI-ASSESSED STRUCTURAL CHANGES IN THE KNEES OF COMMUNITY-DWELLING OLDER ADULTS

ABSTRACT

The impact of overall physical activity level and sedentary behavior on knee joint tissues in older adults have not been established yet. The purpose of this study was to determine the association between, 1) overall physical activity level and MRI-assessed structural changes in the knees and 2) time spent watching TV and these MRI knee outcomes in community-dwelling older adults.

Health, Aging and Body Composition (Health ABC) Study participants who underwent knee MRI in 1998/99 or 1999/00 were included in this study (911 participants, 1,387 knees). Knee MRI images were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Physical activities in the past 7 days and the hours spent watching TV per week were assessed through interviews at baseline. Participants were classified into three physical activity levels. Inactive was defined as spending ≤2,719 kcal/week in total and <1,000 kcal/week for exercise, and lifestyle active as spending >2,719 kcal/week in total but <1,000 kcal/week for exercise. Exercisers were defined as spending ≥1,000 kcal/week for exercise. Hours watching TV per week were categorized into 0-6 hours, 7-13 hours and ≥14 hours. The associations between physical activity level or time watching TV and MRI-assessed structural knee outcomes were examined using logistic regression models. Participants with pain in one or both knees and those without knee pain were analyzed separately.

Lifestyle active and exercisers had higher prevalence of severe cartilage damage than inactive among participants without knee pain (adjusted odds ratio aOR=2.48 [1.44, 4.27] for lifestyle active, aOR= 2.21 [1.18, 4.11] for exercisers). Overall physical activity level was not associated with knee MRI outcomes in painful knees in participants with knee pain. The amount of time spent watching TV was not associated with these knee outcomes in participants without knee pain. For painful knees in those with knee pain, the odds of bone marrow lesion (BML) in the whole knee was significantly higher in those who spent 7-13 hrs/week or ≥14 hrs/week watching TV than those who spent less than 7 hrs/week (reference) (aOR= 3.49 [1.44, 8.43] for 7-13 hrs/week, aOR= 2.26 [1.1, 4.64] for ≥14 hrs/week).

The joint cartilage may have been vulnerable to high levels of physical activity in these well-functioning older adults. Longitudinal studies using accelerometers are needed to determine the effect of time in sedentary behavior on knee joint tissues.

2.1 INTRODUCTION

Osteoarthritis of the knee (knee OA) is a common joint disorder among older adults. In the United States, 9 million adults were estimated to have symptomatic knee OA in 2005 [13]. Consequences of symptomatic knee OA include pain, functional limitation, and disability [1]. Knee OA is one of the major contributors to physical limitation in the US among chronic diseases. Fifteen to sixteen percent of disability in walking, stair climbing, carrying, and housekeeping was attributed to knee OA, while 2-13% was attributed to heart disease [16]. However, currently there is no approved therapy which reverses degenerative changes in the knee or delays progression of the disease. Because obesity is a risk factor for knee OA [4], the burden of knee OA is expected to increase in aging populations with high prevalence of obesity.

Regular physical activity is beneficial to prevent chronic diseases such as cardiovascular disease, thromboembolic stroke, hypertension, type 2 diabetes mellitus, osteoporosis, obesity, colon cancer, breast cancer, anxiety, and depression [2]. In addition, physical activity may have beneficial effects on cognitive function [52]. Higher physical activity level is associated with better physical function in older adults [53]. Thus, regular physical activity is recommended to all adults[2]. While too much weight bearing physical activity could have an adverse impact on the knee, results of some studies using MRI suggest that physical activity may have beneficial effects on knee cartilage in middle aged people [116,125]. However, the effects of physical activity on tissues in the knee in older adults are not well-established. This information would be important when recommending regular physical activity to older adults especially who are obese and at risk both for knee OA and metabolic diseases.

Older adults spend a substantial amount of time in sedentary behavior. Based on the 2003-2004 NHANES data, 60 to 70% of the waking hours were spent in sedentary behavior in older adults [3]. The time in sedentary behavior was associated with increased mortality taking into account the time spent in moderate-vigorous physical activity [57]. Spending too much time in sedentary behavior might have adverse effects on knee joints. Decline of knee joint cartilage volume has been reported after spinal cord injury (SCI), where knee joint loading and motion are decreased [130]. However, the association between time in sedentary behavior and structural changes in the knees in older adults is not well-established.

The aim of this study was to determine the association between, 1) overall physical activity level and MRI-assessed structural changes in the knee, and 2) the time spent in sedentary behavior and MRI outcomes in community-dwelling older adults. The research hypotheses are 1) older adults with high activity level have more structural changes than those with low levels of physical activity, and 2) older adults who spent longer time in sedentary behavior have more structural changes than people who spent shorter time in sedentary behavior.

2.2 METHODS

2.2.1 Participants

Subjects were a subsample of participants in the Health, Aging and Body Composition (Health ABC) Study. Health ABC study is a prospective cohort study of 3,075 well-functioning black and white men and women who were 70-79 years old at baseline (1997/98). Participants were recruited by mail from specified zip codes surrounding Memphis, TN and Pittsburgh, PA, followed by a telephone eligibility screen. Whites were recruited from a random sample of Medicare beneficiaries, and blacks were recruited from Medicare beneficiaries and all age-eligible residents in these areas. Eligibility criteria were no self-reported difficulty walking a quarter mile or climbing up 10 steps, no difficulty performing basic activities of daily living, and no use of a cane, walker, crutches or other walking aids. Exclusion criteria were having active treatment for cancer in the prior three years, enrolling in a lifestyle intervention and planning to move out of the areas within three years. All participants provided a written informed consent, and the institutional review boards in both sites approved the study.

In 1998/99 (year 2 visit) participants were asked if they had knee symptoms. Knee pain was defined as having pain, aching or stiffness in or around either knee on most days for at least one month in the past 12 months or on most days in the past 30 days or having at least moderate knee pain during the activities in the modified Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain questionnaire in the past 30 days. The pertinent activities were: walking on a flat surface, going up or down stairs, at night while in bed, standing upright, getting in or out of a chair, and getting in or out of a car. At the year 2 visit, 979 participants (32%) reported knee pain in one or both knees, and 1,991 participants (65%) reported no pain (32 participants had died by year 2, and knee pain information was missing in 73 participants, Figure 2). All participants with pain in one or both knees (cases) and a subsample of participants who did not report knee pain (controls) were invited to the knee OA substudy. Of them, 640 knee pain cases and 505 controls underwent knee MRI in 1998/99 or 1999/00 (year 3 visit). MRI images of both knees were obtained in most participants. However, not all the images were read. Participants with available MRI assessment data were included in this analysis (n=965 participants, 1,578 knees). Of these participants, 41 participants were excluded due to missing information for physical activity level (n=1) or for covariates in the final multiple models (knee pain at baseline (1), knee injury history (17), education and/or smoking (6), hypertension (7), metabolic syndrome (9)). The individual's physical activity level would be influenced by the painful knee rather than the knee without pain in those who have pain in one knee. Thus, for individuals with unilateral knee pain, only the painful knee was included. Thus, 113 no pain knees in the participants who had pain in the contralateral knee were excluded. In addition, 13 participants who had knee pain in one knee but in whom MRI data were available only in the contralateral knee were also excluded, leaving 911 participants (1,387 knees, Figure 2 and 3).

2.2.2 Physical Activity

Physical activity and exercise in the past 12 months were assessed at baseline (year 1 of the study) through an interviewer administered questionnaire modified specifically for Health ABC based on physical activity assessments from the Minnesota Leisure Time Physical Activity Questionnaire [104]. Frequency and time spent for a specific activity were asked, which included gardening or yard work, daily household chores, grocery shopping, walking, stair climbing, moderate and high intensity exercise activities, work, and care giving. Time spent for each activity in the past 7 days was multiplied by approximate metabolic equivalent units (MET) and body weight, and energy expenditure for total physical activity and for exercise (walking for exercise, aerobic dance, weight lifting, and other moderate and high intensity exercise activities) were calculated for each participant. Participants were classified into three activity groups based on total physical activity and exercise as previously reported [53]. Inactive was defined as spending ≤2,719 kcal/week in total and <1,000 kcal/week for exercise, and lifestyle active as spending >2,719 kcal/week in total but <1,000 kcal/week for exercise. Exercisers were defined as spending ≥1,000 kcal/week for exercise regardless of total physical activity. (Seven percent of exercisers spent ≥1,000 kcal/week for exercise but ≤ 2,719 kcal/week in total.) The cut-off value of 1,000 kcal/week was based on the Surgeon General's recommendation, and 2,719 kcal/week was the 25th percentile of total physical activity in the whole Health ABC cohort. Hours spent watching TV per week (0 hrs, 1-6 hrs, 7-13 hrs, 14-20 hrs, ≥21 hrs) were also self-reported.

2.2.3 Knee MRI

Knee MRI images were obtained in 1998/99 or 1999/00 using a GE Sigma 1.5T system with a standard unilateral, commercial circumferential knee coil. MRIs were acquired using a coronal T-2 weighted fast spin-echo (FSE) (repetition time (TR) 3,500 msec, echo time (TE) 60 msec, slice thickness 4.0 mm, interslice gap 0.5 mm, excitation 2, Field of View (FOV)140 mm, matrix 256×256 pixels), a sagittal T2-weighted FSE, including the entire synovial cavity with frequency-selective fat suppression (TR 4,127 msec, TE 60 msec, interslice gap 0.5 mm, excitation 2, FOV 140 mm, matrix 256×256 pixels), and a axial T2-weighted FSE localizer (TR 2,500 msec, TE 60 msec, interslice gap 1mm, excitation 1, FOV 120mm, matrix 256×128 pixels). Contraindications for knee MRI were not fitting in the MRI bore or knee coil, cardiac pacemaker, aneurysm clips, metallic fragments in the eyes, vascular clips less than 2 months old, cardiac valve prosthesis, cochlear implants, total knee replacement, and claustrophobia.

Knee MRI images were read by one of five trained radiologists, who were blinded to physical activity levels. Structural changes in the knee were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) [37]. Specifically, 14 subregions (anterior, central, and posterior of the medial/lateral femoral condyles/tibial plateaus and medial/lateral subregions of the patella) were each scored separately for cartilage lesions, osteophytes, subarticular bone marrow lesions, bone cysts, and bone attrition. Size of bone marrow lesions (BMLs) in each subregion was graded as 0 = none, 1 = <25% of the region, 2 = 25-50% of the region and 3 = >50% of the region. Cartilage damage was graded as 0 = normal thickness and signal, 1 = abnormal signal only, 2 = solitary focal defect, 3 = areas of partial-thickness loss with areas of preserved thickness, 4 = diffuse (>75%) partial-thickness loss, 5 = areas of full thickness loss with areas of partial-thickness loss, and 6 = diffuse (>75%) full-thickness loss. Meniscus morphology and tear in anterior horn, body and posterior horn was graded as 0 = intact, 1 = minor radial or parrot break tear, 2 = non-displaced tear or prior surgical repair, 3 = displaced tear, partial maceration or partial resection, and 4 = complete maceration and destruction or complete resection. Synovitis/effusion was graded as 0 = none, 1 = <33% of maximum distension, 2 = 33-66% of maximum distension, and 3 = >66% of distension.

2.2.4 Covariates

Demographic information (age, sex, race), education attainment, smoking status, prevalent diseases (physician diagnosis and medication use), history of knee injury, and knee pain in each knee were collected through a standardized questionnaire at baseline. Knee pain questionnaires were slightly different between 1997/98 and 1998/99. Significant knee pain at baseline was defined as having pain lasting at least one month in the past 12 month, having at least moderate pain in the past 30 days during the activities in the modified WOMAC pain questionnaire, or having pain, aching or stiffness on most days of the past 30 days.

Body weight was measured to the nearest 0.1 kg using a standard balance beam scale, and height was measured to the nearest millimeter using a wall-mounted stadiometer. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Abdominal circumference was measured at the level of largest circumference between the lower rib and the iliac crest using a flexible inelastic fiberglass tape. The measurement was taken at the end of a normal expiration to the nearest 0.1 cm. Blood pressure was measured by the trained staff using a mercury sphygmomanometer after five minutes rest. Blood samples were obtained after an overnight fast at baseline, and serum glucose and plasma lipids were assayed. Prevalent hypertension was defined as self-report of a physician diagnosis combined with hypertension medication use. Prevalent diabetes was defined as self-report of a physician diagnosis of diabetes, use of diabetic medication or fasting serum glucose of ≥126 mg/dL [214]. Metabolic syndrome was defined as meeting at least three of the following criteria: abdominal circumference (>102 cm for men, >88 cm for women), blood pressure (blood pressure ≥130/85 mmHg or anti-hypertensive medication), high glucose (serum glucose ≥110 mg/dL or antidiabetic medication), low High-density lipoprotein (HDL) cholesterol (<40 mg/dL for men, <50 mg/dL for women), and high triglyceride (plasma triglyceride≥150 mg/dL) [215].

2.2.5 Statistical Analysis

Descriptive statistics for characteristics of the participants were calculated and compared by physical activity groups using chi-square tests and logistic regression for categorical variables and Kruskal-Wallis tests for continuous variables.

The prevalence of knee outcomes in each physical activity level was calculated and compared using chi-square tests stratified by knee pain status. The prevalence was also compared between knees without pain and painful knees overall.

The associations between the three physical activity levels and knee MRI outcomes were examined using logistic regression models using inactive group as a reference. Analysis was conducted at the knee level. Participants with pain in one or both knees at baseline were analyzed separately from those without knee pain. Baseline knee pain status was considered most relevant as this was evaluated concurrent with determination of physical activity levels.

The following outcomes were examined in the separate regression models. BML and cartilage damage were examined by compartment (medial tibiofemoral joint (TF) joint, lateral TF joint, and petellofemoral (PF) joint) and in the whole knee. Any BML in each compartment and in the whole knee was defined as the worst WORMS grade of ≥1 (in 5 subregions for medial TF, 5 subregions for lateral TF, 4 subregions for PF or 14 subregions in the whole knee). Severe BML was defined as the worst grade of ≥2 [42]. Any cartilage damage was defined as the worst WORMS grade of ≥ 2, and severe cartilage damage as the worst grade of ≥ 5. Any medial and lateral meniscus damage was defined as meniscus summary score of ≥ 1. Severe meniscus damage was defined as the worst grade in medial or lateral meniscus of ≥ 3. Any synovitis/effusion was defined as synovitis/effusion grade of ≥1, and severe synovitis/effusion as ≥ 2.

Models were adjusted for age (continuous), sex, race (white, black), study site, education (less than high school, high school graduate, post-secondary), BMI (categorical, <25, 25 - <30, 30+), history of knee injury (unknown/not sure being categorized as no injury), smoking status (never, former, current), hypertension, diabetes, metabolic syndrome, and pain in the contralateral knee at baseline (yes/no). Interaction between sex and physical activity was examined. Interaction was statistically significant for any cartilage damage in the medial TF joint and was marginal in the lateral TF joint (p=0.07) in participants without knee pain. Thus, analyses were stratified by sex for these outcomes in those without knee pain. Participants were invited to the knee OA substudy based on knee pain status in the 2nd year of the study while physical activity was assessed at study baseline. Because the participants may have changed their physical activity level from baseline to the 2nd year due to their knee pain, a sensitivity analysis was conducted only with the participants whose pain status in both knees did not change between baseline and the 2nd year.

For the secondary aim, the associations between the time watching TV and knee MRI outcomes were examined similarly using logistic regression models. Time watching TV was categorized into 1) 0-6 hrs/week, 2) 7-13 hrs/week, 3) ≥14 hrs/week, and 0-6 hrs/week was a reference. Because the information on time watching TV was missing in two participants, this analysis was conducted with data from the 909 participants. The same adjustment covariates were included plus sex specific quartiles of total energy expenditure for physical activity.

Generalized estimating equations (GEE) were used to take into account the correlation between two knees within a person. All analyses were conducted using SAS 9.4 (SAS Institute Inc. Cary, NC). All p-values were two-sided, and p-values of less than 0.05 were considered as statistically significant. The significant α level did not take into account multiple comparisons.

2.3 RESULTS

The characteristics of the participants are shown in Table 7. Mean age (± standard deviation, SD) was 73.4 ± 2.9, 545 (59.8 %) were women, and 422 (46.3 %) were black. Mean body mass index (BMI) was 27.5 ± 4.7. In these participants, 202 people (22.2%) were inactive, 494 (54.2%) were lifestyle active and 215 (23.6%) were exercisers. Exercisers were more likely to be men, white, married and had higher education compared with inactive or lifestyle active. Exercisers were less likely to be current smokers and less likely to have hypertension than the others. The prevalence of diabetes was lower in exercisers, although it was not statistically significant. The prevalence of knee injury history was higher in exercisers than the others. BMI was lowest (26.6 ± 5.0) in inactive participants. This may suggest the existence of distinct subpopulations within the inactive group, but the distribution of BMI in this group has a single peak. Inactive participants had shorter height and lighter weight than the other groups and had lower grip strength as well.

More participants in this group stated their general health as fair rather than excellent/very good/good compared with the other groups.

Characteristics of the Health ABC participants who completed the knee MRI with MRI assessment data were compared to those who did not undergo a knee MRI or did not have available MRI assessment data. In knee pain cases, those with knee MRI assessment data were more likely to be women, from Pittsburgh study site, less likely to have knee pain at baseline and less likely to have coronary heart disease (CHD), diabetes or peripheral artery disease. In knee pain controls, those with MRI data were more likely to be women, black and never smokers, less likely to be married and less likely to have CHD or metabolic syndrome. Those with MRI data were shorter in height and lighter than those who were not included.

Table 8 and 9 show the frequency of the knee MRI outcomes by physical activity level and knee pain at baseline. Structural changes were prevalent in these community-dwelling older adults overall. Cartilage damage, especially in the PF joint (67-81%), and synovitis/effusion (62-75%) were common regardless of knee pain status or physical activity level. In knees without pain, significant differences were found between the three physical activity groups in the prevalence of several knee MRI outcomes: any BML in the medial TF (13.7% in inactive, 24.7% in lifestyle active, 23.6% in exercisers, p=0.002), any cartilage damage in the lateral TF (23.9% in inactive, 22.3% in lifestyle active, 14.7% in exercisers, p=0.018), severe BML in the lateral TF (5.6% in inactive, 6.2% in lifestyle active, 1.2% in exercisers, p=0.006), severe cartilage damage in the medial TF (9.4% in inactive, 20.6% in lifestyle active, 18.9% in exercisers, p=0.001), severe cartilage damage in the lateral TF (9.8% in inactive, 9.1% in lifestyle active, 4.3% in exercisers, p=0.033), and severe medial meniscus damage (14.5% in inactive, 15.9% in lifestyle active, 22.4% in exercisers, p=0.034). In painful knees, significant differences existed in the prevalence of the following outcomes: any BML in the medial TF (32.1% in inactive, 44.6% in lifestyle active, 24.0% in exercisers, p=0.004), any cartilage damage in the medial TF (55.1% in inactive, 69.2% in lifestyle inactive, 52% in exercisers, p=0.009), severe BML in the medial TF (14.1% in inactive, 23.7% in lifestyle active, 10.7% in exercisers, p=0.022), severe BML in the whole knee (23.1% in inactive, 36.0% in lifestyle inactive, 24.0% in exercisers, p=0.039), and severe cartilage damage in the medial TF (29.5% in inactive, 40.8% in lifestyle active, 22.7% in exercisers, p=0.010). The prevalence of structural changes was higher in painful knees than knees without pain overall in all MRI outcomes ($p<0.05$) except for any BML in the PF (p=0.960) and severe BML in the PF (p=0.106).

2.3.1 Physical Activity Level and Structural Changes

The covariate adjusted associations between physical activity level and knee MRI outcomes are shown in table 10-12. In the participants without knee pain, lifestyle active had significantly higher odds of BML in the medial TF (adjusted odds ratio, aOR=1.99 [95 CI, 1.24, 3.19]) compared with the inactive (Table 10). The difference between inactive and exercisers was marginally significant (aOR=1.72 [0.99, 2.97]). No significant difference existed between lifestyle active and exercisers for any BML in the medial TF. Lifestyle active and exercisers had significantly higher odds of severe cartilage damage in the medial TF than inactive (aOR=2.48 [1.44, 4.27] for lifestyle active, aOR= 2.21 [1.18, 4.11] for exercisers), with no significant difference between lifestyle active and exercisers. The interaction of sex was statistically significant for cartilage damage in the medial TF (p=0.01) and marginally significant for cartilage damage in the lateral TF (p=0.07) in participants without knee pain. In men, exercisers had significantly higher odds of cartilage damage in the medial TF than inactive (aOR=2.11

[1.10, 4.05]) (Table 11). In women, exercisers had lower odds of cartilage damage in the lateral TF than inactive (aOR= 0.32 [0.15, 0.69]). In the participants who had pain in one or both knees, physical activity level was not differentially associated with knee structural changes (Table 12).

In 565 participants (61%) knee pain status was the same in 1997/98 and 1998/99 in both knees. In a sensitivity analysis of only these participants, the results were overall consistent with the main results for both participants without knee pain, and participants with knee pain (Table 13 and 14). In participants without knee pain, lifestyle active and exercisers had higher odds of severe cartilage damage in the medial TF than inactive, and lifestyle active had higher odds of any BML in the medial TF than inactive.

2.3.2 Association between Time Watching TV and Structural Changes in the Knee

In participants without knee pain, no significant association was found between time watching TV and knee MRI outcomes (Table 15). In those with knee pain, the odds of any BML in the whole knee was significantly higher in those who spent 7-13 hrs/week (aOR= 3.49 [1.44, 8.43]) or ≥14 hrs/week (aOR= 2.26 [1.10, 4.64]) watching TV than those who spent less than 7 hrs/week (Table 16). Compared with people who watched TV for less than 7 hrs/week, those who watched TV for ≥14 hrs/week had more severe cartilage damage in the medial TF (aOR= 2.61 [1.07, 6.37]) and in the whole knee (aOR= 2.50 [1.17, 5.36]). Odds of severe cartilage damages in the lateral TF was higher in participants who watched TV for 7-13 hrs/week (aOR= 3.89 [1.13, 13.48]) compared with those who spent less than 7 hrs/week.

2.4 DISCUSSION

To our knowledge, this is the first study which reports the association between time in sedentary behavior and knee structural changes in older adults. The study found that being in the lifestyle active or the exerciser group was associated with increased odds of severe cartilage damage in the medical TF compared with being in the inactive group in older adults without knee pain. Physical activity level was not associated with different patterns of knee structural changes such as BML, cartilage damage, meniscus damage and synovitis/effusion in the painful knees of participants with pain in one or both knees. The amount of sedentary time was not associated with these knee outcomes in participants without pain, but people who had knee pain and watched TV for 7 hours/week or longer had more BMLs in the whole knee and severe cartilage damage in the medial and lateral TF than those who spent less than 7 hours/week watching TV.

The association between physical activity and radiographic knee OA has been examined in many studies [32,100,101,103,106,132]. However, different types of assessments of physical activity have been used, and the results were not consistent. Among the cross-sectional and longitudinal studies on physical activity and MRI-assessed structural changes in the knee, the results are mixed [116,118,121,124-126,133]. In the current study, higher activity level was associated with severe cartilage damage in the participants without knee pain, which is consistent with studies by Stehling et al. [118] and Dore et al. [126]. Higher frequency and duration of self-reported current vigorous activity was associated with higher cartilage volume and lower odds of prevalent cartilage defects in a community-based cohort [116]. Sessions of strenuous exercise assessed using questionnaires were associated with lower risk of cartilage defect progression in 2.3 years in the lateral TF but not in the medial TF in adults with a history of parental knee replacement and randomly selected controls [125]. Cross-sectional studies by Hanna et al. [124] and by Davies-Tuck [133] did not find an association between self-reported current physical activity and cartilage volume or defects. Other studies reported an association between higher physical activity level and worse outcomes in people with risk factors for knee OA or existing damage. In the Osteoarthritis Initiative (OAI), higher physical activity levels assessed using the Physical Activity Scale for the Elderly (PASE) [105] was associated with worse WORMS grades for cartilage, meniscus, BML, and effusion in the participants who did not have knee OA at baseline but had knee OA risk factors [118]. Time spent in moderate to vigorous activities assessed using accelerometers was associated with prevalent meniscus damage and BML but not with cartilage damage also in the OAI participants without radiographic knee OA [121]. Dore et al. reported that higher physical activity level assessed using pedometers was associated with worsening of meniscus damage, BMLs, and cartilage defects in 2.7 years especially when there were existing tissue damages at baseline [126]. In Dore's study, higher physical activity level was associated with cartilage volume loss if baseline cartilage volume was low. However, higher physical activity was protective for cartilage loss if baseline cartilage volume was high. Together, these studies suggest that physical activity may have beneficial effects on joint cartilage among healthy individuals but may have adverse impacts in people with risk factors for knee OA or existing structural damage. Older age is a risk factor for knee OA. Animal studies show that moderate exercise induces anabolic changes in joint cartilage. However, high intensity exercise or a sudden increase in exercise in older age leads to catabolism of cartilage [77]. Thus, the joint cartilage in the Health ABC participants may have been vulnerable to higher levels of physical activity as in the people with risk factors for knee OA in the OAI and those with existing tissue damages in the study by Dore et al. Future studies are needed to determine whether higher physical activity levels have beneficial effects on knee joints in younger adults without risk factors for knee OA or existing damage.

In men without knee pain, exercisers had significantly higher odds of any cartilage damage in the medial TF compared with inactive. In women without knee pain, exercisers had the lowest odds of cartilage damage in the lateral TF, which may suggest a beneficial effect of exercise on knee cartilage. The possible reasons for the different results by sex could be differences in physical activity type, knee alignment, and knee kinematics [216] between men and women. For example, the mean energy expenditure for exercise in men was twice as that in women, while the total energy expenditure was not very different by sex in these participants. However, it is also possible that women with cartilage damage were more likely to decrease their physical activity due to knee symptoms from structural changes compared with men even though they did not have significant knee pain. Future prospective studies are needed to examine the possible explanations for differential effect of physical activity in men and women.

Older adults may change their physical activity level due to knee pain. In the current study, the overall physical activity level was not associated with knee MRI outcomes in painful knees of those who had pain in one or both knees. The possible reason for the lack of associations in those with knee pain could be that the participants with knee pain had already decreased their physical activity level due to knee pain.

In spinal cord injury, where the loading and motion of the knee joints have decreased, knee joint cartilage loss has been reported, [130]. However, there have been no epidemiological studies which reported the effect of sedentary time on knee joints of older adults. In the current study, spending more time watching TV was not associated with worse knee MRI outcomes in participants without knee pain. In those who had knee pain, watching TV for ≥7 hours or ≥14 hours per week was associated with higher prevalence of BMLs in the whole knee and severe cartilage damage in the medial TF, lateral TF, and in the whole knee. Because this association was not found in the participants without pain, the association may not be causal. Rather, the explanation for these associations could be that the participants with knee pain in either knee spent more time watching TV due to knee pain. Future longitudinal studies are needed to examine a possible causal relationship between sedentary time and knee structural changes.

To our knowledge, this is the first study which reports the association between time in sedentary behavior and knee structural changes in older adults. The strength of the current study is the wealth of information on lifestyle factors, medication, and prevalent diseases, collected in detail in the well-defined Health ABC study. The overall physical activity level was classified into three levels based on energy expenditure for total physical activity and that for exercise estimated using a comprehensive physical activity questionnaire. This 3-level categorization of physical activity was associated with physical function, suggesting the relevance of this classification [53].

However, a few limitations exist in this study. Physical activity was assessed subjectively. Subjective measures of physical activity tend to underestimate time spent in sedentary behavior compared with accelerometers [61]. Time watching TV was used as a surrogate for the amount of time in sedentary behavior. Therefore, misclassification was possible. Estimation of physical activity might have been less accurate in inactive people than in exercisers. Future studies using accelerometers to assess time spent in sedentary behaviors would be necessary to determine the effects of sedentary time on knee joint tissues in older adults. For the overall physical activity level, the type of the physical activity such as weight-bearing or non-weight-bearing was not available. The benefit of regular physical activity for chronic disease prevention is apparent[2]. The types of physical activity which are safe for knee joints in older adults need to be examined. Full limb radiographs were not taken in Health ABC. Thus, there could be unmeasured sex differences in knee alignment, which could explain some of the sex differences in the association between physical activity and cartilage damage. Participants were quite well-functioning at recruitment. Therefore, older adults with knee pain or knee OA would have likely been under-represented. Consequently, the results may not be generalizable to less well-functioning older populations. In addition, only a subgroup of the participants were invited to the knee OA substudy – all those with knee pain at the year 2 visit and a sample of controls without knee pain. Some demographic, health behavior, comorbidity and knee pain differences existed between older adults in the substudy vs. other participants. Therefore, selection bias and collider bias are possible [217,218]. Covariates, such as, race, education, smoking, history of knee injury, hypertension, diabetes, metabolic syndrome and pain in the contralateral knee were adjusted for, but residual confounding is still possible. Many outcomes were examined for associations with the three levels of overall activity level or sedentary time. However, the significance level was not corrected with $p < 0.05$ used throughout. Finally, because of the cross-sectional design, the direction of causation is unknown.

In conclusion, higher activity levels were associated with severe cartilage damage in the medial TF joint in older adults without knee pain. Higher physical activity levels may have an adverse impact on knee joint cartilage in older adults, especially in men. No association was found between time watching TV and structural changes in participants without knee pain. Future longitudinal studies using accelerometers are needed to determine the recommendations of physical activity and sedentary time for older adults with risk factors for knee OA.

2.5 FIGURES AND TABLES

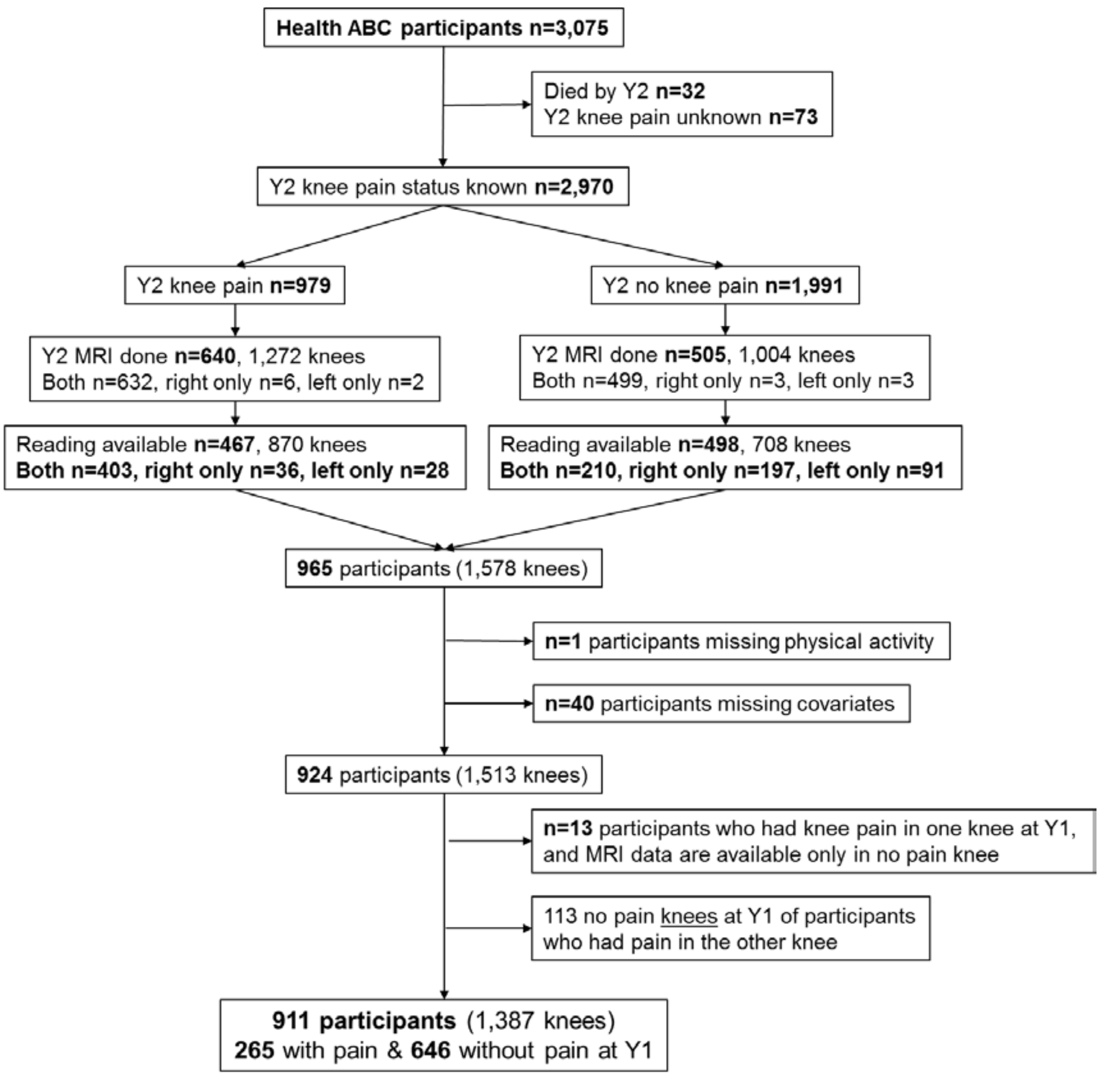

Figure 2. Flow-Chart of the Participants

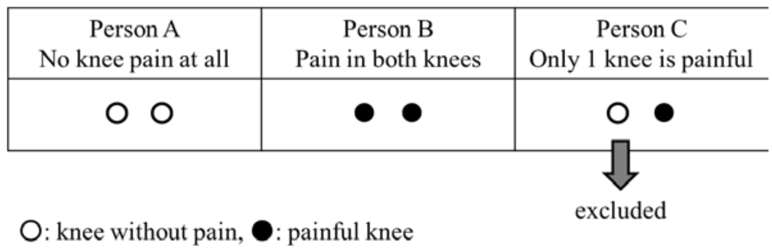

Figure 3. Selection of the Knees

Table 7. Characteristics of the Participants

	All n=911	Inactive n=202	Lifestyle active n=494	Exercisers n=215	p-value	p trend
Age, mean (SD)	73.4 (2.9)	73.8 (2.8)	73.3 (2.9)	73.4 (2.9)	0.132	0.182
Female, n(%)	545 (59.8)	130 (64.4)	315 (63.8)	100 (46.5)	**<.0001**	**0.000**
Black, n(%)	422 (46.3)	104 (51.5)	251 (50.8)	67 (31.2)	**<.0001**	**<.0001**
Site, n(%)					**0.005**	**0.001**
Memphis	429 (47.1)	112 (55.5)	232 (47.0)	85 (39.5)		
Pittsburgh	482 (52.9)	90 (44.6)	262 (53.0)	130 (60.5)		
Married, n(%) n=854	439 (51.4)	78 (39.8)	236 (51.8)	125 (61.9)	**<.0001**	**<.0001**
Education, n(%)					**<.0001**	**<.0001**
Less than High school	213 (23.4)	63 (31.2)	128 (25.9)	22 (10.2)		
High school graduate	310 (34.0)	67 (33.2)	176 (35.6)	67 (31.2)		
Postsecondary	388 (42.6)	72 (35.6)	190 (38.5)	126 (58.6)		
Height (mm), mean (SD)	1651.5 (93.7)	1636.8 (90.3)	1645.1 (91.2)	1680.1 (96.9)	**<.0001**	**<.0001**
Weight (kg), mean (SD)	75.2 (14.7)	71.2 (14.8)	76.4 (14.8)	76.4 (13.6)	**0.0002**	**0.0004**
BMI (kg/m^2), mean (SD)	27.5 (4.7)	26.6 (5.0)	28.2 (4.9)	27.0 (3.9)	**<.0001**	0.362
BMI category, n(%)					**0.008**	0.791
Under 25	262 (28.8)	81 (40.1)	122 (24.7)	59 (27.4)		
25 to 30	413 (45.3)	80 (39.6)	219 (44.3)	114 (53.0)		
30+	236 (25.9)	41 (20.3)	153 (31.0)	42 (19.5)		
Smoking status, n(%)					**0.004**	**0.004**
Never	423 (46.4)	90 (44.6)	239 (48.4)	94 (43.7)		
Current	95 (10.4)	27 (13.4)	58 (11.7)	10 (4.7)		
Former	393 (43.1)	85 (42.1)	197 (39.9)	111 (51.6)		
TV watching, n(%) n=909					**0.001**	
0-6 hrs/week	140 (15.4)	26 (12.9)	79 (16.1)	35 (16.3)		
7-13 hrs/week	226 (24.9)	52 (25.7)	106 (21.5)	68 (31.6)		
14-20 hrs/week	208 (22.9)	40 (19.8)	105 (21.3)	63 (29.3)		
21+ hrs/week	335 (36.9)	84 (41.6)	202 (41.1)	49 (22.8)		

Table 7 Continued

	All n=911	Inactive n=202	Lifestyle active n=494	Exercisers n=215	p-value	p trend
History of knee injury, n(%)	113 (12.4)	18 (8.9)	61 (12.4)	34 (15.8)	0.102	**0.033**
Y1 knee pain, n(%)	265 (29.1)	56 (27.7)	156 (31.6)	53 (24.7)	0.156	0.465
Y2 knee pain, n(%)	445 (48.9)	94 (46.5)	257 (52.0)	94 (43.7)	0.096	0.534
Hypertension, n(%)	392 (43.0)	91 (45.1)	227 (46.0)	74 (34.4)	**0.014**	**0.026**
Coronary heart disease, N(%) n=886	128 (14.5)	29 (14.7)	69 (14.5)	30 (14.2)	0.987	0.870
Cerebrovascular disease, n(%) n=903	74 (8.2)	18 (9.1)	42 (8.6)	14 (6.5)	0.585	0.340
Peripheral arterial disease, n(%) n=890	35 (3.9)	6 (3.1)	17 (3.5)	12 (5.7)	0.320	0.173
Diabetes, n(%)	147 (16.1)	34 (16.8)	87 (17.6)	26 (12.1)	0.177	0.179
Metabolic syndrome, n(%)	313 (34.4)	68 (33.7)	183 (37.0)	62 (28.8)	0.104	0.281
Clinical pulmonary disease, n(%) n=902	109 (12.1)	25 (12.5)	68 (13.9)	16 (7.5)	0.056	0.111
Risk of depression, n(%) n=905	46 (5.1)	12 (6.1)	26 (5.3)	8 (3.7)	0.528	0.271
Cancer, n(%) n=906	170 (18.8)	32 (15.9)	93 (18.9)	45 (21.0)	0.407	0.185
Clinical osteoporosis, n(%) n=898	39 (4.3)	12 (6.1)	21 (4.3)	6 (2.8)	0.276	0.111
Knee OA, N(%) n=903	106 (11.7)	16 (8.0)	71 (14.5)	19 (8.9)	**0.019**	0.850
General health, n(%)					**<.0001**	
Excellent	110 (12.1)	19 (9.4)	47 (9.5)	44 (20.5)		
Very Good	279 (30.6)	50 (24.8)	145 (29.4)	84 (39.1)		
Good	379 (41.6)	87 (43.1)	219 (44.3)	73 (34.0)		
Fair	137 (15.0)	45 (22.3)	79 (16.0)	13 (6.1)		
Poor	5 (0.6)	1 (0.5)	3 (0.6)	1 (0.5)		
Don t Know	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)		
NSAID, n(%) n=906	225 (24.8)	42 (20.9)	139 (28.3)	44 (20.6)	**0.031**	0.889
Knee extensor(Nm), mean (SD), n=805	101.8 (36.8)	92.0 (35.1)	103.3 (35.9)	107.8 (38.7)	**0.0001**	**<.0001**
Grip strength (right1), mean (SD), n=887	29.2 (10.8)	27.0 (9.7)	29.3 (11.1)	30.6 (10.8)	**0.005**	**0.001**
Total activity (kcal/wk), median (IQR)	5038.3 (5565.0)	1744.1 (989.5)	6031.6 (4576.5)	6716.4 (5648.5)	**<.0001**	
Exercise (kcal/wk), median (IQR)	209.0 (949.0)	0.0 (239.2)	0.0 (463.4)	1676.2 (1504.4)	**<.0001**	

SD standard deviation, BMI body mass index, NSAID non-steroidal anti-inflammatory drugs, IQR interquartile range

Table 8. Frequency of Any Knee Structural Changes by Year 1 Knee Pain and Physical Activity Level, n=1387 Knees

	Y1 knee pain -				Y1 knee pain +				
Any damage	Inactive (n=234) n (%)	Lifestyle active (n=530) n (%)	Exercisers (n=259) n (%)	p-value	Inactive (n=78) n (%)	Lifestyle active (n=211) n (%)	Exercisers (n=75) n (%)	p-value	by pain p-value
BML (≥1)									
Medial TF	32 (13.7)	131 (24.7)	61 (23.6)	0.002	25 (32.1)	94 (44.6)	18 (24)	0.004	<.0001
Lateral TF	33 (14.1)	69 (13)	22 (8.5)	0.107	16 (20.5)	45 (21.3)	20 (26.7)	0.581	<.0001
PF	91 (38.9)	236 (44.5)	113 (43.6)	0.340	32 (41)	93 (44.1)	31 (41.3)	0.858	0.960
Knee	119 (50.9)	305 (57.6)	145 (56)	0.227	57 (73.1)	151 (71.6)	50 (66.7)	0.646	<.0001
Cartilage damage (≥2)									
Medial TF	107 (45.7)	268 (50.6)	127 (49)	0.467	43 (55.1)	146 (69.2)	39 (52)	0.009	<.0001
Lateral TF	56 (23.9)	118 (22.3)	38 (14.7)	0.018	29 (37.2)	76 (36)	23 (30.7)	0.647	<.0001
PF	163 (69.7)	378 (71.3)	174 (67.2)	0.491	57 (73.1)	170 (80.6)	54 (72)	0.195	0.008
Knee	189 (80.8)	439 (82.8)	209 (80.7)	0.685	67 (85.9)	189 (89.6)	68 (90.7)	0.591	0.001
Meniscus damage (≥1)									
Medial	71 (30.3)	176 (33.2)	103 (39.8)	0.069	37 (47.4)	110 (52.1)	32 (42.7)	0.349	<.0001
Lateral	33 (14.1)	60 (11.3)	20 (7.7)	0.075	11 (14.1)	45 (21.3)	18 (24)	0.270	<.0001
Knee	86 (36.8)	210 (39.6)	112 (43.2)	0.334	42 (53.9)	130 (61.6)	43 (57.3)	0.464	<.0001
Synovitis/effusion (≥1)	159 (68)	329 (62.1)	169 (65.3)	0.273	52 (66.7)	156 (73.9)	56 (74.7)	0.422	0.004

BML bone marrow lesion, p-values from chi-square test

Table 9. Frequency of Severe Knee Structural Changes by Year 1 Knee Pain and Physical Activity Level, n=1387 Knees

	Y1 knee pain -				Y1 knee pain +				
	Inactive (n=234)	Lifestyle active (n=530)	Exercisers (n=259)		Inactive (n=78)	Lifestyle active (n=211)	Exercisers (n=75)		by pain
Severe damage	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	n (%)	p-value	p-value
BML (≥2)									
Medial TF	14 (6)	52 (9.8)	27 (10.4)	0.163	11 (14.1)	50 (23.7)	8 (10.7)	0.022	<.0001
Lateral TF	13 (5.6)	33 (6.2)	3 (1.2)	0.006	6 (7.7)	16 (7.6)	8 (10.7)	0.692	0.015
PF	32 (13.7)	65 (12.3)	31 (12)	0.823	4 (5.1)	24 (11.4)	6 (8)	0.244	0.106
Knee	50 (21.4)	126 (23.8)	53 (20.5)	0.528	18 (23.1)	76 (36)	18 (24)	0.039	0.001
Cartilage damage (≥5)									
Medial TF	22 (9.4)	109 (20.6)	49 (18.9)	0.001	23 (29.5)	86 (40.8)	17 (22.7)	0.010	<.0001
Lateral TF	23 (9.8)	48 (9.1)	11 (4.3)	0.033	12 (15.4)	37 (17.5)	13 (17.3)	0.908	<.0001
PF	63 (26.9)	151 (28.5)	61 (23.6)	0.340	23 (29.5)	75 (35.6)	23 (30.7)	0.542	0.021
Knee	86 (36.8)	232 (43.8)	97 (37.5)	0.095	43 (55.1)	139 (65.9)	40 (53.3)	0.078	<.0001
Meniscus damage (≥3)									
Medial	34 (14.5)	84 (15.9)	58 (22.4)	0.034	27 (34.6)	82 (38.9)	20 (26.7)	0.163	<.0001
Lateral	16 (6.8)	35 (6.6)	10 (3.9)	0.253	9 (11.5)	33 (15.6)	13 (17.3)	0.574	<.0001
Knee	44 (18.8)	112 (21.1)	64 (24.7)	0.268	34 (43.6)	104 (49.3)	29 (38.7)	0.256	<.0001
Synovitis/effusion (≥2)	31 (13.3)	83 (15.7)	32 (12.4)	0.404	20 (25.6)	70 (33.2)	18 (24)	0.223	<.0001

BML bone marrow lesion, p-values from chi-square test

Table 10. Association between Physical Activity Level and Structural Changes in Knees without Pain, n=646 Participants without Knee Pain, 1023 Knees

Outcome	Activity level	Any damage OR[95% CI]	p-value	Severe damage OR[95% CI]	p-value
BML					
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.99 [1.24, 3.19]	**0.004**	1.57 [0.78, 3.18]	0.210
	Exerciser	1.72 [1.00, 2.97]	0.051	1.86 [0.87, 3.98]	0.112
Lateral TF	Inactive	ref		ref	
	Lifestyle active	0.94 [0.57, 1.57]	0.825	1.19 [0.54, 2.59]	0.671
	Exerciser	0.70 [0.38, 1.31]	0.266	0.28 [0.07, 1.04]	0.057
PF	Inactive	ref		ref	
	Lifestyle active	1.23 [0.85, 1.77]	0.266	0.85 [0.50, 1.44]	0.540
	Exerciser	1.23 [0.79, 1.89]	0.357	0.92 [0.49, 1.74]	0.807
Knee	Inactive	ref		ref	
	Lifestyle active	1.28 [0.89, 1.84]	0.176	1.14 [0.73, 1.77]	0.566
	Exerciser	1.18 [0.77, 1.82]	0.445	1.13 [0.68, 1.89]	0.638
Cartilage damage					
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.17 [0.82, 1.67]	0.384	2.48 [1.44, 4.27]	**0.001**
	Exerciser	1.13 [0.74, 1.73]	0.565	2.21 [1.18, 4.11]	**0.013**
Lateral TF	Inactive	ref		ref	
	Lifestyle active	1.00 [0.65, 1.56]	0.990	1.03 [0.54, 1.98]	0.927
	Exerciser	0.87 [0.50, 1.49]	0.604	0.72 [0.32, 1.65]	0.441
PF	Inactive	ref		ref	
	Lifestyle active	1.09 [0.74, 1.60]	0.668	1.10 [0.74, 1.64]	0.628
	Exerciser	1.15 [0.71, 1.85]	0.571	0.99 [0.61, 1.59]	0.958
Knee	Inactive	ref		ref	
	Lifestyle active	1.16 [0.74, 1.82]	0.529	1.38 [0.95, 2.01]	0.095
	Exerciser	1.23 [0.71, 2.14]	0.465	1.15 [0.74, 1.79]	0.532
Meniscus damage					
Medial	Inactive	ref		ref	
	Lifestyle active	1.22 [0.83, 1.80]	0.319	1.10 [0.68, 1.79]	0.690
	Exerciser	1.41 [0.90, 2.22]	0.137	1.37 [0.77, 2.43]	0.284
Lateral	Inactive	ref		ref	
	Lifestyle active	0.86 [0.51, 1.42]	0.550	1.00 [0.46, 2.16]	0.997
	Exerciser	0.71 [0.37, 1.38]	0.316	0.88 [0.33, 2.31]	0.793
Knee	Inactive	ref		ref	
	Lifestyle active	1.19 [0.82, 1.74]	0.364	1.15 [0.73, 1.81]	0.538
	Exerciser	1.28 [0.83, 1.99]	0.267	1.32 [0.77, 2.25]	0.314
Synovitis/effusion	Inactive	ref		ref	
	Lifestyle active	0.75 [0.52, 1.08]	0.124	1.26 [0.77, 2.07]	0.353
	Exerciser	0.83 [0.53, 1.29]	0.412	1.04 [0.56, 1.94]	0.905

BML bone marrow lesion, OR odds ratio, ORs are adjusted for age, sex, race, study site, education, BMI, smoking, history of knee injury, knee pain in the contralateral knee, hypertension, diabetes and metabolic syndrome

Table 11. Association between Physical Activity and Cartilage Damage in Medial and Lateral Tibiofemoral Joints in Participants without Pain by Sex

Cartilage damage(≥2)	Activity level	Men OR[95% CI]	p-value	Women OR[95% CI]	p-value
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.59 [0.89, 2.82]	0.116	0.93 [0.59, 1.45]	0.737
	Exerciser	2.11 [1.10, 4.05]	**0.024**	0.59 [0.33, 1.06]	0.077
Lateral TF	Inactive	ref		ref	
	Lifestyle active	1.38 [0.61, 3.11]	0.443	0.76 [0.43, 1.31]	0.32
	Exerciser	2.21 [0.91, 5.38]	0.081	0.32 [0.15, 0.69]	**0.004**

BML bone marrow lesion, OR odds ratio

ORs are adjusted for age, race, study site, education, BMI, smoking, history of knee injury, knee pain in the contralateral knee, hypertension, diabetes and metabolic syndrome

Table 12. Association between Physical Activity Level and Structural Changes in Painful Knees, n=265 Participants with Any Knee Pain, 364 Knees

Outcome	Activity level	Any damage OR[95% CI]	p-value	Severe damage OR[95% CI]	p-value
BML					
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.17 [0.59, 2.33]	0.648	1.37 [0.58, 3.27]	0.477
	Exerciser	0.54 [0.22, 1.36]	0.193	0.60 [0.18, 2.08]	0.424
Lateral TF	Inactive	ref		ref	
	Lifestyle active	0.62 [0.30, 1.28]	0.196	0.73 [0.23, 2.37]	0.605
	Exerciser	1.28 [0.49, 3.38]	0.616	1.11 [0.27, 4.60]	0.884
PF	Inactive	ref		ref	
	Lifestyle active	1.12 [0.59, 2.15]	0.725	2.24 [0.68, 7.37]	0.186
	Exerciser	0.97 [0.43, 2.20]	0.946	1.10 [0.25, 4.74]	0.9
Knee	Inactive	ref		ref	
	Lifestyle active	0.58 [0.28, 1.21]	0.147	1.37 [0.71, 2.64]	0.355
	Exerciser	0.45 [0.19, 1.11]	0.085	0.86 [0.35, 2.07]	0.729
Cartilage damage					
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.45 [0.76, 2.79]	0.264	1.06 [0.52, 2.14]	0.881
	Exerciser	0.84 [0.39, 1.83]	0.663	0.50 [0.20, 1.27]	0.145
Lateral TF	Inactive	ref		ref	
	Lifestyle active	0.59 [0.30, 1.16]	0.127	0.71 [0.30, 1.68]	0.436
	Exerciser	0.67 [0.29, 1.56]	0.352	1.03 [0.32, 3.30]	0.955
PF	Inactive	ref		ref	
	Lifestyle active	1.12 [0.53, 2.36]	0.762	1.14 [0.57, 2.27]	0.716
	Exerciser	0.91 [0.38, 2.16]	0.826	0.91 [0.40, 2.07]	0.82
Knee	Inactive	ref		ref	
	Lifestyle active	0.83 [0.32, 2.17]	0.702	0.96 [0.50, 1.84]	0.896
	Exerciser	1.38 [0.40, 4.76]	0.608	0.70 [0.31, 1.56]	0.385
Meniscus damage					
Medial	Inactive	ref		ref	
	Lifestyle active	1.00 [0.52, 1.91]	0.997	0.83 [0.42, 1.64]	0.589
	Exerciser	0.77 [0.34, 1.73]	0.526	0.56 [0.23, 1.35]	0.193
Lateral	Inactive	ref		ref	
	Lifestyle active	1.35 [0.55, 3.28]	0.514	1.10 [0.43, 2.83]	0.837
	Exerciser	1.79 [0.67, 4.75]	0.244	1.57 [0.54, 4.55]	0.406
Knee	Inactive	ref		ref	
	Lifestyle active	1.13 [0.62, 2.07]	0.696	0.82 [0.44, 1.53]	0.534
	Exerciser	1.02 [0.47, 2.22]	0.953	0.65 [0.29, 1.42]	0.278
Synovitis/effusion	Inactive	ref		ref	
	Lifestyle active	0.99 [0.50, 1.96]	0.986	0.74 [0.37, 1.46]	0.384
	Exerciser	1.34 [0.56, 3.22]	0.507	0.49 [0.20, 1.19]	0.115

BML bone marrow lesion, OR odds ratio, ORs are adjusted for age, sex, race, study site, education, BMI, smoking, history of knee injury, knee pain in the contralateral knee, hypertension, diabetes and metabolic syndrome

Table 13. Association between Physical Activity and Structural Changes in Participants without Knee Pain and with Same Knee Pain Status in 1997/98 and 1998/99, n=420 Participants, 601 Knees

Outcome	Activity level	Any damage OR[95% CI]	p-value	Severe damage OR[95% CI]	p-value
BML					
Medial TF	Inactive	ref		ref	
	Lifestyle active	2.36 [1.13, 4.93]	**0.023**	2.57 [0.55, 12.14]	0.232
	Exerciser	2.21 [0.97, 5.06]	0.060	4.29 [0.84, 21.81]	0.080
Lateral TF	Inactive	ref			
	Lifestyle active	0.93 [0.42, 2.02]	0.845	NA	
	Exerciser	0.83 [0.34, 2.03]	0.684		
PF	Inactive	ref		ref	
	Lifestyle active	1.17 [0.72, 1.88]	0.530	0.96 [0.45, 2.05]	0.919
	Exerciser	1.08 [0.62, 1.89]	0.787	1.00 [0.42, 2.40]	0.996
Knee	Inactive	ref		ref	
	Lifestyle active	1.29 [0.81, 2.06]	0.281	1.23 [0.62, 2.43]	0.548
	Exerciser	1.10 [0.64, 1.89]	0.730	1.39 [0.63, 3.06]	0.419
Cartilage damage					
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.09 [0.69, 1.75]	0.706	3.69 [1.41, 9.65]	**0.008**
	Exerciser	1.09 [0.64, 1.88]	0.743	2.78 [1.02, 7.56]	**0.045**
Lateral TF	Inactive	ref			
	Lifestyle active	1.19 [0.64, 2.21]	0.593	NA	
	Exerciser	1.28 [0.62, 2.64]	0.498		
PF	Inactive	ref		ref	
	Lifestyle active	0.95 [0.58, 1.56]	0.833	0.97 [0.58, 1.62]	0.910
	Exerciser	0.98 [0.54, 1.77]	0.949	0.77 [0.41, 1.42]	0.399
Knee	Inactive	ref		ref	
	Lifestyle active	1.18 [0.69, 2.02]	0.553	1.42 [0.87, 2.30]	0.160
	Exerciser	1.40 [0.73, 2.68]	0.312	1.02 [0.58, 1.80]	0.932
Meniscus damage					
Medial	Inactive	ref		ref	
	Lifestyle active	1.70 [0.93, 3.11]	0.085	1.66 [0.65, 4.29]	0.292
	Exerciser	2.11 [1.10, 4.06]	**0.025**	2.44 [0.82, 7.26]	0.108
Lateral	Inactive	ref			
	Lifestyle active	1.01 [0.47, 2.18]	0.975	NA	
	Exerciser	0.62 [0.24, 1.55]	0.306		
Knee	Inactive	ref		ref	
	Lifestyle active	1.58 [0.90, 2.78]	0.111	1.60 [0.70, 3.70]	0.268
	Exerciser	1.78 [0.96, 3.32]	0.069	2.17 [0.84, 5.62]	0.112
Synovitis/effusion	Inactive	ref		ref	
	Lifestyle active	0.74 [0.46, 1.19]	0.220	1.38 [0.66, 2.87]	0.387
	Exerciser	0.89 [0.51, 1.57]	0.697	1.17 [0.46, 2.99]	0.740

BML bone marrow lesion, OR odds ratio, ORs are adjusted for age, race, study site, education, BMI, smoking, history of knee injury, knee pain in the contralateral knee, hypertension, diabetes and metabolic syndrome

Table 14. Association between Physical Activity and Structural Changes in Participants with Knee Pain and Same Knee Pain Status in 1997/98 and 1998/99, n=145 Participants, 210 Knees

Outcome	Activity level	Any damage OR[95% CI]	p-value	Severe damage OR[95% CI]	p-value
BML					
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.08 [0.44, 2.67]	0.864	1.45 [0.47, 4.46]	0.521
	Exerciser	0.52 [0.16, 1.66]	0.271	0.69 [0.15, 3.20]	0.638
Lateral TF	Inactive	ref			
	Lifestyle active	0.70 [0.24, 2.04]	0.511	NA	
	Exerciser	1.44 [0.36, 5.76]	0.609		
PF	Inactive	ref			
	Lifestyle active	1.47 [0.59, 3.68]	0.405	NA	
	Exerciser	1.96 [0.66, 5.83]	0.227		
Knee	Inactive	ref		ref	
	Lifestyle active	0.55 [0.19, 1.53]	0.248	1.31 [0.59, 2.92]	0.509
	Exerciser	0.43 [0.13, 1.38]	0.155	0.78 [0.26, 2.36]	0.665
Cartilage damage					
Medial TF	Inactive	ref		ref	
	Lifestyle active	1.51 [0.62, 3.69]	0.361	1.94 [0.71, 5.29]	0.195
	Exerciser	0.65 [0.23, 1.88]	0.43	0.69 [0.19, 2.47]	0.573
Lateral TF	Inactive	ref		ref	
	Lifestyle active	0.64 [0.28, 1.47]	0.296	1.03 [0.29, 3.67]	0.968
	Exerciser	0.97 [0.33, 2.85]	0.957	1.42 [0.30, 6.81]	0.659
PF	Inactive	ref		ref	
	Lifestyle active	1.39 [0.46, 4.24]	0.559	1.19 [0.44, 3.25]	0.735
	Exerciser	1.38 [0.43, 4.45]	0.594	1.06 [0.35, 3.22]	0.922
Knee	Inactive			ref	
	Lifestyle active	NA		0.95 [0.39, 2.31]	0.908
	Exerciser			0.94 [0.33, 2.68]	0.907
Meniscus damage					
Medial	Inactive	ref		ref	
	Lifestyle active	0.76 [0.29, 2.00]	0.579	0.82 [0.30, 2.19]	0.685
	Exerciser	0.52 [0.17, 1.58]	0.251	0.33 [0.09, 1.16]	0.085
Lateral	Inactive	ref		ref	
	Lifestyle active	1.28 [0.41, 3.93]	0.672	0.96 [0.28, 3.26]	0.949
	Exerciser	1.31 [0.33, 5.15]	0.702	1.21 [0.27, 5.38]	0.807
Knee	Inactive	ref		ref	
	Lifestyle active	0.70 [0.28, 1.75]	0.441	0.68 [0.28, 1.66]	0.396
	Exerciser	0.63 [0.22, 1.81]	0.393	0.38 [0.13, 1.14]	0.085
Synovitis/effusion	Inactive	ref		ref	
	Lifestyle active	0.98 [0.40, 2.39]	0.957	1.64 [0.67, 4.00]	0.278
	Exerciser	1.14 [0.38, 3.45]	0.82	0.81 [0.26, 2.52]	0.717

BML bone marrow lesion, OR odds ratio, ORs are adjusted for age, race, study site, education, BMI, smoking, history of knee injury, knee pain in the contralateral knee, hypertension, diabetes and metabolic syndrome

Table 15. Association between Time Watching TV and Structural Changes in Knees without Pain, n=645 Participants without Knee Pain, 1022 Knees

Outcome	TV	Any damage OR[95% CI]	p-value	Severe damage OR[95% CI]	p-value
BML					
Medial TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.63 [0.36, 1.09]	0.097	1.21 [0.54, 2.71]	0.646
	≥14 hrs/w	0.82 [0.51, 1.32]	0.415	1.24 [0.58, 2.63]	0.582
Lateral TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.59 [0.3, 1.19]	0.140	0.59 [0.21, 1.64]	0.308
	≥14 hrs/w	1.06 [0.6, 1.85]	0.848	0.69 [0.28, 1.73]	0.434
PF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.67 [0.43, 1.05]	0.079	0.92 [0.47, 1.82]	0.818
	≥14 hrs/w	0.84 [0.56, 1.25]	0.385	0.81 [0.45, 1.48]	0.498
Knee	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.67 [0.43, 1.04]	0.074	0.97 [0.56, 1.69]	0.921
	≥14 hrs/w	0.87 [0.58, 1.31]	0.515	0.90 [0.55, 1.47]	0.666
Cartilage damage					
Medial TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.80 [0.51, 1.25]	0.329	0.98 [0.54, 1.78]	0.942
	≥14 hrs/w	1.03 [0.69, 1.53]	0.885	0.88 [0.52, 1.50]	0.638
Lateral TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.67 [0.38, 1.17]	0.156	0.51 [0.22, 1.17]	0.111
	≥14 hrs/w	0.87 [0.53, 1.43]	0.590	0.88 [0.45, 1.71]	0.704
PF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.73 [0.45, 1.18]	0.204	0.83 [0.50, 1.38]	0.477
	≥14 hrs/w	0.96 [0.62, 1.48]	0.843	0.90 [0.58, 1.39]	0.638
Knee	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.82 [0.47, 1.45]	0.504	0.99 [0.63, 1.56]	0.959
	≥14 hrs/w	0.96 [0.57, 1.61]	0.884	0.88 [0.59, 1.32]	0.542
Meniscus damage					
Medial	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.78 [0.48, 1.27]	0.311	0.83 [0.46, 1.49]	0.524
	≥14 hrs/w	1.06 [0.68, 1.64]	0.798	0.77 [0.45, 1.30]	0.320
Lateral	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.55 [0.27, 1.12]	0.099	0.92 [0.26, 3.29]	0.897
	≥14 hrs/w	0.84 [0.49, 1.45]	0.535	2.15 [0.77, 5.97]	0.143
Knee	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.74 [0.46, 1.18]	0.201	0.83 [0.47, 1.45]	0.513
	≥14 hrs/w	0.97 [0.64, 1.48]	0.903	0.98 [0.60, 1.59]	0.919
Synovitis/effusion	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.98 [0.63, 1.51]	0.926	0.73 [0.40, 1.34]	0.307
	≥14 hrs/w	1.16 [0.78, 1.72]	0.466	0.84 [0.49, 1.43]	0.527

BML bone marrow lesion, OR odds ratio, ORs are adjusted for age, sex, race, study site, education, BMI, smoking, history of knee injury, knee pain in the contralateral knee, total physical activity, hypertension, diabetes and metabolic syndrome

Table 16. Association between Time Watching TV and Structural Changes in Painful Knees, n=264 Participants with Any Knee Pain, 363 Knees

Outcome	TV	Any damage OR[95% CI]	p-value	Severe damage OR[95% CI]	p-value
BML					
Medial TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	1.95 [0.72, 5.32]	0.192	1.35 [0.42, 4.32]	0.614
	≥14 hrs/w	1.20 [0.50, 2.87]	0.682	1.08 [0.37, 3.14]	0.882
Lateral TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	1.80 [0.59, 5.54]	0.302	6.59 [0.84, 51.80]	0.073
	≥14 hrs/w	1.52 [0.54, 4.22]	0.427	5.22 [0.78, 35.14]	0.089
PF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	1.61 [0.69, 3.77]	0.273	1.00 [0.22, 4.51]	1.000
	≥14 hrs/w	1.48 [0.70, 3.11]	0.307	1.53 [0.40, 5.76]	0.532
Knee	0-6 hrs/w	ref		ref	
	7-13 hrs/w	3.49 [1.44, 8.43]	**0.006**	1.48 [0.55, 3.98]	0.434
	≥14 hrs/w	2.26 [1.10, 4.64]	**0.026**	1.51 [0.63, 3.64]	0.356
Cartilage damage					
Medial TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	1.59 [0.66, 3.83]	0.298	2.40 [0.91, 6.30]	0.076
	≥14 hrs/w	2.14 [0.96, 4.81]	0.064	2.61 [1.07, 6.37]	**0.035**
Lateral TF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	2.18 [0.84, 5.70]	0.111	3.89 [1.13, 13.48]	**0.032**
	≥14 hrs/w	1.02 [0.41, 2.53]	0.961	2.87 [0.93, 8.85]	0.067
PF	0-6 hrs/w	ref		ref	
	7-13 hrs/w	2.05 [0.80, 5.29]	0.137	1.11 [0.43, 2.85]	0.824
	≥14 hrs/w	1.65 [0.75, 3.62]	0.216	1.34 [0.58, 3.09]	0.489
Knee	0-6 hrs/w	ref		ref	
	7-13 hrs/w	2.66 [0.68, 10.4]	0.159	2.02 [0.84, 4.84]	0.116
	≥14 hrs/w	1.63 [0.57, 4.63]	0.361	2.50 [1.17, 5.36]	**0.019**
Meniscus damage					
Medial	0-6 hrs/w	ref		ref	
	7-13 hrs/w	0.99 [0.42, 2.35]	0.989	2.00 [0.79, 5.08]	0.143
	≥14 hrs/w	1.19 [0.53, 2.69]	0.677	1.70 [0.73, 3.95]	0.221
Lateral	0-6 hrs/w	ref		ref	
	7-13 hrs/w	1.30 [0.50, 3.40]	0.586	1.10 [0.38, 3.18]	0.865
	≥14 hrs/w	0.87 [0.36, 2.08]	0.751	1.01 [0.36, 2.77]	0.991
Knee	0-6 hrs/w	ref		ref	
	7-13 hrs/w	1.33 [0.59, 2.99]	0.496	2.20 [0.97, 5.01]	0.059
	≥14 hrs/w	1.27 [0.60, 2.69]	0.533	1.83 [0.87, 3.86]	0.113
Synovitis/effusion	0-6 hrs/w	ref		ref	
	7-13 hrs/w	1.70 [0.70, 4.14]	0.240	1.32 [0.49, 3.57]	0.579
	≥14 hrs/w	1.69 [0.76, 3.76]	0.199	1.07 [0.42, 2.72]	0.882

BML bone marrow lesion, OR odds ratio, ORs are adjusted for age, sex, race, study site, education, BMI, smoking, history of knee injury, knee pain in the contralateral knee, total physical activity, hypertension, diabetes and metabolic syndrome

3.0 ASSOCIATION OF GENERAL AND CENTRAL ADIPOSITY WITH MRI-ASSESSED STRUCTURAL CHANGES IN THE KNEES OF COMMUNITY-DWELLING OLDER ADULTS

ABSTRACT

Obesity is an established risk factor for knee osteoarthritis (OA). However, it is not established whether a mechanical or metabolic mechanism is more important for the development of knee OA. The study aim was to examine the associations of 1) total body fat mass and appendicular lean mass, 2) abdominal subcutaneous adipose tissue (SAT), and 3) visceral adipose tissue (VAT) with structural changes in the knees of community-dwelling older adults.

The participants were 866 older adults (525 women, mean age 73.5±2.9) in the Health, Aging, and Body Composition Study. Body composition from whole body DXA, and abdominal SAT and VAT areas on CT were assessed at baseline (1997/98). Knee MRI images obtained at the 1998/99 or 1999/00 visit were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS). The associations between body composition and presence of structural outcomes were examined using logistic regression stratified by sex. Total body fat mass and appendicular lean mass were examined in the same models. VAT and SAT areas per body weight were examined in the separate models. Adjusted covariates were age, race, height, study site, education, history of knee injury, knee pain, smoking status, alcohol drinking, total physical activity, time spent watching TV, and use of NSAIDs at baseline.

In men, higher appendicular lean mass was associated with higher odds of bone marrow lesion (BML) in the lateral tibiofemoral joint (TF) and in the patellofemoral joint (PF) (aOR=1.16 [1.04, 1.29] and 1.13 [1.04,1.22], respectively), cartilage damage in the lateral TF (aOR=1.12 [1.01,1.24]), meniscus damage (aOR=1.14 [1.05,1.25] in medial, 1.19 [1.04,1.35] in lateral) and synovitis/effusion (aOR= 1.13 [1.03,1.23]). However, higher total fat mass was associated only with lower odds of meniscus damage (aOR=0.96 [0.93, 0.99] in medial, 0.95 [0.90, 0.99] in lateral). Similarly in women, higher appendicular lean mass was associated with higher odds of BML in the medial TF (aOR=1.27 [1.13, 1.42]), cartilage damage in the medial TF and PF (aOR=1.12 [1.02, 1.23] and 1.12 [1.02, 1.24], respectively) and medial meniscus damage (aOR=1.20 [1.08, 1.33]). Higher total fat mass was associated only with higher odds of BML in the PF (aOR=1.03 [1.00, 1.06]). Only in women, higher abdominal SAT was associated with higher odds of BML in all compartments (aOR=1.35 [1.14, 1.60] in the medial TF, 1.25 [1.02, 1.54] in the lateral TF, and 1.30 [1.11, 1.52] in the PF) and cartilage damage in the PF (aOR=1.27 [1.07, 1.51]). These associations were not explained by inflammatory markers, adipokines, insulin resistance, lipids or cardiometabolic diseases. In men, higher VAT was associated with lower odds of MRI outcomes (BML in the lateral TF: aOR=0.52 [0.32, 0.86]; cartilage damage: aOR=0.54 [0.36, 0.80] in the lateral TF, 0.71 [0.51, 0.99] in the PF; lateral meniscus damage: aOR=0.56 [0.34, 0.91]). In women, no association was found between VAT and MRI outcomes.

The significant associations between knee MRI outcomes and lean mass rather than total fat mass, the lack of positive associations with VAT, and the absence of mediation by inflammatory and cardiometabolic factors suggest the importance of overall higher weight as a mechanical factor rather than general or central adiposity for knee tissue degeneration.

3.1 INTRODUCTION

Osteoarthritis of the knee (knee OA) is a common joint disorder among older adults. In the United States, 9 million adults were estimated to have symptomatic knee OA in 2005 [13]. Consequences of symptomatic knee OA include pain, functional limitation and disability [1]. Knee OA is one of the major contributors to physical limitations in the US among chronic diseases [16]. Because obesity is a risk factor for knee OA, the burden of knee OA is expected to increase in aging populations with high prevalence of obesity. However, currently, no approved disease modifying osteoarthritic OA drugs (DMOADs) exist which reverse degenerative changes in the knee or delays progression of the disease.

Obesity is one of the few modifiable risk factors for knee OA [4]. Both mechanical (higher joint load) and metabolic mechanisms due to obesity have been assumed. The recent literature has reported the association between metabolic syndrome or components of it and incidence of knee OA or structural changes in the knee [5,166,168]. However, it is not established whether a mechanical or metabolic mechanism is more important for the development of knee OA.

Central adiposity is associated with an increased risk of cardiovascular disease and cardiovascular disease mortality [8,9], whereas gluteofemoral adipose tissue may not be associated with an increased risk of cardiovascular disease and metabolic risk [11,12]. Women have more subcutaneous adipose tissue (SAT) in abdominal and gluteofemoral areas than men, and men have higher visceral adipose tissue (VAT) than women [138]. If central adipose tissues such as VAT are more related with knee OA than peripheral adipose tissue, it would suggest the importance of the metabolic mechanism. However, the association between fat distribution and risk of knee OA is not well-established. Previous studies reported that waist circumference and waist-to-hip ratio were associated with a higher prevalence of radiographic knee OA and a higher risk of total knee replacement [181,182,193]. However, studies which assessed central adiposity using imaging in the context of knee OA are few and inconclusive. Whether VAT and/or abdominal SAT are associated with structural changes in the knee has not been reported. If the metabolic mechanism is more or equally important as the mechanical mechanism, the targets for knee OA prevention could include an increased focus on the control of metabolic risk factors in addition to weight control.

The aim of this cross-sectional study was to examine whether 1) total fat mass and appendicular lean mass, 2) abdominal SAT, and 3) VAT are associated with MRI-assessed structural changes in the knees of community-dwelling older adults.

3.2 METHODS

3.2.1 Participants

Subjects were a subsample of the participants in the Health, Aging and Body Composition (Health ABC) Study. Health ABC study is a prospective cohort study of 3,075 well-functioning black and white men and women who were 70-79 years old at baseline (1997/98). Participants were recruited by mail from specified zip codes surrounding Memphis, TN and Pittsburgh, PA, followed by a telephone eligibility screen. Whites were recruited from a random sample of Medicare beneficiaries, and blacks were recruited from Medicare beneficiaries and all age-eligible residents in these areas. Eligibility criteria were no self-reported difficulty walking a quarter mile or climbing up 10 steps, no difficulty performing basic activities of daily living and no use of a cane, walker, crutches or other walking aids. Exclusion criteria were having active treatment for cancer in the prior three years, enrolling in a lifestyle intervention, and planning to move out of the areas within three years. All participants provided a written informed consent, and the institutional review boards in both sites approved the study.

At the 1998/99 visit participants were asked about their knee symptoms. Knee pain was defined as having pain, aching or stiffness in or around either knee on most days for at least one month in the past 12 months or on most days in the past 30 days or having at least moderate knee pain during the activities in the modified Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain questionnaire in the past 30 days. The pertinent activities were: walking on a flat surface, going up or down stairs, at night while in bed, standing upright, getting in or out of a chair, and getting in or out of a car. At the 1998/99 visit, 979 participants (32%) reported pain in one or both knees, and 1,991 participants (65%) reported no pain (32 participants had died by 1998/99, and knee pain information was missing in 73 participants) (Figure 4). All participants with pain in one or both knees (cases) and a gender-race stratified proportionate subsample of participants who did not report knee pain (controls) were invited to the knee OA substudy. Of them, 640 cases and 505 controls underwent baseline knee MRI at the 1998/99 or 1999/00 visit. MRI images of both knees were obtained in most participants. However, not all of these images were read (Figure 4). Participants with available MRI assessment data were included in this analysis (n = 965 participants, 1,578 knees). Of these participants, 61 participants were excluded due to missing information on adiposity measures, with a few more omitted due to missing data on important risk-factors for knee OA and/or body composition: (knee injury (n=17), knee pain (1), education, smoking or time watching TV (9), alcohol drinking (6), NSAID use (5), total n = 38), leaving 866 participants (1,413 knees).

3.2.2 Body Composition and Central Adiposity

Body composition was assessed using whole body DXA (Hologic QDR 4500) at the 1997/98 visit. Total body fat mass and fat-free mass were measured. Total lean mass was obtained by subtracting bone mineral content from fat-free mass.

Abdominal computerized tomography (CT) scans were obtained at the 1997/98 visit using GE 9800 Advantage (General Electric, Milwaukee, WI) at Pittsburgh site and Siemens Somatom Plus 4 (Siemens, Erlangen, Germany) or Picker PQ 2000S (Marconi Medical Systems, Cleveland, OH) at Memphis site. A single, 10 mm thickness axial image (140kVp, 300-360mAs) was obtained at the level of disc space between the fourth and fifth lumber vertebrae (L4-L5). Areas were calculated by multiplying the number of pixels of a given tissue type by the pixel area. Tissue type was determined based on the histogram of the distribution of CT numbers in fat tissues and muscles [219]. CT numbers were defined on a Hounsfield Unit (HU) scale. VAT area was separated from abdominal SAT by manually drawing a line through the abdominal muscles or the fascial plane that separates the two fat compartments.

3.2.3 Knee MRI

Knee MRI images were obtained at the 1998/99 or 1999/00 visit using a Sigma GE 1.5T system with a standard unilateral, commercial circumferential knee coil. MRIs were acquired using a coronal T-2 weighted fast spin-echo (FSE) (repetition time (TR) 3,500 msec, echo time (TE) 60 msec, slice thickness 4.0 mm, interslice gap 0.5 mm, excitation 2, Field of View (FOV)140 mm, matrix 256 × 256 pixels), a sagittal T2-weighted FSE, including the entire synovial cavity with frequency-selective fat suppression (TR 4,127 msec, TE 60 msec, interslice gap 0.5 mm, excitation 2, FOV 140 mm, matrix 256 × 256 pixels), and a axial T2-weighted FSE localizer (TR 2,500 msec, TE 60 msec, interslice gap 1mm, excitation 1, FOV 120mm, matrix 256 × 128 pixels). Contraindications for knee MRI were not fitting in the MRI bore or knee coil, cardiac pacemaker, aneurysm clips, metallic fragments in the eyes, vascular clips less than 2 months old, cardiac valve prosthesis, cochlear implants, total knee replacement, and claustrophobia.

Knee MRI images were read by one of five trained radiologists, who was blinded to the adiposity measures. Structural changes in the knee were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) [37]. Specifically, 14 subregions (anterior, central, and posterior of the medial/lateral femoral condyles/tibial plateaus and medial/lateral subregions of the patella) were each scored separately for cartilage lesions, osteophytes, subarticular bone marrow lesions, bone cysts, and bone attrition. Bone marrow lesions (BMLs) in each subregion were graded as 0 = none, 1 = <25% of the region, 2 = 25-50% of the region and 3 = >50% of the region. Cartilage damage was graded as 0 = normal thickness and signal, 1 = abnormal signal only, 2 = solitary focal defect, 3 = areas of partial-thickness loss with areas of preserved thickness, 4 = diffuse (>75%) partial-thickness loss, 5 = areas of full thickness loss with areas of partial-thickness loss, and 6 = diffuse (>75%) full-thickness loss. Meniscus morphology and tear in the anterior horn, body, and posterior horn was graded as 0 = intact, 1 = minor radial or parrot break tear, 2 = non-displaced tear or prior surgical repair, 3 = displaced tear, partial maceration or partial resection, and 4 = complete maceration and destruction or complete resection. Synovitis/effusion was graded as 0 = none, 1 = <33% of maximum distension, 2 = 33-66% of maximum distension, and 3 = >66% of distension.

3.2.4 Covariates

Information on age, sex, race, education (less than high school, high school graduate, post-secondary), smoking status (never, former, current), alcohol intake per week in the past 12 months, physician diagnosis of prevalent diseases, history of knee injury, and knee pain in each knee were collected through a standardized questionnaire at baseline. The knee pain questionnaire at the 1997/98 baseline was slightly different from that used in 1998/99 for selection into the knee-OA substudy. Pain in the index knee at baseline was defined as having pain lasting at least one month in the past 12 months, having at least moderate pain during the activities in the modified WOMAC pain questionnaire in the past 30 days, or having pain, aching or stiffness on most days of the past 30 days. Physical activity and exercise in the past 12 months and past 7 days were also assessed through an interviewer-administered questionnaire which was modified specifically for Health ABC based on physical activity assessments from the Minnesota Leisure Time Physical Activity Questionnaire [104]. Frequency and time spent for a specific activity were asked, which included gardening or yard work, daily household chores, grocery shopping, walking, stair climbing, moderate and high-intensity exercise activities, work, and care giving. Time spent for each activity in past 7 days was multiplied by approximate metabolic equivalent units (MET) and body weight to calculate the total energy expenditure for physical activity (kcal/week). Hours spent watching TV per week (Zero, 1-6 hrs, 7-13 hrs, 14-20 hrs, ≥21hrs/week) were also self-reported.

Anthropometric measurements were made by trained technicians. Body weight was measured to the nearest 0.1 kg using a standard balance beam scale. Height was measured to the nearest millimeter using a wall-mounted stadiometer. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Abdominal circumference was measured at the level of largest circumference between the lower rib and the iliac crest using a flexible inelastic fiberglass tape. The measurement was taken at the end of a normal expiration to the nearest 0.1 cm. Blood pressure was measured by the trained staff using a mercury sphygmomanometer after five minutes rest.

The participants were asked to bring all prescription and nonprescription medications used in the preceding two weeks with them to the baseline visit. Trained clinic staff reviewed all medications and transcribed the name and current dose from the container. Baseline nonsteroidal anti-inflammatory drug (NSAIDs) use was determined.

Prevalent hypertension was defined as self-report of a physician diagnosis combined with hypertension medication use. Prevalent diabetes was defined as self-report of a physician diagnosis of diabetes, use of diabetic medication or fasting serum glucose of ≥126 mg/dL [214]. Metabolic syndrome was defined as meeting at least three of the following criteria: abdominal circumference (>102 cm for men, >88 cm for women), blood pressure (blood pressure ≥130/85 mmHg or antihypertensive medication), high glucose (glucose ≥110 mg/dL or antidiabetic medication), low HDL (HDL <40 mg/dL for men, <50 mg/dL for women), and high triglyceride (triglyceride ≥150 mg/dL) (adapted from Ford et al.[215]).

Blood samples were obtained after an overnight fast, and after processing, biospecimens were stored at -70 ˚C until assayed. Inflammatory markers (C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6)), adipokines (leptin, adiponectin), fasting serum glucose, fasting serum insulin, lipids (fasting plasma total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG)) were measured in the Health ABC core laboratory at the University of Vermont. Serum CRP was measured by a colorimetric competitive enzyme-linked immunosorbent Assay (ELISA) based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). Plasma TNF-α and serum IL-6 were measured by the quantitative sandwich enzyme immune assay technique using Quantikine® HS kit (R&D Systems Inc., Minneapolis, MN). Serum leptin was measured by a competitive radioimmunoassay (RIA) using the Sensitive Human Leptin RIA kit (Linco Research, Inc., St. Charles, MO). Adiponectin was measured by the double antibody/PEG technique using the Millipore radioimmune assay (Linco Research). Fasting serum glucose was measured using the automated glucose oxidase method (VITROS system, Ortho-Clinical Diagnostics, Inc., Rochester, NY). Fasting serum insulin was measured using a microparticle enzyme immunoassay (MEIA) on the Abbot IMx[TX] (Abbott Laboratories Diagnostics Division, South Pasadena, CA). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as glucose × insulin / 405 [220]. Fasting plasma total cholesterol, HDL and triglycerides were measured by the enzymatic method using a commercially available analyzer (VITROS system). LDL was calculated by the Friedwald equation [221].

3.2.5 Statistical Analysis

Descriptive statistics for characteristics of the participants were calculated by total fat mass quartile groups and compared by chi-square tests and logistic regression for categorical variables and Kruskal-Wallis tests and linear regression for continuous variables.

The associations between baseline body composition/adiposity measures and knee MRI outcomes one to two years later were examined using logistic regression models. The analysis was conducted at the knee level. Correlation between right and left knees within a subject was taken into account by using generalized estimating equations (GEE).

The following knee MRI outcomes were examined in separate regression models. Bone marrow lesions and cartilage damage were examined by compartment (medial tibiofemoral joint (TF) joint, lateral TF joint, and patellofemoral (PF) joint and in the whole knee. Any BML in each compartment or in the whole knee was defined as the worst WORMS grade of ≥1 (5 subregions for the medial TF, 5 subregions for the lateral TF, 4 subregions for the PF and 14 subregions in the whole knee). Severe BML were defined as the worst grade of ≥2 [42]. Any cartilage damage was defined as the worst WORMS grade of ≥ 2, and severe cartilage damage as the worst grade of ≥5. Any medial and lateral meniscus damage were defined as meniscus summary score of ≥1. Severe meniscus damage was defined as the worst grade in the medial or lateral meniscus of ≥3. Any synovitis/effusion was defined as synovitis/effusion grade of ≥1, and severe synovitis/effusion as ≥2.

The baseline body composition/adiposity measures examined were total fat mass (kg), appendicular lean mass (kg), abdominal SAT area (cm^2) and VAT area (cm^2). The distributions of these adiposity measures were approximately normal. The correlations between these variables were examined using Pearson correlation coefficients. Total fat mass and appendicular lean mass were entered simultaneously in the same regression models as if decomposing total mass into fat and lean. Correlations between total fat mass and appendicular lean mass was moderate (r = 0.43 in men, r = 0.69 in women, both p<0.001). SAT and VAT were examined in the separated regression models. Because body weight was substantially correlated with SAT and VAT (r = 0.78 in men, r = 0.84 in women, both p<0.001 between weight and SAT, r = 0.61 in men, r = 0.60 in women, both p<0.001 between weight and VAT), adjustment for body weight could cause multicollinearity problems. To address this, SAT and VAT were divided by body weight (cm^2/kg) to transform them into measures relative to body weight. Initially, these adiposity measures were categorized into quintiles to examine potential curvilinear associations with knee MRI outcomes. Quadratic terms of these variables were also tested for curvilinear associations. Since no obvious curvilinear associations were found, adiposity measures were treated as continuous variables.

Due to sex differences in body composition/fat distribution and risk of knee OA, all analyses were stratified by sex. In multiple models, height, age (continuous), race, study site, history of knee injury (unknown/not sure was treated as no injury), knee pain in the index knee at baseline (yes/no), education, smoking status, alcohol consumption, total physical activity (sex-specific quartiles), time spent watching TV, and NSAIDs use at baseline were adjusted as covariates. Alcohol consumption in a typical week in the past 12 months was categorized as none, 1-7/week, and >7/week for men, and none, <1/week, and ≥1week for women. Due to the low frequency, zero/week and 1-6 hrs/week categories were combined for time watching TV. Multicollinearity problems were not detected based on each model's largest condition index and variance of decomposition proportions (VDPs). Odds ratios (OR) for each outcome per 1 kg increase in total fat mass or appendicular lean mass and OR per 1 unit increase (cm^2/kg) in SAT or VAT were reported.

Attenuation effects by inflammation markers, serum adipokines, fasting glucose, fasting serum insulin, insulin resistance (HOMA), cardiometabolic diseases (hypertension, diabetes, and metabolic syndrome) and plasma lipids were examined for significant positive associations between adiposity measures and knee MRI outcomes by adding each of these measures separately into the fully adjusted models. Over 10% change in the point estimate of OR was considered as meaningful mediation.

All analyses were conducted using SAS 9.4 (SAS Institute Inc. Cary, NC). All p-values were two-sided, and p-values of less than 0.05 were considered as statistically significant. The significant α level was not corrected by the number of the outcomes.

3.3 RESULTS

The mean age of the participants was 73.5 ± 2.9 years, 60.6% were women and 45.5% were blacks. About 20% of men and 30% of women were obese. In the comparison of total fat mass quartile groups in men, the prevalence of metabolic syndrome and knee pain was significantly higher and that of hypertension tended to be higher in men with higher total fat mass (Table 17). In women, those in the higher total fat mass quartile groups were more likely to be black, have higher total physical activity, spent more hours watching TV, and have knee pain, hypertension, diabetes and metabolic syndrome than lower quartile groups (Table 18). There was a trend that women with higher total fat mass were more likely to use NSAIDs.

Mean total fat mass (kg) was higher in women (29.2 ± 8.7 in women vs. 24.2 ± 7.3 in men, $p<0.001$), whereas mean appendicular lean mass (kg) was higher in men (24.2 ± 3.6 in men vs. 16.7 ± 3.0 in women, $p<0.001$). Abdominal SAT area (cm^2) was higher in women (344.5 ± 126.2 in women vs. 226.2 ± 85.5 in men, $p<0.001$), whereas VAT area was higher in men (155.1 ± 73.9 in men vs. 130.2 ± 58.6 in women, $p<0.001$).

The frequencies of knee outcomes are shown in table 19. Structural changes in the knee were prevalent. Especially, BML in the PF joint (41-45%), cartilage damage in the PF joint (67-75%) and synovitis/effusion (64-72%) were common. The prevalence of severe cartilage damage in the medial TF joint was 26% in men and 19% in women.

Total fat mass and appendicular lean mass

The associations between total fat mass, appendicular lean mass, and knee MRI outcomes are shown in table 20 and 21. In men higher appendicular lean mass was associated with significantly higher odds of any BML in the lateral TF (aOR=1.16 [1.04, 1.29]), any BML in the PF (aOR=1.13 [1.04, 1.22]), any BML in the whole knee (aOR=1.15 [1.05,1.26]), any cartilage damage in the lateral TF (aOR=1.12 [1.01,1.24]), any cartilage damage in the whole knee (aOR=1.18 [1.04,1.33]), medial meniscus damages (aOR=1.14 [1.05,1.25]), lateral meniscus damage (aOR=1.19 [1.04,1.35]) and any synovitis/effusion (aOR= 1.13 [1.03,1.23]) in the adjusted models (Table 20). Contrarily, higher total fat mass was associated only with lower odds of any medial meniscus damage (aOR=0.96 [0.93, 0.99]) and lateral meniscus damage (aOR=0.95 [0.90, 0.99]). Higher appendicular lean mass was also associated with higher odds of severe BML (aOR=1.23 [1.09, 1.40] in the PF and aOR=1.13 [1.03, 1.23] in the whole knee), severe cartilage damage (aOR= 1.11 [1.02, 1.22] in the PF and aOR=1.10 [1.01,1.20] in the whole knee), severe meniscus damages (aOR=1.10 [1.01,1.20] in medial and aOR=1.23 [1.03,1.46] in lateral) and severe synovitis/effusion (aOR=1.18 [1.06,1.31]), but total fat mass was not associated with any of the severe damages.

Similarly in women, higher appendicular lean mass was associated with higher odds of any BML in the medial TF (aOR=1.27 [1.13, 1.42]), any BML in the whole knee (aOR=1.16 [1.05, 1.28]), any cartilage damage in the medial TF (aOR=1.12 [1.02, 1.23]), any cartilage damage in the PF (aOR=1.12 [1.02, 1.24]) and any medial meniscus damage (aOR=1.20 [1.08, 1.33]) (Table 21). Higher total fat mass was associated only with higher odds of BML in the PF (aOR=1.03 [1.00, 1.06]) and in the whole knee (aOR=1.04 [1.01, 1.07]). The point estimates for any BML in the whole knee were smaller for fat mass than appendicular lean mass. Higher appendicular lean mass was associated with higher odds of severe BML (aOR=1.36 [1.17,1.58] in the medial TF and aOR=1.13 [1.02,1.26] in the whole knee), severe cartilage damage (aOR=1.27 [1.12,1.43] in the medial TF and aOR= 1.16 [1.05,1.28] in the whole knee), severe meniscus damage (aOR=1.22 [1.08,1.37] in medial and aOR=1.16 [1.01,1.32] in lateral) and severe synovitis effusion (aOR=1.18 [1.06,1.32]), but total fat mass was not associated with any of the severe damage.

Abdominal SAT

In men, no association was found between abdominal SAT area per body weight and the knee outcomes except that higher abdominal SAT was associated with lower odds of cartilage damage in the medial TF (aOR=0.75 [0.56, 0.98]). In women, higher abdominal SAT was associated with higher odds of any BML in all compartments (aOR=1.35 [1.14,1.60] in the medial TF, aOR=1.25 [1.02,1.54] in the lateral TF, aOR=1.30 [1.11,1.52] in the PF, and aOR=1.45 [1.23,1.70] in the whole knee), any cartilage damage in the PF (aOR=1.27 [1.07,1.51]), severe BML in the whole knee (aOR=1.19 [1.00,1.41]), severe cartilage damage in the whole knee (aOR=1.22 [1.04,1.43]) and severe medial meniscus damage (aOR=1.37 [1.07,1.74]) (Table 22).

VAT

In men, higher VAT was associated with lower odds of any BML in the lateral TF (aOR=0.52 [0.32, 0.86]), any cartilage damage in the lateral TF (aOR=0.54 [0.36, 0.80]), any cartilage damage in the PF (aOR=0.71 [0.51, 0.99]), and any lateral meniscus damage (aOR=0.56 [0.34, 0.91]) (Table 23). VAT was not associated with severe structural changes in men. No association was found between VAT and any knee MRI outcomes in women.

Mediation analysis

The positive associations between abdominal SAT and knee outcomes (BML, cartilage damage, and meniscus damage) found only in women were not attenuated by the inflammation markers (CRP, TNF-α, IL-6), adipokines (leptin and adiponectin), fasting glucose, fasting serum insulin, HOMA IR, cardiometabolic diseases (hypertension, diabetes, and metabolic syndrome) or lipids (total cholesterol, LDL, HDL, and triglyceride) overall. Although positive associations for any BML in the lateral TF and for severe BML in the whole knee became non-significant with adjustment for some potential mediators, point estimates did not change over 10%.

3.4 DISCUSSION

This is the first study that reports the associations of structural changes in the knee with VAT and abdominal SAT, which were assessed using CT. Appendicular lean mass rather than total fat mass was associated with higher prevalence of MRI-assessed structural changes in the knee such as BML, cartilage damage, meniscus damage and synovitis/effusion in community-dwelling well-functioning older adults. Significant associations were found between higher abdominal SAT and higher odds of BML, cartilage damage in the PF and severe medial meniscus damage only in women. However, these associations were not explained by factors known to be related to metabolic mechanisms. Higher VAT was not associated with higher odds of structural changes in the knees in either men or women.

The previous studies that examined body composition and radiographic knee OA reported that both higher fat mass and higher lean mass were associated with higher risk of knee OA when they were entered in the same regression models as in the current study [183,184]. Sowers et al. reported that both fat mass and lean mass were associated with higher odds of radiographic knee OA in middle-aged women in the Michigan Bone Health study [183]. Similarly, Blumenfeld et al. reported that higher fat mass in the lower limbs and higher lean mass in the lower limbs were associated with higher odds of radiographic knee OA in the middle-aged participants in the Chingford Study [184]. In the studies that examined fat mass and lean mass simultaneously in relation to MRI-assessed structural changes in the knee, the results have been inconsistent. Wang et al. reported that higher fat mass but not fat-free mass was associated with higher odds of cartilage defects in the tibia or femur in the middle-aged and older participants in the Melbourne Collaborative Cohort study [188]. In the recent large cross-sectional study by Visser et al., structural knee OA was defined based on the several MRI-assessed structural changes in the knee in people who were 45-65 years old. Both higher fat mass and lean mass examined in the same regression models were associated with higher odds of structural knee OA, although significance was marginal for fat mass in men and lean mass in women [190]. In the current study, higher lean mass rather than fat mass was associated with prevalent structural changes. The study population in the current study was older than the abovementioned studies, and the definitions of the outcomes were different from those in the study by Visser et al., which used a composite outcome comprising several structural changes. Therefore, the results may not be compared directly with those of the previous studies. However, the current study would support the previous studies in that higher lean mass is associated with higher odds of degenerative changes in the knee joint.

It should not be concluded that lean mass is harmful to the knee joint solely based on the results of the regression models that included fat mass and lean mass simultaneously. In the above study by Visser et al. when percentage lean mass was examined by itself, a higher percentage of lean mass was associated with lower odds of structural OA in women [152]. In addition, when fat mass to lean mass ratio was examined, a higher ratio was associated with higher odds of skeletal OA in women. In the regression models that included total body fat mass and appendicular lean mass, body weight was not adjusted due to its strong correlation with total body fat mass and with appendicular lean mass. Thus, the associations between appendicular lean mass and structural knee outcomes are not independent of the effect of weight of lean mass or fat mass. The current study did not find evidence that fat mass is more strongly associated with worse knee outcomes than lean mass. The results suggest the importance of weight as a mechanical factor rather than adiposity or metabolic mechanisms for knee tissue degeneration. The reason why the associations were significant in appendicular lean mass rather than total body fat mass is unknown. One of the possible explanations would be residual confounding by past physical activity.

Abdominal SAT was associated with worse knee structural outcomes in women, but not in men. VAT per body weight was not associated with higher prevalence of structural changes in the knee in the current study. Rather, higher VAT was associated with reduced odds of BML, cartilage damage and meniscus damage, especially in the lateral compartment in men. These results would suggest different mechanisms between knee OA and cardiometabolic disease. Both VAT and abdominal SAT are associated with cardiometabolic risk factors [10]. However, VAT had stronger associations than abdominal SAT in the Framingham Heart Study [10]. Moreover, in obese individuals, whereas the prevalence of hypertension, impaired fasting glucose, and metabolic syndrome increased as VAT increased [10], an analogous trend was not found corresponding to increased abdominal SAT [222]. Blumenfeld et al. reported that higher abdominal fat mass was associated with lower odds of radiographic knee OA adjusted for lower limb fat mass and lean mass simultaneously [184]. This study and the current study may suggest that given the association between higher body weight and higher odds of knee OA or structural changes, other components of total body mass than abdominal fat or VAT are relatively more important. SAT secretes a higher level of leptin compared with VAT [223], and the previous studies reported the association between higher serum leptin levels and worse knee outcomes [175,176]. In the current study, positive associations between abdominal SAT and BML or other outcomes were not attenuated by serum leptin, adiponectin, inflammatory markers, insulin resistance, cardiometabolic diseases or lipid profile. This would suggest that the associations between higher SAT and knee MRI outcomes are attributed to the other mechanisms such as the weight of SAT rather than adipokines or metabolic mechanisms. This result and the lack of positive associations between VAT and knee outcomes would further support the importance of higher body weight as a mechanical factor rather than metabolic mechanisms.

The results for SAT and VAT were different between men and women. Sex differences in associations between metabolic risk factors and knee OA participants in the NHANES III have been reported, although the reason for the sex-related differences is unknown [137]. In the current study, the prevalence of obesity was 20% in men and 30% in women. In addition, higher weight or higher BMI was associated with knee structural outcomes more consistently in women than in men. Therefore, the results for SAT and VAT may not be comparable between men and women in this study.

This is the first study that reports the associations of structural changes in the knee with VAT and abdominal SAT assessed using CT. Covariates such as race, education, smoking, alcohol consumption, physical activity, sedentary time, knee injury, knee pain, and NSAIDs use were adjusted for. However, a few limitations exist in this study. The design of the current study was cross-sectional. Because it would have taken several years for the development of knee OA, body composition before participants were recruited into the study could be more predictive of prevalent structural changes in the knee measured during the second and third year of the study. Abdominal superficial SAT and deep SAT, which are separated by a fascial plane, have morphological differences [224], but they were not separated in the current study. Future studies are needed to determine whether deep and superficial SAT are differently associated with structural changes in the knee. Participants were relatively well-functioning at the recruitment. Thus, older adults with knee pain or knee OA may have been underrepresented. Consequently, the results may not be generalizable to less well-functioning populations. If a participant had a joint replacement surgery in either knee by the 2nd year of the study, that knee was not examined with MRI. Therefore, survivor bias would be possible. In addition, only a subgroup of the participants were invited to the knee OA substudy based on their knee pain status, and participants with knee pain were overrepresented in this sample. The controls were sampled proportionately in race-gender strata to better represent the subset of the full cohort without knee pain. Odds-ratios are generally more robust when using this type of sampling design. Nevertheless, some selection bias would be possible. Many outcomes were examined, but the α-level for statistical significance was kept at 0.05 and was not corrected. Thus, type I error is possible. Higher thigh muscle attenuation, which reflects lower muscle fat infiltration, was associated with higher muscle strength in older adults [152]. Thus, future studies are needed to examine the role of muscle fat infiltration in the positive association between lean mass and structural changes in the knee.

In conclusion, significant associations between structural changes in the knee and lean mass rather than fat mass, the lack of positive association with VAT, and the absence of mediation by inflammatory and cardiometabolic factors suggest the importance of weight as a mechanical factor rather than general or central adiposity for degenerative changes in the knee. Future studies are needed to examine the longitudinal associations between adiposity and structural changes in the knee as well as the role of muscle quality on the associations between lean mass and these outcomes.

3.5 FIGURE AND TABLES

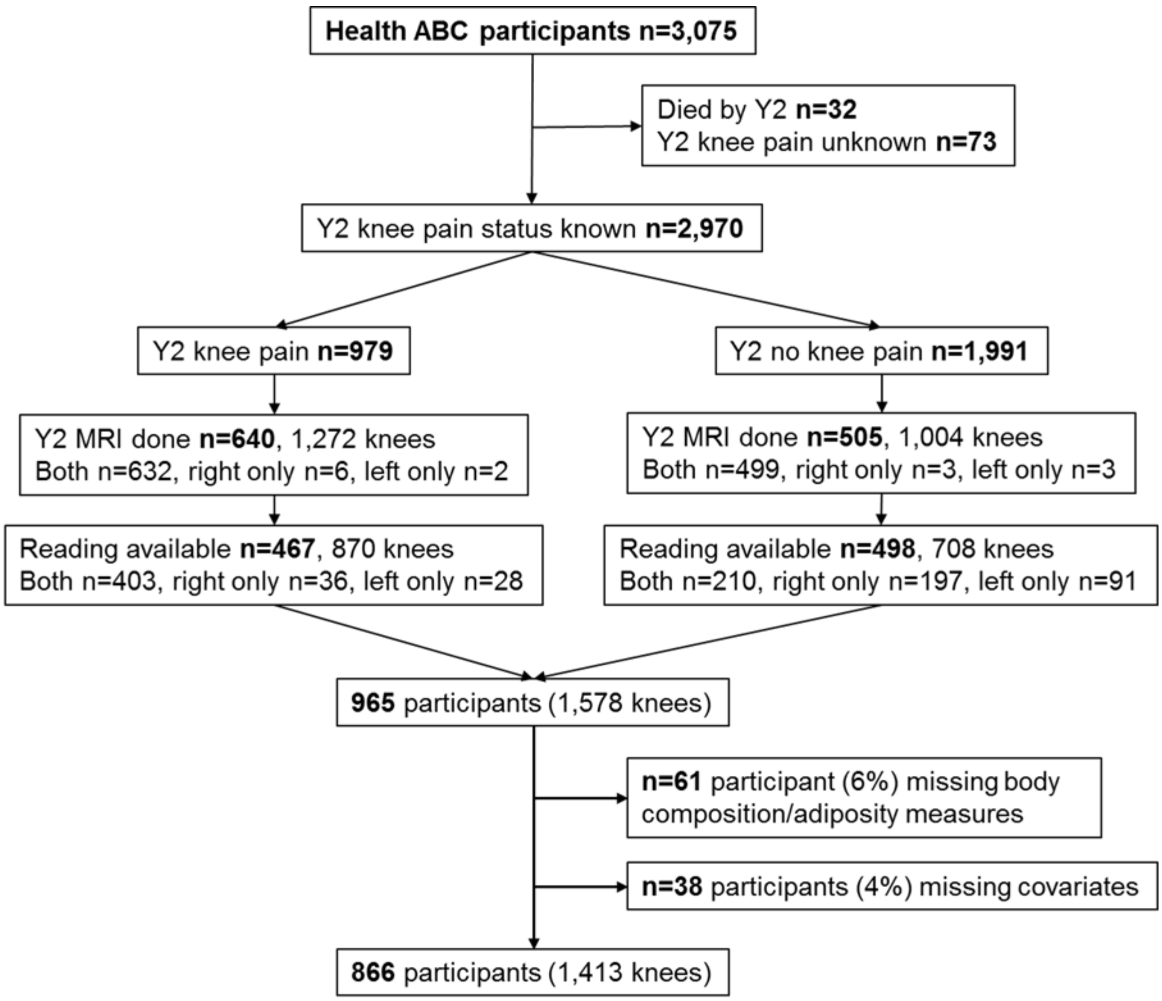

Figure 4. Flow Chart of the Participants

Table 17. **Characteristics of the Participants by Fat Mass Quartiles, Men (n = 341)**

Variables	**Q1 (n=85)**	**Q2 (n=86)**	**Q3 (n=85)**	**Q4 (n=85)**		
mean total fat mass (SD)	**16 (2.7)**	**21 (1.2)**	**25.5 (1.7)**	**34.1 (4.6)**	**p-value**	**p trend†**
Age, mean (SD)	73.3 (2.9)	73.2 (2.7)	73.8 (2.9)	73.5 (2.6)	0.511	0.401
Black, n (%)	43 (50.6)	37 (43)	34 (40)	30 (35.3)	0.23	0.042
Site, n (%)					0.262	0.678
Memphis	37 (43.5)	48 (55.8)	36 (42.4)	38 (44.7)		
Pittsburgh	48 (56.5)	38 (44.2)	49 (57.7)	47 (55.3)		
Married, n (%) n=330	55 (66.3)	62 (73.8)	62 (75.6)	59 (72.8)	0.562	0.329
Education, n (%)					0.335	0.611
Less than High school	26 (30.6)	21 (24.4)	22 (25.9)	17 (20)		
High school graduate	20 (23.5)	21 (24.4)	27 (31.8)	23 (27.1)		
Postsecondary	39 (45.9)	44 (51.2)	36 (42.4)	45 (52.9)		
BMI (kg/m^2), mean (SD)	23.3 (2.5)	25.9 (1.7)	27.8 (2)	31.3 (2.8)	**<.0001**	**<.0001**
BMI category, n (%)					**<.0001**	**<.0001**
Under 25	62 (72.9)	27 (31.4)	2 (2.4)	0 (0)		
25 to 30	23 (27.1)	59 (68.6)	73 (85.9)	29 (34.1)		
30+	0 (0)	0 (0)	10 (11.8)	56 (65.9)		
Smoking status, n (%)					**0.002**	**0.03**
Never	26 (30.6)	29 (33.7)	33 (38.8)	18 (21.2)		
Current	18 (21.2)	4 (4.7)	6 (7.1)	8 (9.4)		
Former	41 (48.2)	53 (61.6)	46 (54.1)	59 (69.4)		
Drinking per week, n (%)					0.847	
None	34 (40)	36 (41.9)	39 (45.9)	29 (34.1)		
1-7/week	41 (48.2)	39 (45.4)	36 (42.4)	45 (52.9)		
8+ /week	10 (11.8)	11 (12.8)	10 (11.8)	11 (12.9)		
Total activity (kcal/wk), mean (SD)	6040.9 (4608.7)	6649.7 (4385)	7264.1 (6476.5)	6900.1 (5586.4)	0.595	0.217
TV watching, n (%)					0.505	
0-6 hrs/week	16 (18.8)	11 (12.8)	11 (12.9)	12 (14.1)		
7-13 hrs/week	19 (22.4)	32 (37.2)	23 (27.1)	18 (21.2)		
14-20 hrs/week	23 (27.1)	18 (20.9)	22 (25.9)	24 (28.2)		
≥21hrs/week	27 (31.8)	25 (29.1)	29 (34.1)	31 (36.5)		

Table 17 Continued

Variables	Q1 (n=85)	Q2 (n=86)	Q3 (n=85)	Q4 (n=85)	p-value	p trend†
History of knee injury, n (%)	7 (8.2)	11 (12.8)	8 (9.4)	12 (14.1)	0.577	0.352
Y1 knee pain, n (%)	18 (21.2)	17 (19.8)	20 (23.5)	29 (34.1)	0.121	0.043
Knee OA, n (%) n=338	4 (4.8)	5 (5.9)	8 (9.4)	9 (10.7)	0.417	0.104
Hypertension, n (%) n=340	24 (28.2)	32 (37.2)	33 (38.8)	36 (42.9)	0.244	0.053
CHD, n (%) n=336	14 (16.7)	15 (17.9)	14 (16.7)	24 (28.6)	0.153	0.078
Diabetes, n (%)	12 (14.1)	15 (17.4)	21 (24.7)	20 (23.5)	0.258	0.068
Metabolic syndrome, n (%) n=337	9 (10.7)	18 (21.7)	31 (36.5)	40 (47.1)	**<.0001**	**<.0001**
NSAID, n (%)	14 (16.5)	11 (12.8)	16 (18.8)	18 (21.2)	0.514	0.272
Statin, n (%)	5 (5.9)	10 (11.6)	12 (14.1)	9 (10.6)	0.36	0.268
CRP (ug/mL), mean (SD) n=337	2.23 (3.29)	2.7 (4.72)	2.16 (2.14)	2.64 (2.7)	**0.001**	0.682
TNFA (pg/mL), mean (SD) n=324	3.19 (1.54)	3.18 (1.03)	3.26 (1.25)	3.61 (1.3)	**0.037**	**0.035**
IL6 (pg/mL), mean (SD) n=329	2.69 (2.34)	2.05 (1.47)	2.23 (1.58)	2.48 (1.74)	0.293	0.61
Serum leptin (ng/mL), mean (SD) n=338	3.14 (3.22)	6.05 (3.55)	8.68 (4.59)	14.61 (11.49)	**<.0001**	**<.0001**
Serum adiponectin (ng/mL), mean (SD) n=338	10.3 (6.26)	8.24 (4.62)	9.02 (5.92)	8.06 (4.67)	0.086	0.026
Fasting serum glucose (mg/dL), mean (SD) n=336	94.7 (15.25)	105.81 (34.92)	111.06 (40.08)	108.61 (32.07)	**0.0004**	**0.003**
Fasting serum insulin (uIU/mL), mean (SD) n=301	5.11 (2.39)	7.33 (3.07)	8.11 (6.23)	10.58 (6.41)	**<.0001**	**<.0001**
HOMA IR, mean (SD) n=301	1.2 (0.64)	1.85 (0.87)	2.12 (1.69)	2.83 (2.13)	**<.0001**	**<.0001**
Total cholesterol (mg/dL), mean (SD) n=333	189.68 (32.54)	191.1 (30.67)	196.96 (33.59)	189.13 (30.59)	0.305	0.79
LDL (mg/dL), mean (SD) n=330	112.45 (31.09)	119.91 (27.02)	123.37 (31.87)	117.56 (30.2)	0.064	0.201
HDL (mg/dL), mean (SD) n=333	54.75 (16.94)	46.12 (12)	46.17 (12.1)	44.93 (12.39)	**<.0001**	**<.0001**
Triglycerides (mg/d), mean (SD) n=333	112.35 (49.51)	125.18 (61.02)	143.73 (78.83)	142.85 (77.87)	**0.001**	**0.001**

SD standard deviation, †p-value from logistic regression for categorical variables and linear regression for continuous variables
CHD coronary heart disease, HOMA-IR homeostatic model assessment of insulin resistance

Table 18. Characteristics of the Participants by Fat Mass Quartiles, Women (N = 525)

Variables	Q1 (n=132)	Q2 (n=136)	Q3 (n=132)	Q4 (n=125)		
mean total fat mass (SD)	18.8 (3.2)	26 (1.8)	31.8 (1.7)	41.1 (4.9)	p-value	p trend[‡]
Age, mean (SD)	74 (2.8)	73.4 (2.9)	73.5 (3)	73.2 (2.8)	0.152	0.065
Black, n (%)	39 (29.6)	58 (42.7)	68 (51.5)	85 (68)	**<.0001**	**<.0001**
Site, n (%)					0.147	0.071
Memphis	66 (50)	61 (44.9)	64 (48.5)	46 (36.8)		
Pittsburgh	66 (50)	75 (55.2)	68 (51.5)	79 (63.2)		
Married, n (%) n=483	39 (32.8)	51 (40.5)	51 (41.5)	41 (35.7)	0.459	0.62
Education, n (%)					0.144	0.019
Less than High school	23 (17.4)	22 (16.2)	30 (22.7)	30 (24)		
High school graduate	52 (39.4)	55 (40.4)	48 (36.4)	59 (47.2)		
Postsecondary	57 (43.2)	59 (43.4)	54 (40.9)	36 (28.8)		
BMI (kg/m^2), mean (SD)	22.1 (2.3)	26 (2.1)	28.9 (2.3)	34.4 (3.5)	**<.0001**	**<.0001**
BMI category, n (%)					**<.0001**	**<.0001**
Under 25	117 (88.6)	40 (29.4)	3 (2.3)	0 (0)		
25 to 30	15 (11.4)	91 (66.9)	96 (72.7)	9 (7.2)		
30+	0 (0)	5 (3.7)	33 (25)	116 (92.8)		
Smoking status, n (%)					**0.013**	**0.012**
Never	78 (59.1)	79 (58.1)	80 (60.6)	62 (49.6)		
Current	21 (15.9)	12 (8.8)	10 (7.6)	8 (6.4)		
Former	33 (25)	45 (33.1)	42 (31.8)	55 (44)		
Drinking per week, n (%)					0.128	
None	80 (60.6)	65 (47.8)	82 (62.1)	80 (64)		
<1 /week	22 (16.7)	35 (25.7)	26 (19.7)	22 (17.6)		
1+ /week	30 (22.7)	36 (26.5)	24 (18.2)	23 (18.4)		
Total activity (kcal/wk), mean (SD)	4412.1 (3893.5)	5728.7 (3988.8)	5980.4 (4040.9)	8042.9 (7256.3)	**<.0001**	**<.0001**
TV watching, n (%)					**0.003**	
0-6 hrs/week	34 (25.8)	18 (13.2)	19 (14.4)	12 (9.6)		
7-13 hrs/week	31 (23.5)	38 (27.9)	30 (22.7)	29 (23.2)		
14-20 hrs/week	26 (19.7)	26 (19.1)	38 (28.8)	20 (16)		
≥21hrs/week	41 (31.1)	54 (39.7)	45 (34.1)	64 (51.2)		

Table 18 Continued

Variables	Q1 (n=132)	Q2 (n=136)	Q3 (n=132)	Q4 (n=125)	p-value	p trend[‡]
History of knee injury, n (%)	14 (10.6)	21 (15.4)	19 (14.4)	17 (13.6)	0.688	0.55
Y1 knee pain, n (%)	30 (22.7)	36 (26.5)	52 (39.4)	55 (44)	**0.0004**	**<.0001**
Knee OA, n (%)	14 (10.7)	16 (11.9)	22 (16.7)	24 (19.5)	0.154	0.026
Hypertension, n (%) n=519	41 (31.1)	60 (44.4)	67 (51.2)	73 (60.3)	**<.0001**	**<.0001**
CHD, n (%) n=506	20 (15.6)	15 (11.4)	7 (5.5)	14 (11.9)	0.076	0.156
Diabetes, n (%)	7 (5.3)	14 (10.3)	27 (20.5)	21 (16.8)	**0.001**	**0.001**
Metabolic syndrome, n (%) n=521	19 (14.6)	52 (38.5)	60 (45.5)	66 (53.2)	**<.0001**	**<.0001**
NSAID, n (%)	31 (23.5)	34 (25)	41 (31.1)	45 (36)	0.099	0.015
Statin, n (%)	17 (12.9)	19 (14)	20 (15.2)	13 (10.4)	0.71	0.653
CRP (ug/mL), mean (SD) n=521	2.06 (2.7)	2.77 (4.8)	3.49 (4.55)	4.27 (4.48)	**<.0001**	**<.0001**
TNF-α (pg/mL), mean (SD) n=480	3.18 (1.75)	3.27 (1.41)	3.26 (1.26)	3.49 (1.42)	**0.047**	0.124
IL-6 (pg/mL), mean (SD) n=504	2.01 (1.85)	2.13 (2.07)	2.58 (2.43)	2.97 (2.46)	**<.0001**	**0.0002**
Serum leptin (ng/mL), mean (SD) n=519	9.85 (7.87)	18.41 (9.43)	24.95 (11.59)	33.75 (14.89)	**<.0001**	**<.0001**
Serum adiponectin (ng/mL), mean (SD) n=523	17.06 (8.43)	13.29 (6.85)	11.67 (6.48)	10.38 (5.59)	**<.0001**	**<.0001**
Fasting serum glucose (mg/dL), mean (SD) n=509	90.87 (19.54)	96.06 (21.81)	105.56 (34.75)	105.66 (30.25)	**<.0001**	**<.0001**
Fasting serum insulin (uIU/mL), mean (SD) n=469	5.67 (3.22)	8 (5.53)	9.22 (6.36)	11.58 (6.7)	**<.0001**	**<.0001**
HOMA IR, mean (SD) n=469	1.26 (0.8)	1.84 (1.36)	2.34 (2.06)	2.92 (2.01)	**<.0001**	**<.0001**
Total cholesterol (mg/dL), mean (SD) n=507	212.19 (36.13)	216.85 (42.4)	215.55 (41.44)	217.44 (38.29)	0.738	0.363
LDL (mg/dL), mean (SD) n=499	122.13 (34.57)	125.42 (37.54)	126.91 (38.12)	132.81 (34.57)	0.108	0.024
HDL (mg/dL), mean (SD) n=507	65.16 (17.92)	62.19 (19.78)	60.62 (16.67)	56.16 (15.53)	**<.0001**	**<.0001**
Triglycerides (mg/d), mean (SD) n=507	125.86 (76.46)	148.69 (142.26)	140.15 (68.56)	144.93 (79.4)	**0.011**	0.205

SD standard deviation, †p-value from logistic regression for categorical variables and linear regression for continuous variables
CHD coronary heart disease, HOMA-IR homeostatic model assessment of insulin resistance

Table 19. Frequency of Structural Changes in the Knee

	Men n=550		Women n=863	
Any damage	**n**	**(%)**	**n**	**(%)**
Bone marrow lesion (≥1)				
Medial TF	174	(31.6)	186	(21.6)
Lateral TF	60	(10.9)	145	(16.8)
PF	227	(41.3)	388	(45.0)
Knee	328	(59.6)	516	(59.8)
Cartilage damage (≥2)				
Medial TF	315	(57.3)	422	(48.9)
Lateral TF	103	(18.7)	236	(27.4)
PF	369	(67.1)	645	(74.7)
Knee	451	(82.0)	723	(83.8)
Meniscus damage (≥1)				
Medial	278	(50.6)	256	(29.7)
Lateral	56	(10.2)	130	(15.1)
Knee	301	(54.7)	329	(38.1)
Synovitis/effusion (≥1)	393	(71.5)	556	(64.4)
Severe damage	**n**	**(%)**	**n**	**(%)**
Bone marrow lesion (≥2)				
Medial TF	74	(13.5)	80	(9.3)
Lateral TF	18	(3.3)	61	(7.1)
PF	62	(11.3)	108	(12.5)
Knee	133	(24.2)	208	(24.1)
Cartilage damage (≥5)				
Medial TF	141	(25.6)	167	(19.4)
Lateral TF	32	(5.8)	107	(12.4)
PF	138	(25.1)	268	(31.1)
Knee	242	(44.0)	402	(46.6)
Meniscus damage (≥3)				
Medial	177	(32.2)	138	(16.0)
Lateral	27	(4.9)	91	(10.5)
Knee	194	(35.3)	206	(23.9)
Synovitis/effusion (≥2)	103	(18.7)	146	(16.9)

BML bone marrow lesion
TF tibiofemoral, PF patellofemoral

Table 20. Association between Fat Mass, Appendicular Lean Mass and Structural Changes in the Knee, Men, 550 Knees

Outcome	Exposure	Any damage OR [95% CI]†	Any damage p-value	Severe damage OR [95% CI]†	Severe damage p-value
BML					
Medial TF	Total fat	1.01 [0.97,1.05]	0.763	1.01 [0.96,1.06]	0.668
	Appendicular lean	1.07 [0.98,1.16]	0.140	1.03 [0.91,1.16]	0.611
Lateral TF	Total fat	0.96 [0.92,1.01]	0.144	1.02 [0.94,1.10]	0.704
	Appendicular lean	**1.16 [1.04,1.29]**	**0.010**	1.09 [0.90,1.31]	0.381
PF	Total fat	1.01 [0.98,1.05]	0.426	0.99 [0.94,1.04]	0.620
	Appendicular lean	**1.13 [1.04,1.22]**	**0.004**	**1.23 [1.09,1.40]**	**0.001**
Knee	Total fat	1.01 [0.97,1.04]	0.720	1.00 [0.96,1.04]	0.915
	Appendicular lean	**1.15 [1.05,1.26]**	**0.003**	**1.13 [1.03,1.23]**	**0.008**
Cartilage damage					
Medial TF	Total fat	0.97 [0.93,1.00]	0.055	1.01 [0.97,1.05]	0.652
	Appendicular lean	1.09 [0.99,1.20]	0.060	1.08 [0.98,1.19]	0.132
Lateral TF	Total fat	0.98 [0.93,1.02]	0.272	1.00 [0.93,1.07]	0.958
	Appendicular lean	**1.12 [1.01,1.24]**	**0.029**	1.17 [0.99,1.37]	0.064
PF	Total fat	0.99 [0.95,1.02]	0.496	1.01 [0.98,1.04]	0.585
	Appendicular lean	1.08 [0.98,1.18]	0.106	**1.11 [1.02,1.22]**	**0.018**
Knee	Total fat	0.98 [0.94,1.02]	0.360	1.01 [0.98,1.05]	0.460
	Appendicular lean	**1.18 [1.04,1.33]**	**0.009**	**1.10 [1.01,1.20]**	**0.036**
Meniscus damage					
Medial	Total fat	**0.96 [0.93,0.99]**	**0.016**	0.99 [0.96,1.03]	0.643
	Appendicular lean	**1.14 [1.05,1.25]**	**0.003**	**1.10 [1.01,1.20]**	**0.037**
Lateral	Total fat	**0.95 [0.90,0.99]**	**0.038**	0.97 [0.90,1.05]	0.495
	Appendicular lean	**1.19 [1.04,1.35]**	**0.009**	**1.23 [1.03,1.46]**	**0.023**
Knee	Total fat	**0.96 [0.93,0.99]**	**0.017**	0.99 [0.95,1.02]	0.413
	Appendicular lean	**1.17 [1.07,1.28]**	**0.001**	**1.12 [1.02,1.22]**	**0.013**
Synovitis/Effusion	Total fat	0.98 [0.95,1.01]	0.191	0.97 [0.93,1.01]	0.122
	Appendicular lean	**1.13 [1.03,1.23]**	**0.006**	**1.18 [1.06,1.31]**	**0.002**

BML bone marrow lesion, TF tibiofemoral, PF patellofemoral, †OR per 1 kg increase

Odds ratios are adjusted for height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time watching TV and NSAIDs use.

Table 21. Association between Fat Mass, Appendicular Lean Mass and Structural Changes in the Knee, Women, 863 Knees

		Any damage		Severe damage	
Outcome	**Exposure**	**OR [95% CI]†**	**p-value**	**OR [95% CI]†**	**p-value**
BML					
Medial TF	Total fat	1.02 [0.99,1.05]	0.136	1.02 [0.97,1.06]	0.460
	Appendicular lean	**1.27 [1.13,1.42]**	**<.0001**	**1.36 [1.17,1.58]**	**<.0001**
Lateral TF	Total fat	1.03 [0.99,1.07]	0.086	1.02 [0.97,1.08]	0.421
	Appendicular lean	1.07 [0.94,1.23]	0.315	1.06 [0.86,1.30]	0.570
PF	Total fat	**1.03 [1.00,1.06]**	**0.043**	1.01 [0.97,1.05]	0.584
	Appendicular lean	1.06 [0.96,1.17]	0.222	0.98 [0.85,1.14]	0.832
Knee	Total fat	**1.04 [1.01,1.07]**	**0.008**	1.02 [0.99,1.05]	0.261
	Appendicular lean	**1.16 [1.05,1.28]**	**0.003**	**1.13 [1.02,1.26]**	**0.024**
Cartilage damage					
Medial TF	Total fat	1.02 [0.99,1.05]	0.136	1.01 [0.98,1.05]	0.443
	Appendicular lean	**1.12 [1.02,1.23]**	**0.014**	**1.27 [1.12,1.43]**	**0.0001**
Lateral TF	Total fat	1.02 [0.99,1.05]	0.175	1.03 [0.99,1.07]	0.162
	Appendicular lean	1.09 [0.97,1.21]	0.135	1.05 [0.89,1.23]	0.564
PF	Total fat	1.03 [0.99,1.06]	0.104	1.02 [0.99,1.05]	0.238
	Appendicular lean	**1.12 [1.01,1.24]**	**0.034**	1.07 [0.97,1.18]	0.177
Knee	Total fat	1.03 [0.99,1.06]	0.152	1.03 [0.99,1.06]	0.058
	Appendicular lean	1.13 [0.99,1.29]	0.058	**1.16 [1.05,1.28]**	**0.004**
Meniscus damage					
Medial	Total fat	0.99 [0.96,1.02]	0.653	1.02 [0.98,1.06]	0.407
	Appendicular lean	**1.20 [1.08,1.33]**	**0.001**	**1.22 [1.08,1.37]**	**0.001**
Lateral	Total fat	1.02 [0.99,1.06]	0.238	1.01 [0.97,1.05]	0.598
	Appendicular lean	1.12 [0.99,1.27]	0.074	**1.16 [1.01,1.32]**	**0.033**
Knee	Total fat	1.01 [0.98,1.04]	0.409	1.03 [0.99,1.06]	0.103
	Appendicular lean	**1.18 [1.07,1.29]**	**0.001**	**1.20 [1.08,1.33]**	**0.001**
Synovitis/Effusion	Total fat	1.01 [0.98,1.04]	0.371	1.00 [0.96,1.04]	0.959
	Appendicular lean	1.10 [0.99,1.21]	0.059	**1.18 [1.06,1.32]**	**0.003**

BML bone marrow lesion, TF tibiofemoral, PF patellofemoral, †OR per 1 kg increase
Odds ratios are adjusted for height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time watching TV and NSAIDs use.

Table 22. Association between Abdominal Subcutaneous Adipose Tissue and Structural Changes in the Knee, Women, 863 Knees

	Any damage		Severe damage	
Outcome	**OR [95% CI]‡**	**p-value**	**OR [95% CI]‡**	**p-value**
BML				
Medial TF	**1.35 [1.14,1.60]**	**0.001**	1.21 [0.95,1.53]	0.122
Lateral TF	**1.25 [1.02,1.54]**	**0.031**	1.17 [0.86,1.59]	0.320
PF	**1.30 [1.11,1.52]**	**0.001**	1.10 [0.88,1.38]	0.391
Knee	**1.45 [1.23,1.70]**	**<.0001**	**1.19 [1.00,1.41]**	**0.048**
Cartilage damage				
Medial TF	1.10 [0.94,1.28]	0.248	1.12 [0.92,1.38]	0.260
Lateral TF	1.10 [0.92,1.31]	0.309	1.14 [0.90,1.43]	0.279
PF	**1.27 [1.07,1.51]**	**0.005**	1.12 [0.95,1.32]	0.183
Knee	1.15 [0.95,1.40]	0.148	**1.22 [1.04,1.43]**	**0.015**
Meniscus damage				
Medial	1.01 [0.84,1.21]	0.923	**1.37 [1.07,1.74]**	**0.011**
Lateral	1.09 [0.89,1.33]	0.386	1.07 [0.84,1.37]	0.588
Knee	1.04 [0.88,1.24]	0.608	**1.32 [1.07,1.62]**	**0.009**
Synovitis/effusion	1.12 [0.95,1.31]	0.165	1.13 [0.91,1.41]	0.280

BML bone marrow lesion, TF tibiofemoral, PF patellofemoral, ‡OR per 1 unit (cm^2/kg) increase
Odds ratios are adjusted for height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time watching TV and NSAIDs use.

Table 23. Association between Visceral Adipose Tissue and Structural Changes in the Knee, Men, 550 Knees

	Any damage		Severe damage	
Outcome	**OR [95% CI]‡**	**p-value**	**OR [95% CI]‡**	**p-value**
BMLs				
Medial TF	0.90 [0.63,1.31]	0.590	0.77 [0.49,1.20]	0.246
Lateral TF	**0.52 [0.32,0.86]**	**0.010**	0.79 [0.39,1.60]	0.518
PF	0.86 [0.63,1.16]	0.318	0.99 [0.65,1.50]	0.954
Knee	0.81 [0.59,1.10]	0.176	0.80 [0.58,1.11]	0.189
Cartilage damage				
Medial TF	0.81 [0.60,1.09]	0.160	0.82 [0.57,1.19]	0.302
Lateral TF	**0.54 [0.36,0.80]**	**0.002**	0.97 [0.57,1.63]	0.896
PF	**0.71 [0.51,0.99]**	**0.044**	0.93 [0.67,1.29]	0.667
Knee	0.69 [0.48,1.00]	0.050	0.85 [0.62,1.17]	0.324
Meniscus damage				
Medial	0.81 [0.60,1.11]	0.187	0.87 [0.63,1.19]	0.376
Lateral	**0.56 [0.34,0.91]**	**0.020**	1.00 [0.58,1.71]	0.992
Knee	0.78 [0.57,1.07]	0.120	0.88 [0.64,1.19]	0.404
Synovitis/effusion	0.75 [0.57,1.00]	0.051	0.66 [0.44,1.01]	0.057

BML bone marrow lesion, TF tibiofemoral, PF patellofemoral, ‡OR per 1 unit (cm^2/kg) increase
Odds ratios are adjusted for height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time watching TV and NSAIDs use.

4.0 THIGH COMPOSITION AND STRUCTURAL CHANGES IN THE KNEES OF COMMUNITY-DWELLING OLDER ADULTS

ABSTRACT

Fat infiltration in thigh muscle is associated with knee extensor strength, and case-control studies suggest that higher fat infiltration is associated with radiographic knee osteoarthritis. The aim of this study was to examine the associations of MRI-assessed structural changes in the knees with 1) thigh muscle density as a measure of intramuscular fat, 2) thigh intermuscular adipose tissue (IMAT) area, 3) thigh subcutaneous adipose tissue (SAT) area, and 4) quadriceps specific strength (knee extensor strength per quadriceps area) in community-dwelling older adults.

The participants were 913 older adults (549 women, mean age 73.5±2.9) in the Health, Aging and Body Composition Study. Quadriceps density, hamstring density, IMAT area, and SAT area were measured on mid-thigh CT, and knee extensor strength was measured using Kin-Com at baseline (1997/98). Knee MRI images were taken in 1998/99 or 1999/00 and assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Participants were categorized into quartile groups (Q1-Q4) for thigh adiposity measures and tertile groups (T1-T3) for quadriceps specific strength. Associations between thigh adiposity measures or specific strength and knee structural outcomes were examined using logistic regression. Adjusted covariates were body weight, height, age, race, study site, history of knee injury, knee pain in the

index knee, education, smoking status, alcohol intake, total physical activity, time spent watching TV, NSAIDs use, and muscle areas (not for strength).

In men, higher quadriceps density was associated with lower odds of bone marrow lesion (BML) in the medial tibiofemoral (TF) joint (OR=0.55 [0.32, 0.93] in Q2, OR=0.33 [0.17, 0.63] in Q4, p-trend=0.002). In women, no association was found. Higher hamstring density was associated with lower odds of BML in the patellofemoral (PF) joint (OR=0.56 [0.37, 0.83] in Q2, OR=0.33 [0.20, 0.56] in Q4, p-trend<0.001) and lower odds of cartilage damage in the PF (OR=0.51 [0.30, 0.86] in Q2, OR=0.34 [0.19, 0.61] in Q4, p-trend=0.001) in women. Women with the greatest hamstring density (Q4) had lower odds of synovitis/effusion compared with Q1 (OR=0.44 [0.27, 0.73]). In contrast, no association was found in men.

For quadriceps specific strength, the second tertile group had significantly lower odds of BML in the PF (OR=0.43[0.22, 0.84]) compared with the lowest tertile in men. In women, the highest tertile group had significantly lower odds of BML (OR=0.20 [0.08, 0.48]), cartilage damage (OR=0.43 [0.22, 0.81]), and meniscus damage (OR=0.36 [0.16, 0.82]) in the lateral compartment, and synovitis/effusion (OR=0.33 [0.19, 0.59]) compared with the lowest tertile.

Higher quadriceps density in men or higher hamstring density in women, both of which reflect lower intra-muscular fat, and higher extensor strength were associated with lower odds of structural changes in the knee. Exercise which helps to maintain muscle density and muscle strength might be beneficial for knee joints of older adults. Prospective studies are warranted to determine whether thigh muscle quality is associated with changes in knee structural outcomes.

4.1 INTRODUCTION

Osteoarthritis of the knee (knee OA) is one of the major causes of disability [16,17]. Exercise, especially quadriceps muscle strengthening, is effective to control knee pain and improve physical function in knee OA patients [55,135] , although damage in joint cartilage and meniscus is essentially irreversible. The association between muscle strength and development of knee OA is inconclusive. In the Multicenter Osteoarthritis (MOST) study, higher knee extensor strength at baseline was not associated with the incidence of radiographic OA (ROA), but was associated with a lower incidence of symptomatic knee OA in 30 months [206]. In this cohort, thigh muscle mass was not associated with the incidence of knee OA. However, higher specific strength, defined as knee extensor strength per thigh muscle mass (Nm/kg), was associated with lower incidence of symptomatic OA in women [208]. Lower muscle strength was associated with greater knee cartilage loss in 24-30 months in middle-aged people without knee OA and in older adults with knee OA[117,209]. Measurement of knee extensor strength could be influenced by knee pain or other knee symptoms due to early degenerative changes in the knee which cannot be detected in radiographs. Thus, it is challenging to examine whether quadriceps muscle strength is causally associated with the development of knee OA.

Age-related changes in muscle composition may also contribute to knee OA in old age. However, because of the lack of standardized parameters that reflect muscle quality, there have been very few studies that investigated muscle quality and knee OA. Adiposity of thigh muscle is associated with muscle strength in older adults [152]. Ectopic fat refers to lipid deposits within and around non-adipose tissues and organs such as liver, pancreas and skeletal muscle [141]. Ectopic fat in the skeletal muscle includes two fat depots: inter-muscular adipose tissue (IMAT, visible fat beneath the fascia lata) and intra-muscular adipose tissue (fat between muscle fibers, extra-myocellular fat, and intra-myocellular (IMCL) fat) [144]. Muscle density measured by computerized tomography (CT) reflects fat infiltration in muscle, such as intra-muscular adipose tissue [158]. Both inter- and intra- muscular fat increase with aging, regardless of body weight change [151,225]. Thigh muscle density on CT was associated with lower knee extensor strength and strength per muscle area [152]. Thigh muscle density was also associated with incident mobility limitation independent of total body fat, muscle area, and muscle strength in Health ABC participants [153]. Therefore, an increase in adiposity in thigh muscles could be associated with knee OA, through decreased muscle strength and other mechanisms such as inflammation and adipokines in older adults [172].

Case-control studies suggest that quadriceps intra-muscular fat and thigh muscle density are associated with radiographic knee OA[212,213]. However, whether adiposity of thigh muscles is associated with structural changes in the knees of older adults is unknown. Thus, the aim of this cross-sectional study was to examine the associations of MRI-assessed structural changes in the knees with 1) thigh muscle density as a measure of intra-muscular fat, 2) thigh inter-muscular adipose tissue (IMAT), 3) thigh subcutaneous adipose tissue (SAT), and 4) quadriceps specific strength (defined as knee extensor strength per quadriceps muscle area) in community-dwelling older adults.

4.2 METHODS

4.2.1 Participants

Subjects were a subsample of participants in the Health ABC Study who underwent knee MRI. The Health ABC study is a prospective cohort study of 3,075 well-functioning black and white men and women who were 70-79 years old at baseline (1997/98). Participants were recruited by mail from specified zip codes surrounding Memphis, TN and Pittsburgh, PA, followed by a telephone eligibility screen. Whites were recruited from a random sample of Medicare beneficiaries, and blacks were recruited from Medicare beneficiaries and all age-eligible residents in these areas. Eligibility criteria were no self-reported difficulty walking a quarter mile or climbing up 10 steps, no difficulty performing basic activities of daily living, and no use of a cane, walker, crutches or other walking aids. Exclusion criteria were having active treatment for cancer in the prior three years, enrolling in a lifestyle intervention, and planning to move out of the areas within three years. All participants provided a written informed consent, and the institutional review boards in both sites approved the study.

In 1998/99 (year 2 visit) participants were asked about knee symptoms. Knee pain was defined as having pain, aching or stiffness in or around either knee on most days for at least one month in the past 12 months or on most days in the past 30 days or having at least moderate knee pain during the activities in the modified Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain questionnaire in the past 30 days. The pertinent activities were: walking on a flat surface, going up or down stairs, at night while in bed, standing upright, getting in or out of a chair, and getting in or out of a car. In 1998/99, 979 participants (32%) reported pain in one or both knees, and 1,991 participants (65%) reported no pain (32 participants had died by 1998/99, and knee pain information was missing in 73 participants). All participants with pain in one or both knees (cases) and a subsample of participants who did not report knee pain (controls) were invited to the knee OA sub-study. Of them, 640 knee pain cases and 505 controls underwent knee MRI in 1998/99 or 1999/00. MRI images of both knees were obtained in most participants. However, not all of these images were read (Figure 5). Participants with available MRI assessment data were included in this analysis (n = 965 participants, 1,578 knees). Of these participants, 52 participants were excluded due to missing information in thigh CT data (n =14) or in main covariates in the final models (knee injury (n=17), knee pain (1), education, smoking, or time watching TV (9), alcohol intake (6), NSAIDs (5), total n =38), leaving 913 participants (1,493 knees).

4.2.2 Thigh Adipose Tissue Assessment

Mid-thigh CT scans were obtained in 1997/98 using GE 9800 Advantage (General Electric, Milwaukee, WI) at the Pittsburgh site and Siemens Somatom Plus 4 (Siemens, Erlangen, Germany) or Picker PQ 2000S (Marconi Medical Systems, Cleveland, OH) at the Memphis site. A single, 10mm thickness, axial image (120kVp and 200-250mAs) was obtained at the femoral midpoint, including the entire circumference of both thighs in the field of view. The femoral length was measured in cranial-caudal dimension on the anterior-posterior scout scan of the entire femur. The scan position was determined as the midpoint of the distance between the medial edge of the greater trochanter and the intercondyloid fossa. Tissue type was determined based on the histogram of the distribution of CT numbers in fat tissues and muscles [219]. CT numbers were defined on a Hounsfield Unit (HU) scale. Areas were calculated by multiplying the number of pixels of a given tissue type by the pixel area. The inter-muscular and visible intra-muscular adipose tissue was separated from SAT by drawing a line along the deep fascial plane surrounding the thigh muscles. After the segmentation of adipose tissues, the individual muscles were segmented by drawing muscle borders manually. The border of the femur was defined as any pixel greater than 150 HU. The mean attenuation coefficient values (density) of quadriceps and hamstring muscles (HU) were determined by averaging the CT number values of the muscle region, and were used as an indicator of fat infiltration in the muscle. Skeletal muscle attenuation determined by CT was associated with skeletal muscle lipid content in biopsy specimens [158].

4.2.3 Knee Extensor Strength Assessment

Knee extensor concentric strength was measured using Kin-Com 125 AP Dynamometer at baseline. The right leg was tested, unless the participants had knee pain, injury, arthritis, or other conditions which prevented the measurement of the right leg. Measurement was conducted three times, and the average maximum torque (Nm) was calculated. The exclusion criteria for Kin-Com measurement were cerebral aneurysm, cerebral bleeding, stroke, blood pressure ≥200/110 mmHg, severe bilateral knee pain, and previous total knee replacement. Quadriceps specific strength was calculated as knee extensor average maximum torque (Nm) per quadriceps area (cm^2) on thigh CT of the same leg.

4.2.4 Knee MRI

Knee MRI images were obtained using a GE Sigma 1.5T system with a standard unilateral, commercial circumferential knee coil. MRIs were acquired using a coronal T-2 weighted fast spin-echo (FSE) (repetition time (TR) 3,500 msec, echo time (TE) 60 msec, slice thickness 4.0 mm, interslice gap 0.5 mm, excitation 2, Field of View (FOV)140 mm, matrix 256 × 256 pixels), a sagittal T2-weighted FSE, including the entire synovial cavity with frequency-selective fat suppression (TR 4,127 msec, TE 60 msec, interslice gap 0.5mm, excitation 2, FOV 140 mm, matrix 256 × 256 pixels), and a axial T2-weighted FSE localizer (TR 2,500 msec, TE 60 msec, interslice gap 1mm, excitation 1, FOV 120mm, matrix 256 × 128 pixels). Contraindications for knee MRI were not fitting in the MRI bore or knee coil, cardiac pacemaker, aneurysm clips, metallic fragments in the eyes, vascular clips less than 2 months old, cardiac valve prosthesis, cochlear implants, total knee replacement, and claustrophobia.

Knee MRI images were read by one of five trained radiologists, who were blinded to the thigh CT measures. Structural changes in the knee were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) [37]. Specifically, 14 subregions (anterior, central, and posterior of the medial/lateral femoral condyles/tibial plateaus and medial/lateral subregions of the patella) were each scored separately for cartilage lesions, osteophytes, subarticular bone marrow lesions, bone cysts, and bone attrition. Bone marrow lesions (BMLs) in each subregion were graded as 0 = none, 1 = <25% of the region, 2 = 25-50% of the region and 3 = >50% of the region. Cartilage damage was graded as 0 = normal thickness and signal, 1 = abnormal signal only, 2 = solitary focal defect, 3 = areas of partial-thickness loss with areas of preserved thickness, 4 = diffuse (>75%) partial-thickness loss, 5 = areas of full thickness loss with areas of partial-thickness loss, and 6 = diffuse (>75%) full-thickness loss. Meniscus morphology and tear in anterior horn, body and posterior horn was graded as 0 = intact, 1 = minor radial or parrot break tear, 2 = non-displaced tear or prior surgical repair, 3 = displaced tear, partial maceration or partial resection, and 4 = complete maceration and destruction or complete resection.

Synovitis/effusion was graded as 0 = none, 1 = <33% of maximum distension, 2 = 33-66% of maximum distension, and 3 = >66% of distension. Any BML in each compartment and in the whole knee was defined as the worst WORMS grade of ≥1 (in 5 subregions for the medial tibiofemoral joint (TF), 5 subregions for the lateral TF, 4 subregions for the patellofemoral joint (PF), and 14 subregions in the whole knee). Any cartilage damage in each compartment and in the whole knee was defined as the worst WORMS grade of ≥2. Any medial and lateral meniscus damage was defined as meniscus summary score of ≥1. Any synovitis/effusion was defined as synovitis/effusion grade of ≥1.

4.2.5 Covariates

Information on age, sex, race, education (less than high school, high school graduate, post-secondary), smoking status (never, former, current), alcohol intake per week in the past 12 months, physician diagnosis of prevalent diseases, history of knee injury, and knee pain in each knee was collected through a standardized questionnaire in 1997/98. Prevalent hypertension was defined as self-report of a physician diagnosis combined with hypertension medication use. Prevalent diabetes was defined as self-report of a physician diagnosis of diabetes, use of diabetic medication, or fasting serum glucose of ≥126 mg/dL [214]. Metabolic syndrome was defined as meeting at least three of the following criteria: abdominal circumference (>102 cm for men, >88 cm for women), blood pressure (blood pressure ≥130/85 mmHg or anti-hypertensive medication), high glucose (glucose ≥ 110 mg/dL or antidiabetic medication), low high-density lipoprotein (HDL) (<40 mg/dL for men, <50 mg/dL for women), and high triglyceride (triglyceride≥150 mg/dL) (adapted from Ford et al.) [215]. The knee pain questionnaire at the 1997/98 baseline was slightly different from that used in 1998/99 for selection into the knee OA substudy. Pain in the index knee at baseline was defined as having pain lasting at least one month in the past 12 month, having at least moderate pain during the activities in the modified WOMAC pain questionnaire in the past 30 days, or having pain, aching or stiffness on most days of the past 30 days. Physical activity and exercise in the past 12 months and past 7 days were also assessed through an interviewer-administered questionnaire which was modified specifically for Health ABC based on physical activity assessments from the Minnesota Leisure Time Physical Activity Questionnaire [104]. Frequency and time spent for each specific activity were asked. Time spent for each activity in the past 7 days was multiplied by approximate metabolic equivalent units (MET) and body weight to calculate the total energy expenditure for physical activity (kcal/week). Hours spent watching TV per week (Zero, >0-<7hrs, 7-<14hrs, 14-<21hrs, ≥21hrs/week) were also self-reported.

Anthropometric measurements were made by trained technicians. Body weight was measured to the nearest 0.1 kg using a standard balance beam scale. Height was measured to the nearest millimeter using a wall-mounted stadiometer. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Abdominal circumference was measured at the level of largest circumference between the lower rib and the iliac crest using a flexible inelastic fiberglass tape. The measurement was taken at the end of a normal expiration to the nearest 0.1 cm. Blood pressure was measured by trained staff using a mercury sphygmomanometer after five minutes rest.

The participants were asked to bring all prescription and nonprescription medications used in the preceding two weeks with them to the baseline visit. Trained clinic staff reviewed all medications and transcribed the name and current dose from the container. Baseline nonsteroidal anti-inflammatory drug (NSAIDs) use was determined. Blood samples were obtained after an overnight fast, and serum glucose and plasma lipids were measured.

4.2.6 Statistical Analysis

Descriptive statistics for characteristics of the participants were calculated by sex and by sex-specific quartile groups of average quadriceps density. These groups were compared by chi-square tests and logistic regression for categorical variables and Kruskal-Wallis tests and linear regression for continuous variables. Percentile cutoffs used to create groups for a given adiposity measure were based on all participants in the HABC study with the available measures. The frequencies of knee outcomes were compared by quadriceps density on the same side using chi-square tests.

The main analysis was conducted at the knee level. The associations between thigh adiposity measures at baseline and knee MRI outcomes of the same leg were examined using logistic regression models. Correlation between right and left knees within a person was taken into account by using generalized estimating equations (GEE). The associations between quadriceps specific strength and knee outcomes were examined in the subgroup of the participants with muscle strength. Because muscle strength was measured only on one side in each participant, one knee per participant was analyzed. Participants were categorized into three groups based on sex-specific tertiles of quadriceps specific strength in the study sample.

Thigh adiposity measures examined were quadriceps density, hamstring density, thigh IMAT area (cm^2), and thigh SAT area (cm^2). Initially, thigh adiposity measures were categorized into sex-specific quintiles to examine potential curvilinear associations with knee MRI outcomes. Quadratic terms of these variables were also tested for curvilinear associations. Because curvilinear associations between thigh adiposity measures and knee outcomes were suspected in some instances, thigh adiposity measures were categorized into quartile groups (Q1: lowest quartile, Q4: highest quartile) in the final analyses rather than being treated as continuous variables. The Q1 was used as the reference category. Body weight, quadriceps area, and hamstring area were adjusted for each thigh adiposity measure. No apparent curvilinear associations of body weight, quadriceps area, and hamstring area with knee outcomes were detected. Therefore, these variables were treated as continuous variables. Correlation between thigh adiposity measures and body weight were moderate except for thigh SAT in women (Pearson r=0.74, p=<0.001). Quadriceps area or hamstring area and thigh adiposity measures (muscle density, IMAT, SAT) were weakly correlated (Pearson r=-0.19-0.35) both in men and women.

Any BML, cartilage damage, meniscus damage, and synovitis/effusion were examined in separate regression models. BML and cartilage damage were examined by compartment (i.e., medial TF joint, lateral TF joint, and PF joint) and in the whole knee.

All analyses were stratified by sex. In the final models, body weight, height, quadriceps area, hamstring area, age (continuous), race, study site, history of knee injury (unknown/not sure being categorized as no injury), knee pain in the index knee at baseline (yes/no), education, smoking status, alcohol consumption, total physical activity (sex-specific quartiles), time spent watching TV, and NSAIDs use at baseline were adjusted. Alcohol consumption in a typical week in the past 12 months was categorized as none, 1-7/week, and >7/week for men, and none, <1/week, and ≥1/week for women. Due to the low frequency, zero/week and >0-<7hrs/week categories were combined for time spent watching TV. For quadriceps specific strength, the same covariates, except for quadriceps area and hamstring area, were adjusted. The odds ratio (OR) and 95% confidence interval (CI) for each outcome were reported.

All analyses were conducted using SAS 9.4 (SAS Institute Inc. Cary, NC). All p-values were two-sided, and p-values of less than 0.05 were considered as statistically significant. The significant α level did not take into account multiple comparisons.

4.3 RESULTS

The characteristics of the participants are shown in Table 24. In the 913 participants, 549 (60.1%) were women and 422 (46.2%) were black. The mean age was 73.5 ± 2.9. Twenty percent of men and 30% of women were obese.

Men and women with lower quadriceps density were older, had higher weight and BMI, did less exercise and were more likely to have knee pain and use NSAIDs than those with higher quadriceps density (all $p<0.05$). Men with lower quadriceps density were more likely to have diabetes than men with higher quadriceps density (all $p<0.05$). Women with lower quadriceps density were more likely to be black, spent longer time watching TV and were more likely to have hypertension and metabolic syndrome (all $p<0.05$).

The frequencies of the knee outcomes by quadriceps density quartile groups are shown in Table 25. In men, the prevalence of BML in the medial TF ($p<0.001$), PF ($p=0.012$) and the whole knee ($p<0.001$), and cartilage damage in the lateral TF ($p=0.001$), PF ($p=0.020$) and the whole knee ($p=0.026$) were higher in lower quadriceps density groups. In women, the prevalence of BML, cartilage damage and meniscus damage in all compartments, and synovitis effusion were higher in lower quadriceps density groups ($p<0.001$).

Quadriceps Density

In men, higher quadriceps density was associated with significantly lower odds of BML in the medial TF (OR=0.55 [0.32, 0.93] in Q2, OR=0.54 [0.29, 0.99] in Q3, OR=0.33 [0.17, 0.63] in Q4, p-trend=0.002) (Table 26). Q3 and Q4 groups had significantly lower odds of cartilage damage in the lateral TF compared with Q1, although overall p-value was 0.053 (OR=0.65 [0.33, 1.29] in Q2, OR=0.44 [0.20, 0.94] in Q3 and OR=0.31[0.12, 0.75] in Q4, p-trend=0.006). In women, no significant association was found.

Hamstring Density

In men, no significant association was found between hamstring density and knee outcomes (Table 27). In women, higher hamstring density was associated with lower odds of BML in the PF (OR=0.56 [0.37, 0.83] in Q2, OR=0.61 [0.39, 0.96] in Q3, OR=0.33 [0.20, 0.56] in Q4, p-trend<0.001) and BML in the whole knee (OR=0.58 [0.37, 0.91] in Q2, OR=0.57 [0.35, 0.93] in Q3, OR=0.39 [0.23, 0.65] in Q4, p-trend=0.001). Higher hamstring density was also associated with lower odds of cartilage damage in the PF (OR=0.51 [0.30, 0.86] in Q2, OR=0.47 [0.27, 0.84] in Q3, OR=0.34 [0.19, 0.61] in Q4, p-trend=0.001) and in the whole knee (OR=0.52 [0.27, 1.00] in Q2, OR=0.43 [0.22, 0.84] in Q3, OR=0.32 [0.16, 0.63] in Q4, p-trend=0.001) in women, although the difference between Q1 and Q2 were marginal for cartilage damage in the whole knee. Q4 groups had significantly lower odds of synovitis/effusion compared with Q1 (OR=0.44 [0.27, 0.73]).

Thigh IMAT Area

No significant association was found between thigh IMAT and knee outcomes in men or women, except that Q2 group had significantly higher odds of lateral meniscus damage compared with Q1 (OR=3.09 [1.17, 8.18]) in men.

Thigh SAT area

In men, the Q3 group had significantly lower odds of BML in the medial TF compared with Q1 (OR=0.47 [0.24, 0.93]), however, no dose-response pattern was found in this outcome. Higher thigh SAT area was associated with lower odds of cartilage damage in the medial TF (OR=0.54 [0.30, 0.97] in Q2, OR=0.25 [0.13, 0.45] in Q3, OR=0.36 [0.17, 0.78] in Q4, p-trend=0.001). In women, no significant association was found between thigh SAT and knee outcomes.

Quadriceps specific strength

In this analysis, 272 men and 429 women were included. In men, the second tertile group had significantly lower odds of BML in the lateral TF (OR=0.24 [0.07, 0.85]) and in the PF (OR=0.43 [0.22, 0.84]) compared with the lowest tertile (Table 28). In women, the highest tertile group had lower odds of BML in the lateral TF (OR=0.20 [0.08, 0.48]), cartilage damage in the lateral TF (OR=0.43 [0.22, 0.81]), lateral meniscus damage (OR=0.36 [0.16, 0.82]), and synovitis/effusion (OR=0.33 [0.19, 0.59]) compared with the lowest tertile.

4.4 DISCUSSION

This study is the first study to examine the association between thigh muscle composition and MRI-assessed structural changes in the knees of community-dwelling older adults. The results suggest that thigh muscle quality (density and strength) are important for structural changes in the knees rather than adipose tissue per se. In men, higher quadriceps density, as an indicator of less intra-muscular fat, was associated with lower odds of BML in the medial TF joint and cartilage damage in the lateral TF joint, independent of body weight and thigh muscle areas. In women, higher hamstring density was associated with lower odds of BML in the PF joint, cartilage damage in the PF joint, and synovitis effusion. Regarding quadriceps specific strength, the prevalence of BML, cartilage damage, and meniscus damage in the lateral TF joint, and synovitis/effusion were significantly lower in women in the highest tertile compared with the lowest tertile. Thigh IMAT or SAT was not generally associated with structural changes in the knee in men or women, except that higher thigh SAT was associated with lower odds of cartilage damage in the medial TF joint in men.

The results of the current study suggest that not only quadriceps but hamstrings are important for structural changes in the knee. The results are consistent with the association between lower thigh muscle density and prevalent radiographic knee OA in the Health ABC participants [213]. In women, but not in men, higher hamstring density was associated with lower odds of BML and cartilage damage in the PF and synovitis/effusion. Kumar et al. reported that intra-muscular fat fraction in quadriceps was significantly higher in radiographic knee OA cases than in controls, but no significant difference was found in intra-muscular fat fraction in hamstrings [212]. In their study, the participants were younger (mean age 57.7 years in cases and 50.7 years in controls), and the sample size was smaller (n=96) than the current study. In addition, intra-muscular fat on thigh MRI rather than muscle density on CT was measured.

Sex differences in knee kinematics could be related to the different results in men and women. Coactivation of knee extensor quadriceps and knee flexor hamstring provides stability of the knee joint [226]. Segal et al. reported that higher hamstring to quadriceps strength ratio was not associated with knee OA incidence but was mildly associated with risk of joint space narrowing in older women [206,227]. In the studies of young adults, women demonstrated a quadriceps dominance over hamstring in muscle activation compared with men during exercise [228,229]. Another study showed that women had greater peak knee flexion than men during walking as well as greater peak hip internal rotation and adduction [216]. It is possible that sex differences existed in knee kinematics in these older adults, which may partly explain why quadriceps in men and hamstring in women were associated with structural changes in the knees.

These sex-based differences may also be explained by muscle fiber type composition. Studies reported that biceps femoris in hamstrings consisted of a higher proportion of slow type I fiber than fast type II fiber, whereas the proportion of type II fiber was similar or slightly higher than type I fiber in vastus lateralis, vastus medialis, and rectus femoris in quadriceps [230-232]. Type I fiber contained 2-3 times higher triglyceride contents than type II fiber [233]. With aging, muscle fiber area, especially type II fiber area, decreases [234]. Therefore, effects of aging on muscle lipid contents and muscle fiber size could differ between quadriceps and hamstring due to the difference in muscle fiber type composition. However, future studies are needed to determine whether age effects on each muscle group differ by sex and whether that plays some role in the different results by sex.

Women with the highest quadriceps specific strength had fewer structural changes in the lateral compartment. Segal et al. reported that knee extensor strength per thigh muscle mass was not associated with risk of radiographic OA in 30 months, but was associated with significantly lower risk of symptomatic knee OA in women adjusting for age, BMI and history of knee surgery[208]. Structural changes which cannot be observed in knee radiographs, such as BML in the lateral TF and lateral meniscus damage, which were associated with lower specific strength in the current study, may be the cause of knee symptoms. This could explain why muscle strength was associated with symptomatic knee OA but not with incident radiographic knee OA in the previous studies. It is unknown why quadriceps specific strength was associated with structural changes in the lateral compartment rather than the medial compartment in women in the current study. It is speculated that lower extensor specific strength would have affected the kinematics of knee joint load, which resulted in the structural changes in the lateral compartment.

Thigh IMAT was not associated with worse knee outcomes in men or women. This result is consistent with the study by Beattie et al. [211]. They reported that neither baseline thigh inter-muscular fat volume nor longitudinal change of it in two years was different between women with symptomatic radiographic knee OA and those without. Thigh SAT was not associated with worse knee outcomes overall in the current study, except that a higher thigh SAT area was associated with lower odds of cartilage damage in the medial TF in men. This result is worth noting because cartilage damage in the medial TF is a characteristic of knee OA.

The results of the current study suggest that the muscle component or intra-muscular fat is important rather than thigh IMAT or SAT for structural changes in the knee. Previous studies reported the association between higher serum leptin levels and worse knee outcomes, suggesting that adipose tissue would be related to the development of knee OA through secretion of adipokines [175,176]. Higher intra-muscular fat is associated with insulin resistance [235]. Higher IMAT is also associated with cardiovascular disease risk independent of visceral adipose tissue [155]. The absence of associations between IMAT or SAT and knee outcomes suggest that mechanical mechanisms are important for the development of knee OA rather than metabolic mechanisms. In the Health ABC, higher thigh muscle density was associated with higher knee extensor specific strength, but IMAT or thigh SAT was not [152]. In these older adults, quadriceps density and hamstring density were strongly correlated with each other (Pearson $r=0.80-0.82$, $p<0.001$). Therefore, the associations between thigh muscle density and structural changes in the knee were possibly mediated by knee extensor strength, which may explain why intra-muscular fat, but not IMAT or SAT, was associated with the knee outcomes.

The benefits of exercise programs in knee OA for pain control and physical function have been established [55,56]. The positive effects of exercise on knee OA symptoms are mediated by an increase in knee extensor and flexor strength, a decrease of extension impairment, and improvement of proprioception [194]. Taaffe et al. found that muscle density in quadriceps and hamstrings significantly decreased following detraining and then increased following retraining in healthy community-dwelling older adults (n=13) regardless of whether participants were randomized to strength training or power training [236]. The result of the current study suggests that higher thigh muscle density and higher extensor strength may be the mediators in exercises improving knee OA outcomes. Exercise which helps to keep thigh muscle quality –muscle density and muscle strength− in older adults might be beneficial for knee joints.

This is the first study to examine the associations between thigh fat composition and MRI-assessed structural changes in the knees of community-dwelling older adults. Covariates such as, body weight, thigh muscle areas, knee OA risk factors, and variables related to body composition were adjusted for. No established HU ranges exist which define muscle and adipose tissue on CT[237]. Muscle and adipose tissue were separated base on the bimodal histogram determination, which is the strength of this study, taking into account the variabilities in CT numbers between individuals. However, a few limitations exist. Muscle density on CT would reflect both extra- and intra-myocellular lipids in intramuscular fat, but they cannot be distinguished. Magnetic resonance spectroscopy quantifies them separately [237], although this was not available. The participants were quite well-functioning at baseline and their age range was narrow. Thus, the results may not be generalizable to other older populations. Future prospective studies are needed to examine whether thigh muscle quality is associated with changes in knee structural outcomes. Clinical trials are needed to determine whether exercise interventions that help to maintain and improve muscle quality prevent the development of structural changes in the knee.

In conclusion, higher quadriceps density in men, higher hamstring density in women, and higher quadriceps strength were associated with lower odds of structural changes in the knees in community-dwelling older adults. Thigh IMAT or SAT was not generally associated with these knee outcomes. Exercise which helps to maintain thigh muscle density and muscle strength in older adults may be beneficial for knee joints. Future prospective studies are needed to determine whether thigh muscle composition is causally associated with the development of knee OA.

4.5 FIGURE AND TABLES

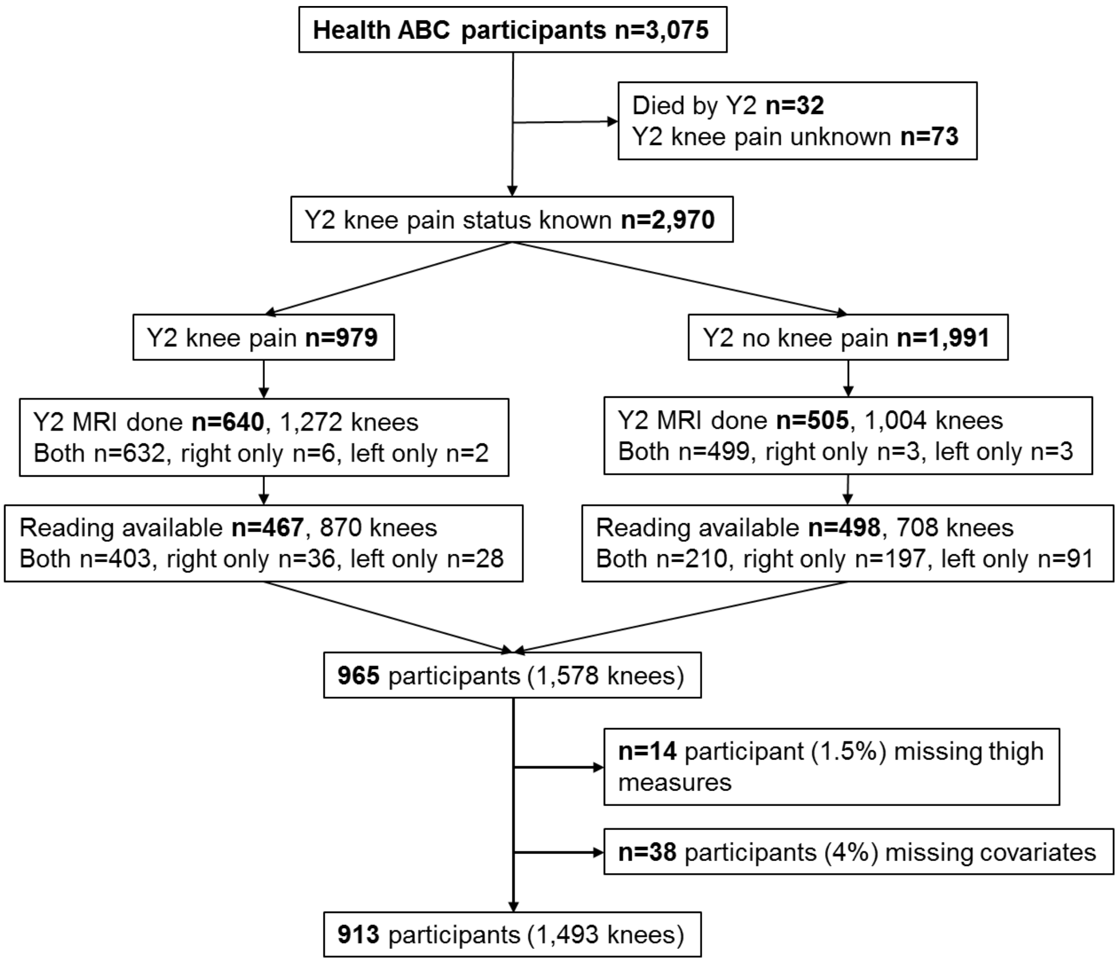

Figure 5. Flow-Chart of the Participants

Table 24. Characteristics of the Participants, n=913

Variables	All n=913	Men n=364	Women n=549	p-value*
Age, mean (SD)	73.5 (2.9)	73.5 (2.8)	73.5 (2.9)	0.867
Race, n (%)				0.165
Black	422 (46.2)	158 (43.4)	264 (48.1)	
Site, n (%)				0.374
Memphis	425 (46.6)	176 (48.4)	249 (45.4)	
Pittsburgh	488 (53.5)	188 (51.7)	300 (54.6)	
Married, n (%) n=856	439 (51.3)	252 (71.4)	187 (37.2)	**<.0001**
Education, n (%)				**<.0001**
Less than High school	212 (23.2)	100 (27.5)	112 (20.4)	
High school graduate	317 (34.7)	95 (26.1)	222 (40.4)	
Postsecondary	384 (42.1)	169 (46.4)	215 (39.2)	
Height (mm), mean (SD)	1650.4 (93.8)	1735 (67.1)	1594.3 (61.3)	**<.0001**
Weight (kg), mean (SD)	75.2 (14.6)	81.5 (12.9)	71 (14.2)	**<.0001**
BMI, kg/m^2, mean (SD)	27.6 (4.7)	27 (3.7)	27.9 (5.3)	0.087
BMI category, n (%)				**<.0001**
<25	261 (28.6)	96 (26.4)	165 (30.1)	
25 to 30	414 (45.4)	197 (54.1)	217 (39.5)	
≥30	238 (26.1)	71 (19.5)	167 (30.4)	
Smoking status, n (%)				**<.0001**
Never	430 (47.1)	115 (31.6)	315 (57.4)	
Current	94 (10.3)	41 (11.3)	53 (9.7)	
Former	389 (42.6)	208 (57.1)	181 (33)	
Drinking per week, n (%)				**<.0001**
None	472 (51.7)	150 (41.2)	322 (58.7)	
1-7/week	378 (41.4)	169 (46.4)	209 (38.1)	
≥8 /week	63 (6.9)	45 (12.4)	18 (3.3)	
Drinking per week, n (%)				**<.0001**
None	472 (51.7)	150 (41.2)	322 (58.7)	
<1 /week	188 (20.6)	78 (21.4)	110 (20)	
≥1 /week	253 (27.7)	136 (37.4)	117 (21.3)	

Table 24 continued

Variables	All n=913	Men n=364	Women n=549	p-value
Total activity (kcal/wk), mean (SD)	6288.9 (5232)	6673 (5318.5)	6034.3 (5163)	**0.031**
Exercise (kcal/wk), mean (SD) n=912	724.1 (1414.5)	1034.2 (1856)	518.2 (969.5)	**<.0001**
TV watching, n (%)				0.176
0-6 hrs/week	139 (15.2)	51 (14)	88 (16)	
7-13 hrs/week	226 (24.8)	94 (25.8)	132 (24)	
14-20 hrs/week	212 (23.2)	96 (26.4)	116 (21.1)	
≥21 hrs/week	336 (36.8)	123 (33.8)	213 (38.8)	
History of knee injury, n (%)	114 (12.5)	40 (11)	74 (13.5)	0.265
Y1 knee pain, n (%)	271 (29.7)	89 (24.5)	182 (33.2)	**0.005**
Hypertension, n (%) n=906	391 (43.2)	134 (36.9)	257 (47.3)	**0.002**
CHD, n (%) n=887	127 (14.3)	70 (19.6)	57 (10.8)	**0.0003**
Diabetes, n (%)	150 (16.4)	79 (21.7)	71 (12.9)	**0.001**
Metabolic syndrome, n (%) n=904	310 (34.3)	106 (29.5)	204 (37.4)	**0.014**
NSAID, n (%)	222 (24.3)	63 (17.3)	159 (29)	**<.0001**
Osteoporosis drugs, n (%)	38 (4.2)	0 (0)	38 (6.9)	**<.0001**
Statin, n (%)	109 (11.9)	39 (10.7)	70 (12.8)	0.353
Extensor strength (Nm), mean (SD) n=811	102.36 (36.96)	133.32 (32.7)	81.87 (22.55)	**<.0001**
Quadriceps density (HU), mean (SD)	40.72 (7.45)	43.95 (6.72)	38.58 (7.13)	**<.0001**
Hamstrings density (HU), mean (SD)	28.99 (8.78)	31.59 (8.43)	27.26 (8.6)	**<.0001**
Thigh IMAT area (cm^2), mean (SD)	10.57 (7.02)	10.18 (7.55)	10.83 (6.64)	0.062
Thigh SAT area (cm^2), mean (SD)	84.64 (47.68)	46.72 (19.43)	109.79 (44.09)	**<.0001**
Quadriceps area (cm^2), mean (SD)	50.27 (12.85)	61.76 (10.04)	42.66 (7.91)	**<.0001**
Hamstrings area (cm^2), mean (SD)	26.78 (6.69)	31.7 (6.22)	23.53 (4.72)	**<.0001**

SD standard deviation, *p-value comparing men vs. women
CHD coronary heart disease, HU Hounsfield unit,
IMAT intermuscular adipose tissue, SAT subcutaneous adipose tissue
Thigh muscle density, muscle area, IMAT area, SAT area are mean of the right and left legs

Table 25. Frequencies of Knee Outcomes by Quadriceps Density

Men n=590 **Outcome**		**Q1 n=152** **n (%)**	**Q2 n=141** **n (%)**	**Q3 n=129** **n (%)**	**Q4 n=168** **n (%)**	**p-value**
BML	Medial TF	68 (44.7)	43 (30.5)	39 (30.2)	32 (19.1)	**<.0001**
	Lateral TF	25 (16.5)	18 (12.8)	12 (9.3)	12 (7.1)	0.053
	PF	79 (52)	59 (41.8)	49 (38)	58 (34.5)	**0.012**
	Knee	110 (72.4)	90 (63.8)	76 (58.9)	75 (44.6)	**<.0001**
Cartilage damage	Medial TF	96 (63.2)	81 (57.5)	67 (51.9)	94 (56)	0.287
	Lateral TF	43 (28.3)	29 (20.6)	22 (17.1)	18 (10.7)	**0.001**
	PF	115 (75.7)	100 (70.9)	82 (63.6)	102 (60.7)	**0.020**
	Knee	135 (88.8)	119 (84.4)	107 (83)	128 (76.2)	**0.026**
Meniscus damage	Medial	81 (53.3)	65 (46.1)	72 (55.8)	79 (47)	0.281
	Lateral	21 (13.8)	17 (12.1)	9 (7)	14 (8.3)	0.192
	Any	92 (60.5)	72 (51.1)	77 (59.7)	83 (49.4)	0.110
Synovitis/effusion		117 (77)	97 (68.8)	89 (69)	115 (68.5)	0.292

Women n=903 **Outcome**		**Q1 n=248** **n (%)**	**Q2 n=219** **n (%)**	**Q3 n=209** **n (%)**	**Q4 n=227** **n (%)**	**p-value**
BML	Medial TF	91 (36.7)	51 (23.3)	30 (14.4)	34 (15)	**<.0001**
	Lateral TF	72 (29)	37 (16.9)	24 (11.5)	21 (9.3)	**<.0001**
	PF	138 (55.7)	105 (48)	86 (41.2)	84 (37)	**0.0003**
	Knee	188 (75.8)	143 (65.3)	111 (53.1)	106 (46.7)	**<.0001**
Cartilage damage	Medial TF	157 (63.3)	105 (48)	96 (45.9)	94 (41.4)	**<.0001**
	Lateral TF	102 (41.1)	59 (26.9)	50 (23.9)	39 (17.2)	**<.0001**
	PF	207 (83.5)	172 (78.5)	147 (70.3)	151 (66.5)	**<.0001**
	Knee	226 (91.1)	188 (85.8)	169 (80.9)	176 (77.5)	**0.0003**
Meniscus damage	Medial	100 (40.3)	71 (32.4)	42 (20.1)	59 (26)	**<.0001**
	Lateral	57 (23)	41 (18.7)	25 (12)	16 (7.1)	**<.0001**
	Any	130 (52.4)	95 (43.4)	59 (28.2)	65 (28.6)	**<.0001**
Synovitis/effusion		186 (75)	156 (71.2)	118 (56.5)	124 (54.6)	**<.0001**

BML Bone marrow lesion, TF tibiofemoral, PF patellofemoral
*p-value from chi-square test

Table 26. Association between Quadriceps Density and Knee Outcomes (Men n=590, Women n=903)

Outcome	**Quadriceps density**	**Men OR† [95%CI]**	**p-value** ***p trend***	**Women OR† [95%CI]**	**p-value** ***p trend***
BML medial TF	Q1	ref	**0.011**	ref	0.092
	Q2	0.55 [0.32,0.93]	*0.002*	0.66 [0.43,1.02]	*0.060*
	Q3	0.54 [0.29,0.99]		0.52 [0.30,0.89]	
	Q4	0.33 [0.17,0.63]		0.61 [0.33,1.13]	
BML lateral TF	Q1	ref	0.335	ref	0.235
	Q2	0.87 [0.38,1.95]	*0.088*	0.72 [0.43,1.22]	*0.103*
	Q3	0.52 [0.20,1.36]		0.52 [0.27,0.99]	
	Q4	0.51 [0.21,1.26]		0.66 [0.33,1.29]	
BML PF	Q1	ref	0.779	ref	0.181
	Q2	0.87 [0.51,1.48]	*0.299*	0.78 [0.52,1.16]	*0.031*
	Q3	0.78 [0.43,1.41]		0.71 [0.45,1.10]	
	Q4	0.73 [0.39,1.35]		0.56 [0.34,0.94]	
BML knee	Q1	ref	0.209	ref	0.150
	Q2	0.92 [0.53,1.60]	*0.050*	0.71 [0.45,1.12]	*0.026*
	Q3	0.81 [0.44,1.50]		0.63 [0.39,1.02]	
	Q4	0.54 [0.29,1.03]		0.54 [0.32,0.92]	
Cartilage medial TF	Q1	ref	0.769	ref	0.063
	Q2	0.93 [0.54,1.60]	*0.460*	0.60 [0.39,0.90]	*0.128*
	Q3	0.73 [0.39,1.36]		0.80 [0.50,1.26]	
	Q4	0.82 [0.42,1.57]		0.59 [0.35,0.99]	
Cartilage lateral TF	Q1	ref	0.053	ref	0.233
	Q2	0.65 [0.33,1.29]	*0.006*	0.68 [0.44,1.03]	*0.090*
	Q3	0.44 [0.20,0.94]		0.65 [0.39,1.11]	
	Q4	0.31 [0.12,0.75]		0.61 [0.34,1.07]	
Cartilage PF	Q1	ref	0.381	ref	0.106
	Q2	0.89 [0.50,1.61]	*0.101*	0.82 [0.50,1.35]	*0.014*
	Q3	0.67 [0.35,1.26]		0.61 [0.35,1.06]	
	Q4	0.63 [0.33,1.20]		0.51 [0.29,0.91]	
Cartilage knee	Q1	ref	0.679	ref	0.242
	Q2	0.78 [0.37,1.63]	*0.261*	0.71 [0.37,1.37]	*0.043*
	Q3	0.82 [0.35,1.93]		0.60 [0.30,1.19]	
	Q4	0.60 [0.26,1.40]		0.50 [0.25,1.00]	

Table 26 Continued

Outcome	Quadriceps density	Men OR† [95%CI]	p-value *p trend*	Women OR† [95%CI]	p-value *p trend*
Meniscus medial	Q1	ref	0.417	ref	0.480
	Q2	1.11 [0.67,1.83]	*0.678*	0.87 [0.56,1.36]	*0.485*
	Q3	1.52 [0.86,2.67]		0.68 [0.41,1.14]	
	Q4	1.08 [0.58,2.01]		0.88 [0.50,1.55]	
Meniscus lateral	Q1	ref	0.399	ref	0.278
	Q2	1.02 [0.42,2.47]	*0.523*	1.16 [0.71,1.88]	*0.122*
	Q3	0.56 [0.22,1.42]		0.83 [0.47,1.46]	
	Q4	0.80 [0.28,2.30]		0.56 [0.26,1.20]	
Meniscus any	Q1	ref	0.595	ref	0.465
	Q2	0.93 [0.53,1.64]	*0.933*	0.97 [0.63,1.50]	*0.250*
	Q3	1.27 [0.70,2.30]		0.72 [0.44,1.15]	
	Q4	0.96 [0.50,1.83]		0.79 [0.46,1.36]	
Synovitis/effusion	Q1	ref	0.522	ref	0.061
	Q2	0.69 [0.39,1.23]	*0.849*	0.81 [0.51,1.29]	*0.008*
	Q3	0.72 [0.38,1.33]		0.58 [0.34,0.98]	
	Q4	0.86 [0.45,1.64]		0.49 [0.28,0.86]	

OR odds ratio, BML bone marrow lesion, TF tibiofemoral joint, PF patellofemoral joint,
†ORs are adjusted for body weight, quadriceps area, hamstring area, height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time watching TV and NSAIDs use.
p-value overall p-value from Score statistics

Table 27. Association between Hamstring Density and Knee Outcomes (Men n=590, Women n=903)

Outcome	**Hamstring density**	**Men OR† [95%CI]**	**p-value** *p* **trend**	**Women OR† [95%CI]**	**p-value** ***p trend***
BML medial TF	Q1	ref	0.597	ref	0.482
	Q2	0.81 [0.45,1.48]	*0.181*	0.96 [0.60,1.53]	*0.154*
	Q3	0.74 [0.39,1.40]		0.91 [0.54,1.53]	
	Q4	0.62 [0.32,1.21]		0.63 [0.33,1.19]	
BML lateral TF	Q1	ref	0.289	ref	0.784
	Q2	1.77 [0.79,4.00]	*0.437*	0.86 [0.52,1.41]	*0.411*
	Q3	1.17 [0.46,3.01]		0.71 [0.37,1.35]	
	Q4	0.81 [0.31,2.13]		0.80 [0.41,1.56]	
BML PF	Q1	ref	0.791	ref	**0.0002**
	Q2	0.99 [0.57,1.74]	*0.842*	0.56 [0.37,0.83]	*0.0001*
	Q3	0.87 [0.49,1.53]		0.61 [0.39,0.96]	
	Q4	1.10 [0.59,2.07]		0.33 [0.20,0.56]	
BML knee	Q1	ref	0.872	ref	**0.005**
	Q2	1.06 [0.59,1.88]	*0.566*	0.58 [0.37,0.91]	*0.001*
	Q3	0.86 [0.46,1.58]		0.57 [0.35,0.93]	
	Q4	0.87 [0.44,1.70]		0.39 [0.23,0.65]	
Cartilage medial TF	Q1	ref	0.068	ref	0.471
	Q2	0.47 [0.26,0.84]	*0.233*	0.85 [0.58,1.25]	*0.165*
	Q3	0.68 [0.37,1.23]		0.72 [0.46,1.11]	
	Q4	0.56 [0.29,1.06]		0.73 [0.45,1.18]	
Cartilage lateral TF	Q1	ref	0.099	ref	0.927
	Q2	1.01 [0.49,2.08]	*0.019*	1.10 [0.71,1.72]	*0.749*
	Q3	0.62 [0.30,1.26]		0.98 [0.59,1.64]	
	Q4	0.41 [0.18,0.95]		0.93 [0.52,1.66]	
Cartilage PF	Q1	ref	0.149	ref	**0.002**
	Q2	1.39 [0.77,2.52]	*0.707*	0.51 [0.30,0.86]	*0.001*
	Q3	0.76 [0.41,1.41]		0.47 [0.27,0.84]	
	Q4	1.04 [0.53,2.04]		0.34 [0.19,0.61]	
Cartilage knee	Q1	ref	0.590	ref	**0.008**
	Q2	0.67 [0.27,1.66]	*0.215*	0.52 [0.27,1.00]	*0.001*
	Q3	0.55 [0.22,1.39]		0.43 [0.22,0.84]	
	Q4	0.55 [0.21,1.45]		0.32 [0.16,0.63]	

Table 27 continued

Outcome	Hamstring density	Men OR† [95%CI]	p-value p trend	Women OR† [95%CI]	p-value *p trend*
Meniscus medial	Q1	ref	0.146	ref	0.448
	Q2	0.60 [0.35,1.03]	*0.445*	1.00 [0.65,1.54]	*0.498*
	Q3	0.90 [0.5,1.62]		0.71 [0.42,1.18]	
	Q4	0.66 [0.35,1.25]		0.92 [0.53,1.58]	
Meniscus lateral	Q1	ref	0.778	ref	0.362
	Q2	1.02 [0.42,2.43]	*0.600*	1.25 [0.74,2.11]	*0.378*
	Q3	1.14 [0.48,2.72]		0.73 [0.39,1.37]	
	Q4	0.74 [0.27,2.00]		0.81 [0.38,1.72]	
Meniscus any	Q1	ref	0.116	ref	0.478
	Q2	0.60 [0.34,1.05]	*0.442*	1.06 [0.68,1.67]	*0.324*
	Q3	0.93 [0.51,1.71]		0.74 [0.45,1.22]	
	Q4	0.65 [0.34,1.26]		0.83 [0.48,1.44]	
Synovitis/effusion	Q1	ref	0.982	ref	**0.015**
	Q2	1.01 [0.55,1.85]	*0.963*	0.72 [0.48,1.08]	*0.002*
	Q3	1.08 [0.58,2.01]		0.66 [0.42,1.05]	
	Q4	0.97 [0.48,1.97]		0.44 [0.27,0.73]	

OR odds ratio, BML bone marrow lesion, TF tibiofemoral joint, PF patellofemoral joint,
†ORs are adjusted for body weight, quadriceps area, hamstring area, height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time watching TV and NSAIDs use.
p-value overall p-value from Score statistics

Table 28. Associations between Quadriceps Specific Strength and Knee Outcomes (men n=272, women n=429)

Outcome	Specific strength	Men OR‡ [95%CI]	p-value *p trend*	Women OR‡ [95%CI]	p-value *p trend*
BML medial TF	T1	ref	0.110	ref	0.672
	T2	0.73 [0.36,1.49]	*0.207*	0.92 [0.49,1.72]	*0.565*
	T3	1.52 [0.77,2.97]		1.23 [0.64,2.36]	
BML lateral TF	T1	ref	0.087	ref	**0.001**
	T2	0.24 [0.07,0.85]	*0.400*	0.94 [0.50,1.76]	*0.001*
	T3	0.68 [0.26,1.83]		0.20 [0.08,0.48]	
BML PF	T1	ref	**0.004**	ref	0.272
	T2	0.43 [0.22,0.84]	*0.413*	1.07 [0.65,1.77]	*0.227*
	T3	1.30 [0.68,2.50]		0.71 [0.42,1.22]	
BML knee	T1	ref	**0.049**	ref	0.187
	T2	0.52 [0.27,1.02]	*0.689*	1.02 [0.59,1.75]	*0.126*
	T3	1.13 [0.58,2.22]		0.65 [0.37,1.14]	
Cartilage medial TF	T1	ref	0.067	ref	0.365
	T2	0.48 [0.25,0.93]	*0.656*	0.93 [0.56,1.52]	*0.180*
	T3	0.85 [0.45,1.63]		0.70 [0.41,1.18]	
Cartilage lateral TF	T1	ref	0.402	ref	**0.005**
	T2	0.57 [0.24,1.31]	*0.676*	1.16 [0.65,2.06]	*0.012*
	T3	0.86 [0.39,1.91]		0.43 [0.22,0.81]	
Cartilage PF	T1	ref	0.340	ref	**0.008**
	T2	0.63 [0.31,1.27]	*0.210*	1.58 [0.85,2.92]	*0.093*
	T3	0.64 [0.32,1.26]		0.61 [0.34,1.10]	
Cartilage knee	T1	ref	0.194	ref	**0.009**
	T2	0.46 [0.19,1.11]	*0.164*	1.48 [0.71,3.12]	*0.045*
	T3	0.52 [0.22,1.25]		0.50 [0.25,1.01]	
Meniscus medial	T1	ref	0.255	ref	0.584
	T2	1.05 [0.55,1.97]	*0.134*	1.27 [0.73,2.20]	*0.339*
	T3	1.62 [0.86,3.06]		1.32 [0.74,2.36]	
Meniscus lateral	T1	ref	0.492	ref	**0.044**
	T2	1.10 [0.44,2.77]	*0.355*	0.83 [0.41,1.68]	*0.017*
	T3	0.61 [0.22,1.66]		0.36 [0.16,0.82]	
Meniscus any	T1	ref	0.836	ref	0.395
	T2	0.93 [0.48,1.79]	*0.703*	0.89 [0.53,1.51]	*0.185*
	T3	1.13 [0.59,2.17]		0.68 [0.39,1.19]	
Synovitis/effusion	T1	ref	0.242	ref	**0.0003**
	T2	0.53 [0.25,1.11]	*0.322*	0.75 [0.44,1.29]	*0.0001*
	T3	0.68 [0.32,1.41]		0.33 [0.19,0.59]	

OR odds ratio, BML bone marrow lesion, TF tibiofemoral joint, PF patellofemoral joint,
‡ORs are adjusted for height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time watching TV and NSAIDs use.
p-value overall p-value/ from Score statistics

5.0 DISSERTATION DISCUSSION

5.1 SUMMARY OF THE FINDINGS

The overall aim of this dissertation was to examine lifestyle-related factors such as physical activity, body composition and thigh composition in relation to structural changes in the knees of older adults. The association between physical activity and radiographic or clinical knee OA have been inconclusive [32,100,101,103,106,132]. Recent studies using MRI suggest that physical activity would be beneficial for healthy knee joints but may have adverse effects if an individual has risk factors for knee OA and/or existing tissue damage [116,118,125,126]. However, the effects of physical activity on knee joints of older adults have not been established. Obesity is an established risk factor for knee OA. Recent literature highlights the metabolic aspect of knee OA [5,166,168]. However, there are few studies which examine the association between each fat depot and knee outcomes to support metabolic mechanisms. Whether mechanical or metabolic mechanisms are more important has not been investigated.

Higher physical activity levels were associated with two times higher odds of severe cartilage damage in the medial TF joint compared with being inactive in older adults without knee pain in the Health ABC. Physical activity level was defined based on total energy expenditure and energy expenditure for exercise which were estimated using a comprehensive activity questionnaire. In addition, sex differences were found. Male exercisers had more cartilage damage in the lateral TF joint compared with inactive, whereas female exercisers had less cartilage damage in the medial TF joint compared with inactive participants. Although the design of this study was cross-sectional, the results suggest that knee joint cartilage in older adults may be vulnerable to higher physical activity levels.

Older adults spend substantial time in sedentary behavior [3]. Time in sedentary behavior is associated with higher mortality even after taking into account the time spent in moderate-vigorous activity [57]. Knee joint cartilage volume loss after spinal cord injury in humans has been reported, where the loading and motion in the knee joint have decreased [130]. However, the effect of sedentary time on the knee joints is unknown. The current study found no association between hours watching TV and structural changes in the knees in older adults who did not have knee pain. In those with pain in one or both knees, watching TV for ≥7 hours/week was associated with over two times higher odds of BML in the whole knee, and watching TV for ≥14 hours/week was associated with 2.6 times higher odds of severe cartilage damage in the medial TF joint, compared to watching TV for <7 hours/week. The results in those without knee pain suggest that sedentary time is not causally associated with structural changes in the knee, but that older adults may have spent more time in sedentary behavior due to knee pain from structural changes in the knee. Since knee OA is one of the major causes of disability [16], the current study underlines the importance of controlling symptoms of knee OA and prevention efforts to decrease sedentary lifestyle, disability, and mortality in older adults.

Obesity is one of the few established and modifiable risk factors for knee OA [4]. However, the detailed mechanisms have not been established. The recent literature highlights the association between metabolic risk factors and knee OA [5,166,168]. First, higher appendicular lean mass rather than total body fat mass was associated with structural changes in the knees.

Consequently, the study did not find evidence that higher fat mass is more strongly associated with worse knee outcomes when concurrently adjusting for appendicular lean mass. Secondly, greater VAT area per body weight was not associated with higher odds of worse knee outcomes. Thirdly, 1 cm^2 increase in abdominal SAT area per body weight was associated with over 20% higher odds of any BML, cartilage damage in PF joint, and severe meniscus damage only in women, and the associations were not attenuated by inflammatory markers, adipokines, insulin resistance, lipids or cardiometabolic diseases. These three findings suggest that higher overall body weight rather than total adiposity or central adiposity may be the more primary mechanism for structural changes in the knee.

The associations between knee extensor muscle strength and the development of knee OA/structural changes have been inconclusive [117,206,208,209]. One of the mitigating reasons could be that the measurement of maximum knee extensor force can be hindered by knee symptoms from early degenerative changes which are not detected on knee radiographs. Adipose tissues in skeletal muscles are associated with lower muscle strength [152] and incident mobility limitation[153]. Muscle fat infiltration could be associated with the development of knee OA through lower muscle strength. This dissertation found that higher thigh density (indicating lower intramuscular fat), specifically for quadriceps in men and hamstrings in women, was associated with lower odds of structural changes in the knees, such as BML and cartilage damage, independent of body weight and thigh muscle area. Higher quadriceps specific strength was associated with lower odds of structural changes in the lateral compartment in women. Thigh IMAT and thigh SAT were generally not associated with the knee outcomes. These results suggest that thigh muscle quality such as intramuscular fat and strength is more important for knee structural changes than adipose tissue per se. Exercise affects thigh intramuscular fat [236] . The positive effects of exercise on knee OA could be mediated by lower thigh fat infiltration as well as higher knee extensor strength.

The results of these studies suggest that mechanical mechanisms such as higher body weight and poor thigh muscle quality are important for structural changes in the knee rather than metabolic mechanisms. In addition, the results show that knee joint cartilage of older adults would be vulnerable to higher levels of physical activity, which is also primarily a mechanical factor.

5.2 PUBLIC HEALTH SIGNIFICANCE

Knee OA is a common disorder in older adults. The estimated prevalence of radiographic knee OA was 37 % among people aged 60 years or older in the US [1]. Knee OA is one of the major causes of functional limitations [16] and the third highest cause of Years Lost to Disability (YLD) in the US [17]. However, currently no approved therapy exists which slows or reverses the progression of knee OA. The current therapy for knee OA is primarily symptom control or joint replacement surgery in severe cases. Being obese is associated with over 2.5 higher risk of knee OA [4]. In the US 35% or 78.6 million adults are obese [238]. The burden of knee OA is expected to increase in aging populations with high prevalence of obesity. Therefore, knee OA is a significant public health issue.

Findings in this dissertation show the importance of mechanical factors such as higher body weight, higher levels of physical activity, lower thigh muscle density, and lower knee extensor strength for structural changes in the knees of older adults rather than metabolic mechanisms. This informs the strategy for knee OA prevention and control. However, the recent literature tends to put great emphasis on the metabolic aspects of knee OA, which might be misguided [5,166,168]. If the metabolic mechanism has a greater impact on knee OA development than the mechanical mechanism, the strategy of modifying metabolic factors such as inflammation, insulin resistance, and lipid profiles might be effective. Based on the findings in this dissertation, controlling body weight, maintaining good muscle quality, and having moderate levels of physical activity would be recommended for knee OA prevention and control. Given that currently there are no approved disease-modifying OA drugs, interventions targeting mechanical factors would be especially important. Exercise which helps to maintain or improve thigh muscle quality – muscle density and muscle strength – might be beneficial for knee joints of older adults.

5.3 FUTURE DIRECTIONS

Since the results consistently found that mechanical risk factors were associated with structural changes in the knees of older adults, future work should focus on elucidating mechanisms for these associations. No association was found between sedentary time and structural changes in the knees of older adults who did not have knee pain. Subjective measures of physical activity tend to underestimate time spent in sedentary behavior compared with objective measurements[61]. In addition, time watching TV was used as a surrogate for the amount of time in sedentary behavior. Future longitudinal studies using accelerometers to assess time spent in sedentary behavior are needed to determine the effects of sedentary time on knee joints and make recommendations for physical activity levels in older adults. The classification of physical activity types, such as weight-bearing or non-weight bearing was not available. Knee injury increases the risk of knee OA by about three times [4]. Thus, future work is necessary to determine the types of physical activities which would be safe for knee joints in older adults.

Findings in this dissertation support the importance of higher weight on knee tissue degeneration. Longitudinal studies are needed to examine the association between body weight change and changes in knee structural outcomes. Especially, more clinical trials are needed to examine the association between weight loss intervention and changes in knee MRI outcomes. Muscle group-compartment specific relationships may exist in the associations between thigh muscle quality and structural changes in the knees, though this needs to be further investigated. The effects of knee alignment on these associations as well as on the sex differences in the effects of physical activity need to be examined. Studying whether intra- and extra-myocellular lipid in intramuscular fat have differential effects on knee tissue degeneration using magnetic resonance spectroscopy is another area of future study. Longitudinal studies are needed to examine the association between thigh muscle quality and changes in knee structural outcomes. A small study found that muscle density increased with training in healthy community-dwelling older adults [236]. Examining whether exercise interventions which maintain and improve muscle quality can prevent structural change in the knees would help to decrease the burden of knee OA.

BIBLIOGRAPHY

1. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *Journal of Rheumatology.* 2006;33(11):2271-2279.
2. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Medicine and science in sports and exercise.* 2007;39(8):1435-1445.
3. Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the United States, 2003-2004. *American journal of epidemiology.* 2008;167(7):875-881.
4. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2010;18(1):24-33.
5. Yoshimura N, Muraki S, Oka H, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2012;20(11):1217-1226.
6. Engstrom G, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2009;17(2):168-173.
7. Kornaat PR, Sharma R, van der Geest RJ, et al. Positive association between increased popliteal artery vessel wall thickness and generalized osteoarthritis: is OA also part of the metabolic syndrome? *Skeletal radiology.* 2009;38(12):1147-1151.
8. Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD. Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2011;12(9):680-687.
9. Wormser D, Kaptoge S, Di Angelantonio E, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet.* 2011;377(9771):1085-1095.
10. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation.* 2007;116(1):39-48.

11. Dulloo AG, Jacquet J, Solinas G, Montani JP, Schutz Y. Body composition phenotypes in pathways to obesity and the metabolic syndrome. *International journal of obesity.* 2010;34 Suppl 2:S4-17.
12. Cameron AJ, Magliano DJ, Soderberg S. A systematic review of the impact of including both waist and hip circumference in risk models for cardiovascular diseases, diabetes and mortality. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2013;14(1):86-94.
13. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis and rheumatism.* 2008;58(1):26-35.
14. Losina E, Weinstein AM, Reichmann WM, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis care & research.* 2013;65(5):703-711.
15. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis and rheumatism.* 1995;38(8):1134-1141.
16. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *American journal of public health.* 1994;84(3):351-358.
17. Michaud CM, McKenna MT, Begg S, et al. The burden of disease and injury in the United States 1996. *Population health metrics.* 2006;4:11.
18. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Annals of the rheumatic diseases.* 2014;73(7):1323-1330.
19. Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study. *Annals of the rheumatic diseases.* 2004;63(4):395-401.
20. de Klerk BM, Schiphof D, Groeneveld FP, et al. No clear association between female hormonal aspects and osteoarthritis of the hand, hip and knee: a systematic review. *Rheumatology.* 2009;48(9):1160-1165.
21. Felson DT, Niu J, Gross KD, et al. Valgus malalignment is a risk factor for lateral knee osteoarthritis incidence and progression: findings from the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative. *Arthritis and rheumatism.* 2013;65(2):355-362.
22. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. *Bmj.* 1996;312(7036):940-943.
23. MacGregor AJ, Li Q, Spector TD, Williams FM. The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee. *Rheumatology.* 2009;48(3):277-280.
24. Ding C, Cicuttini F, Scott F, Stankovich J, Cooley H, Jones G. The genetic contribution and relevance of knee cartilage defects: case-control and sib-pair studies. *The Journal of rheumatology.* 2005;32(10):1937-1942.
25. Sowers M, Lachance L, Hochberg M, Jamadar D. Radiographically defined osteoarthritis of the hand and knee in young and middle-aged African American and Caucasian women. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2000;8(2):69-77.

26. Kopec JA, Sayre EC, Schwartz TA, et al. Occurrence of radiographic osteoarthritis of the knee and hip among African Americans and whites: a population-based prospective cohort study. *Arthritis care & research.* 2013;65(6):928-935.
27. Zhang Y, Xu L, Nevitt MC, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing Osteoarthritis Study. *Arthritis and rheumatism.* 2001;44(9):2065-2071.
28. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. *Arthritis care & research.* 2011;63(8):1115-1125.
29. Tanamas S, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. *Arthritis and rheumatism.* 2009;61(4):459-467.
30. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Annals of the rheumatic diseases.* 1957;16(4):494-502.
31. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2007;15 Suppl A:A1-56.
32. Barbour KE, Hootman JM, Helmick CG, et al. Meeting physical activity guidelines and the risk of incident knee osteoarthritis: a population-based prospective cohort study. *Arthritis care & research.* 2014;66(1):139-146.
33. Felson DT, Zhang Y, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum.* 1995;38(10):1500-1505.
34. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and rheumatism.* 1986;29(8):1039-1049.
35. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2004;12(2):169-174.
36. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2008;16(12):1433-1441.
37. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. *Osteoarthritis & Cartilage.* 2004;12(3):177-190.
38. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2011;19(8):990-1002.
39. Hunter DJ, Lo GH, Gale D, Grainger AJ, Guermazi A, Conaghan PG. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds Osteoarthritis Knee Score). *Annals of the rheumatic diseases.* 2008;67(2):206-211.
40. Felson DT, Lynch J, Guermazi A, et al. Comparison of BLOKS and WORMS scoring systems part II. Longitudinal assessment of knee MRIs for osteoarthritis and suggested

approach based on their performance: data from the Osteoarthritis Initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2010;18(11):1402-1407.
41. Guermazi A, Roemer FW, Haugen IK, Crema MD, Hayashi D. MRI-based semiquantitative scoring of joint pathology in osteoarthritis. *Nature reviews. Rheumatology*. 2013;9(4):236-251.
42. Javaid MK, Kiran A, Guermazi A, et al. Individual magnetic resonance imaging and radiographic features of knee osteoarthritis in subjects with unilateral knee pain: the health, aging, and body composition study. *Arthritis and rheumatism.* 2012;64(10):3246-3255.
43. Wildi LM, Raynauld JP, Martel-Pelletier J, Abram F, Dorais M, Pelletier JP. Relationship between bone marrow lesions, cartilage loss and pain in knee osteoarthritis: results from a randomised controlled clinical trial using MRI. *Annals of the rheumatic diseases.* 2010;69(12):2118-2124.
44. Wildi LM, Raynauld JP, Martel-Pelletier J, et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Annals of the rheumatic diseases.* 2011;70(6):982-989.
45. Bennell KL, Bowles KA, Payne C, et al. Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *Bmj.* 2011;342:d2912.
46. Wang Y, Hall S, Hanna F, et al. Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. *BMC musculoskeletal disorders.* 2011;12:195.
47. Eckstein F, Kwoh CK, Boudreau RM, et al. Quantitative MRI measures of cartilage predict knee replacement: a case-control study from the Osteoarthritis Initiative. *Annals of the rheumatic diseases*. 2013;72(5):707-714.
48. Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. *Radiology.* 2004;232(2):592-598.
49. Urish KL, Keffalas MG, Durkin JR, Miller DJ, Chu CR, Mosher TJ. T2 texture index of cartilage can predict early symptomatic OA progression: data from the osteoarthritis initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2013;21(10):1550-1557.
50. Reichenbach S, Guermazi A, Niu J, et al. Prevalence of bone attrition on knee radiographs and MRI in a community-based cohort. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2008;16(9):1005-1010.
51. Neogi T, Bowes MA, Niu J, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the osteoarthritis initiative. *Arthritis and rheumatism.* 2013;65(8):2048-2058.
52. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of internal medicine.* 2006;144(2):73-81.
53. Brach JS, Simonsick EM, Kritchevsky S, Yaffe K, Newman AB. The association between physical function and lifestyle activity and exercise in the health, aging and body composition study. *Journal of the American Geriatrics Society.* 2004;52(4):502-509.

54. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis & rheumatology (Hoboken, N.J.).* 2014;66(3):622-636.
55. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2014;22(3):363-388.
56. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis care & research.* 2012;64(4):465-474.
57. Matthews CE, George SM, Moore SC, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. *The American journal of clinical nutrition.* 2012;95(2):437-445.
58. Lee IM. *Epidemiologic Methods in Physical Activity Studies* Oxford University Press; 2008.
59. Cain KL, Conway TL, Adams MA, Husak LE, Sallis JF. Comparison of older and newer generations of ActiGraph accelerometers with the normal filter and the low frequency extension. *The international journal of behavioral nutrition and physical activity.* 2013;10:51.
60. Kowalski K, Rhodes R, Naylor PJ, Tuokko H, MacDonald S. Direct and indirect measurement of physical activity in older adults: a systematic review of the literature. *The international journal of behavioral nutrition and physical activity.* 2012;9:148.
61. Gennuso KP, Matthews CE, Colbert LH. Reliability and Validity of Two Self-Report Measures to Assess Sedentary Behavior in Older Adults. *Journal of physical activity & health.* 2014.
62. Colbert LH, Visser M, Simonsick EM, et al. Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging and Body Composition Study. *Journal of the American Geriatrics Society.* 2004;52(7):1098-1104.
63. Groffen DA, Koster A, Bosma H, et al. Unhealthy lifestyles do not mediate the relationship between socioeconomic status and incident depressive symptoms: the Health ABC study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2013;21(7):664-674.
64. Havlik R, Simonsick EM, Sutton-Tyrrell K, et al. Association of physical activity and less vascular stiffness in 70-79 year olds: The Health ABC Study. *J Aging and Physical Activity.* 2003;11:156-166.
65. Hawkins M, Newman AB, Madero M, et al. TV Watching, But Not Physical Activity, is Associated With Change in Kidney Function in Older Adults. *Journal of physical activity & health.* 2014.
66. Koster A, Patel KV, Visser M, et al. Joint effects of adiposity and physical activity on incident mobility limitation in older adults. *Journal of the American Geriatrics Society.* 2008;56(4):636-643.
67. Koster A, Penninx BW, Newman AB, et al. Lifestyle factors and incident mobility limitation in obese and non-obese older adults. *Obesity (Silver Spring, Md.).* 2007;15(12):3122-3132.
68. Kritchevsky SB, Nicklas BJ, Visser M, et al. Angiotensin-converting enzyme insertion/deletion genotype, exercise, and physical decline. *Jama.* 2005;294(6):691-698.

69. Lee JS, Kritchevsky SB, Tylavsky FA, et al. Weight-loss intention in the well-functioning, community-dwelling elderly: associations with diet quality, physical activity, and weight change. *The American journal of clinical nutrition.* 2004;80(2):466-474.
70. Peterson MJ, Giuliani C, Morey MC, et al. Physical activity as a preventative factor for frailty: the health, aging, and body composition study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2009;64(1):61-68.
71. Peterson MJ, Morey MC, Giuliani C, et al. Walking in old age and development of metabolic syndrome: the health, aging, and body composition study. *Metabolic syndrome and related disorders.* 2010;8(4):317-322.
72. Pettee KK, Brach JS, Kriska AM, et al. Influence of marital status on physical activity levels among older adults. *Medicine and science in sports and exercise.* 2006;38(3):541-546.
73. Thorpe RJ, Jr., Kreisle RA, Glickman LT, Simonsick EM, Newman AB, Kritchevsky S. Physical activity and pet ownership in year 3 of the Health ABC study. *Journal of aging and physical activity.* 2006;14(2):154-168.
74. Visser M, Simonsick EM, Colbert LH, et al. Type and intensity of activity and risk of mobility limitation: the mediating role of muscle parameters. *Journal of the American Geriatrics Society.* 2005;53(5):762-770.
75. Wilson VK, Houston DK, Kilpatrick L, et al. Relationship between 25-hydroxyvitamin D and cognitive function in older adults: the Health, Aging and Body Composition Study. *Journal of the American Geriatrics Society.* 2014;62(4):636-641.
76. Yaffe K, Fiocco AJ, Lindquist K, et al. Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology.* 2009;72(23):2029-2035.
77. Griffin TM, Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. *Exercise and sport sciences reviews.* 2005;33(4):195-200.
78. Palmer KT. Occupational activities and osteoarthritis of the knee. *Br Med Bull.* 2012;102:147-170.
79. McWilliams DF, Leeb BF, Muthuri SG, Doherty M, Zhang W. Occupational risk factors for osteoarthritis of the knee: a meta-analysis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2011;19(7):829-839.
80. Martin KR, Kuh D, Harris TB, Guralnik JM, Coggon D, Wills AK. Body mass index, occupational activity, and leisure-time physical activity: an exploration of risk factors and modifiers for knee osteoarthritis in the 1946 British birth cohort. *BMC musculoskeletal disorders.* 2013;14:219.
81. Sohn RS, Micheli LJ. The effect of running on the pathogenesis of osteoarthritis of the hips and knees. *Clin Orthop.* 1985(198):106-109.
82. Panush RS, Schmidt C, Caldwell JR, et al. Is running associated with degenerative joint disease? *Jama.* 1986;255(9):1152-1154.
83. Konradsen L, Hansen EM, Sondergaard L. Long distance running and osteoarthrosis. *The American journal of sports medicine.* 1990;18(4):379-381.
84. Lane NE, Bloch DA, Hubert HB, Jones H, Simpson U, Fries JF. Running, osteoarthritis, and bone density: initial 2-year longitudinal study. *Am J Med.* 1990;88(5):452-459.
85. Lane NE, Michel B, Bjorkengren A, et al. The risk of osteoarthritis with running and aging: a 5-year longitudinal study. *Journal of Rheumatology.* 1993;20(3):461-468.
86. Chakravarty EF, Hubert HB, Lingala VB, Zatarain E, Fries JF. Long distance running and knee osteoarthritis. A prospective study. *Am J Prev Med.* 2008;35(2):133-138.

87. Spector TD, Harris PA, Hart DJ, et al. Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. *Arthritis & Rheumatism.* 1996;39(6):988-995.
88. Thelin N, Holmberg S, Thelin A. Knee injuries account for the sports-related increased risk of knee osteoarthritis. *Scandinavian journal of medicine & science in sports.* 2006;16(5):329-333.
89. Vrezas I, Elsner G, Bolm-Audorff U, Abolmaali N, Seidler A. Case-control study of knee osteoarthritis and lifestyle factors considering their interaction with physical workload.[Erratum appears in Int Arch Occup Environ Health. 2010 Aug;83(6):713]. *Int Arch Occup Environ Health.* 2010;83(3):291-300.
90. Kujala UM, Kaprio J, Sarna S. Osteoarthritis of weight bearing joints of lower limbs in former elite male athletes. *Bmj.* 1994;308(6923):231-234.
91. Sandmark H, Vingard E. Sports and risk for severe osteoarthrosis of the knee. *Scand J Med Sci Sports.* 1999;9(5):279-284.
92. Michaelsson K, Byberg L, Ahlbom A, Melhus H, Farahmand BY. Risk of severe knee and hip osteoarthritis in relation to level of physical exercise: a prospective cohort study of long-distance skiers in Sweden. *PLoS ONE.* 2011;43.
93. Majewski M, Susanne H, Klaus S. Epidemiology of athletic knee injuries: A 10-year study. *The Knee.* 2006;13(3):184-188.
94. Swenson DM, Collins CL, Best TM, Flanigan DC, Fields SK, Comstock RD. Epidemiology of knee injuries among U.S. high school athletes, 2005/2006-2010/2011. *Medicine and science in sports and exercise.* 2013;45(3):462-469.
95. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. *Journal of athletic training.* 2007;42(2):311-319.
96. Szoeke CE, Cicuttini FM, Guthrie JR, Clark MS, Dennerstein L. Factors affecting the prevalence of osteoarthritis in healthy middle-aged women: data from the longitudinal Melbourne Women's Midlife Health Project. *Bone.* 2006;39(5):1149-1155.
97. Szoeke C, Dennerstein L, Guthrie J, Clark M, Cicuttini F. The relationship between prospectively assessed body weight and physical activity and prevalence of radiological knee osteoarthritis in postmenopausal women. *Journal of Rheumatology.* 2006;33(9):1835-1840.
98. Hannan MT, Felson DT, Anderson JJ, Naimark A. Habitual physical activity is not associated with knee osteoarthritis: the Framingham Study. *The Journal of rheumatology.* 1993;20(4):704-709.
99. Felson DT, Zhang Y, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis and rheumatism.* 1997;40(4):728-733.
100. McAlindon TE, Wilson PW, Aliabadi P, Weissman B, Felson DT. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study. *Am J Med.* 1999;106(2):151-157.
101. Felson DT, Niu J, Clancy M, Sack B, Aliabadi P, Zhang Y. Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: the Framingham Study. *Arthritis & Rheumatism.* 2007;57(1):6-12.

102. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis & Rheumatism.* 1999;42(1):17-24.
103. Cooper C, Snow S, McAlindon TE, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis & Rheumatism.* 2000;43(5):995-1000.
104. Taylor HL, Jacobs DR, Jr., Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *Journal of chronic diseases.* 1978;31(12):741-755.
105. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol.* 1993;46(2):153-162.
106. Felson DT, Niu J, Yang T, et al. Physical activity, alignment and knee osteoarthritis: data from MOST and the OAI. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2013;21(6):789-795.
107. Sutton AJ, Muir KR, Mockett S, Fentem P. A case-control study to investigate the relation between low and moderate levels of physical activity and osteoarthritis of the knee using data collected as part of the Allied Dunbar National Fitness Survey. *Annals of the rheumatic diseases.* 2001;60(8):756-764.
108. Verweij LM, van Schoor NM, Deeg DJ, Dekker J, Visser M. Physical activity and incident clinical knee osteoarthritis in older adults. *Arthritis & Rheumatism.* 2009;61(2):152-157.
109. Cheng Y, Macera CA, Davis DR, Ainsworth BE, Troped PJ, Blair SN. Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor? *J Clin Epidemiol.* 2000;53(3):315-322.
110. Rogers LQ, Macera CA, Hootman JM, Ainsworth BE, Blairi SN. The association between joint stress from physical activity and self-reported osteoarthritis: an analysis of the Cooper Clinic data. *Osteoarthritis & Cartilage.* 2002;10(8):617-622.
111. Hootman JM, Macera CA, Helmick CG, Blair SN. Influence of physical activity-related joint stress on the risk of self-reported hip/knee osteoarthritis: a new method to quantify physical activity. *Prev Med.* 2003;36(5):636-644.
112. Manninen P, Riihimaki H, Heliovaara M, Suomalainen O. Physical exercise and risk of severe knee osteoarthritis requiring arthroplasty. *Rheumatology.* 2001;40(4):432-437.
113. Wang Y, Simpson JA, Wluka AE, et al. Is physical activity a risk factor for primary knee or hip replacement due to osteoarthritis? A prospective cohort study. *Journal of Rheumatology.* 2011;38(2):350-357.
114. Ageberg E, Engstrom G, Gerhardsson de Verdier M, Rollof J, Roos EM, Lohmander LS. Effect of leisure time physical activity on severe knee or hip osteoarthritis leading to total joint replacement: a population-based prospective cohort study. *BMC musculoskeletal disorders.* 2012;13:73.
115. Nyland J, Kanouse Z, Krupp R, Caborn D, Jakob R. Total knee arthroplasty in motivated patients with knee osteoarthritis and athletic activity approach type goals: a conceptual decision-making model. *Disability and rehabilitation.* 2011;33(17-18):1683-1692.
116. Racunica TL, Teichtahl AJ, Wang Y, et al. Effect of Physical Activity On Articular Knee Joint Structures in Community-Based Adults. *Arthritis & Rheumatism Arthritis Care & Research.* 2007;57(7):1261-1268.
117. Ding C, Martel-Pelletier J, Pelletier JP, et al. Two-year prospective longitudinal study exploring the factors associated with change in femoral cartilage volume in a cohort

largely without knee radiographic osteoarthritis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2008;16(4):443-449.

118. Stehling C, Lane NE, Nevitt MC, Lynch J, McCulloch CE, Link TM. Subjects with higher physical activity levels have more severe focal knee lesions diagnosed with 3T MRI: analysis of a non-symptomatic cohort of the osteoarthritis initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2010;18(6):776-786.
119. Hovis KK, Stehling C, Souza RB, et al. Physical activity is associated with magnetic resonance imaging-based knee cartilage T2 measurements in asymptomatic subjects with and those without osteoarthritis risk factors. *Arthritis and rheumatism.* 2011;63(8):2248-2256.
120. Stehling C, Liebl H, Krug R, et al. Patellar cartilage: T2 values and morphologic abnormalities at 3.0-T MR imaging in relation to physical activity in asymptomatic subjects from the osteoarthritis initiative. *Radiology.* 2010;254(2):509-520.
121. Kretzschmar M, Lin W, Nardo L, et al. Association of physical activity measured by accelerometer, knee joint abnormalities and cartilage T2-measurements obtained from 3T MRI: Data from the Osteoarthritis Initiative. *Arthritis care & research.* 2015.
122. Kumar D, Souza RB, Singh J, et al. Physical activity and spatial differences in medial knee T1rho and t2 relaxation times in knee osteoarthritis. *J Orthop Sports Phys Ther.* 2014;44(12):964-972.
123. Hanna FS, Bell RJ, Davis SR, et al. Factors affecting patella cartilage and bone in middle-aged women. *Arthritis & Rheumatism.* 2007;57(2):272-278.
124. Hanna F, Ebeling PR, Wang Y, et al. Factors influencing longitudinal change in knee cartilage volume measured from magnetic resonance imaging in healthy men. *Annals of the rheumatic diseases.* 2005;64(7):1038-1042.
125. Foley S, Ding C, Cicuttini F, Jones G. Physical activity and knee structural change: a longitudinal study using MRI. *Medicine and science in sports and exercise.* 2007;39(3):426-434.
126. Dore DA, Winzenberg TM, Ding C, et al. The association between objectively measured physical activity and knee structural change using MRI. *Annals of the rheumatic diseases.* 2013;72(7):1170-1175.
127. Wijayaratne SP, Teichtahl AJ, Wluka AE, et al. The determinants of change in patella cartilage volume--a cohort study of healthy middle-aged women. *Rheumatology.* 2008;47(9):1426-1429.
128. Teichtahl AJ, Wluka AE, Forbes A, et al. Longitudinal effect of vigorous physical activity on patella cartilage morphology in people without clinical knee disease. *Arthritis & Rheumatism.* 2009;61(8):1095-1102.
129. Lin W, Alizai H, Joseph GB, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2013;21(10):1558-1566.
130. Vanwanseele B, Eckstein F, Knecht H, Spaepen A, Stussi E. Longitudinal analysis of cartilage atrophy in the knees of patients with spinal cord injury. *Arthritis and rheumatism.* 2003;48(12):3377-3381.
131. Moriyama H, Yoshimura O, Kawamata S, et al. Alteration in articular cartilage of rat knee joints after spinal cord injury. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2008;16(3):392-398.

132. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis and rheumatism.* 1999;42(1):17-24.
133. Davies-Tuck ML, Wluka AE, Wang Y, et al. The natural history of cartilage defects in people with knee osteoarthritis. *Osteoarthritis & Cartilage.* 2008;16(3):337-342.
134. Teichtahl AJ, Wluka AE, Wang Y, et al. Obesity and adiposity are associated with the rate of patella cartilage volume loss over 2 years in adults without knee osteoarthritis. *Annals of the rheumatic diseases.* 2009;68(6):909-913.
135. Jiang L, Tian W, Wang Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. *Joint, bone, spine : revue du rhumatisme.* 2012;79(3):291-297.
136. Sowers M, Karvonen-Gutierrez CA, Palmieri-Smith R, Jacobson JA, Jiang Y, Ashton-Miller JA. Knee osteoarthritis in obese women with cardiometabolic clustering. *Arthritis and rheumatism.* 2009;61(10):1328-1336.
137. Karvonen-Gutierrez CA, Sowers MR, Heeringa SG. Sex dimorphism in the association of cardiometabolic characteristics and osteophytes-defined radiographic knee osteoarthritis among obese and non-obese adults: NHANES III. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2012;20(7):614-621.
138. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. *Biology of sex differences.* 2012;3(1):13.
139. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *The American journal of clinical nutrition.* 2007;86(2):353-359.
140. Despres JP, Couillard C, Gagnon J, et al. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. *Arteriosclerosis, thrombosis, and vascular biology.* 2000;20(8):1932-1938.
141. Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. *Current opinion in clinical nutrition and metabolic care.* 2010;13(3):260-264.
142. Speliotes EK, Massaro JM, Hoffmann U, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart Study. *Hepatology (Baltimore, Md.).* 2010;51(6):1979-1987.
143. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients.* 2013;5(5):1544-1560.
144. Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: a review of the consequences and causes. *International journal of endocrinology.* 2014;2014:309570.
145. Gaggini M, Saponaro C, Gastaldelli A. Not all fats are created equal: adipose vs. ectopic fat, implication in cardiometabolic diseases. *Hormone molecular biology and clinical investigation.* 2015;22(1):7-18.
146. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *The New England journal of medicine.* 2014;371(12):1131-1141.
147. Perseghin G, Lattuada G, Danna M, et al. Insulin resistance, intramyocellular lipid content, and plasma adiponectin in patients with type 1 diabetes. *American journal of physiology. Endocrinology and metabolism.* 2003;285(6):E1174-1181.

148. Ingram KH, Lara-Castro C, Gower BA, et al. Intramyocellular lipid and insulin resistance: differential relationships in European and African Americans. *Obesity (Silver Spring, Md.).* 2011;19(7):1469-1475.
149. Therkelsen KE, Pedley A, Speliotes EK, et al. Intramuscular fat and associations with metabolic risk factors in the Framingham Heart Study. *Arteriosclerosis, thrombosis, and vascular biology.* 2013;33(4):863-870.
150. Wijsman CA, van Opstal AM, Kan HE, et al. Proton magnetic resonance spectroscopy shows lower intramyocellular lipid accumulation in middle-aged subjects predisposed to familial longevity. *American journal of physiology. Endocrinology and metabolism.* 2012;302(3):E344-348.
151. Delmonico MJ, Harris TB, Visser M, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. *The American journal of clinical nutrition.* 2009;90(6):1579-1585.
152. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *Journal of applied physiology (Bethesda, Md. : 1985).* 2001;90(6):2157-2165.
153. Visser M, Goodpaster BH, Kritchevsky SB, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2005;60(3):324-333.
154. Park YW, Allison DB, Heymsfield SB, Gallagher D. Larger amounts of visceral adipose tissue in Asian Americans. *Obesity research.* 2001;9(7):381-387.
155. Yim JE, Heshka S, Albu JB, Heymsfield S, Gallagher D. Femoral-gluteal subcutaneous and intermuscular adipose tissues have independent and opposing relationships with CVD risk. *Journal of applied physiology (Bethesda, Md. : 1985).* 2008;104(3):700-707.
156. Katzmarzyk PT, Bray GA, Greenway FL, et al. Racial differences in abdominal depot-specific adiposity in white and African American adults. *The American journal of clinical nutrition.* 2010;91(1):7-15.
157. Liska D, Dufour S, Zern TL, et al. Interethnic differences in muscle, liver and abdominal fat partitioning in obese adolescents. *PloS one.* 2007;2(6):e569.
158. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *Journal of applied physiology (Bethesda, Md. : 1985).* 2000;89(1):104-110.
159. Ayvaz G. Methods for Body Composition Analysis in Adults. *The Open Obesity Journal.* 2011;3(1):62-69.
160. Lee SY, Gallagher D. Assessment methods in human body composition. *Current opinion in clinical nutrition and metabolic care.* 2008;11(5):566-572.
161. Velasquez MT, Katz JD. Osteoarthritis: another component of metabolic syndrome? *Metabolic syndrome and related disorders.* 2010;8(4):295-305.
162. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. *The American journal of managed care.* 2002;8(15 Suppl):S383-391.
163. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. *The Journal of rheumatology.* 1995;22(6):1118-1123.

164. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Association of knee osteoarthritis with the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and impaired glucose tolerance in Japanese men and women: the ROAD study. *The Journal of rheumatology.* 2011;38(5):921-930.
165. Han CD, Yang IH, Lee WS, Park YJ, Park KK. Correlation between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination Survey (KNHANES). *BMC public health.* 2013;13:603.
166. Davies-Tuck ML, Hanna F, Davis SR, et al. Total cholesterol and triglycerides are associated with the development of new bone marrow lesions in asymptomatic middle-aged women - a prospective cohort study. *Arthritis research & therapy.* 2009;11(6):R181.
167. Dore D, de Hoog J, Giles G, Ding C, Cicuttini F, Jones G. A longitudinal study of the association between dietary factors, serum lipids, and bone marrow lesions of the knee. *Arthritis research & therapy.* 2012;14(1):R13.
168. Davies-Tuck ML, Wang Y, Wluka AE, et al. Increased fasting serum glucose concentration is associated with adverse knee structural changes in adults with no knee symptoms and diabetes. *Maturitas.* 2012;72(4):373-378.
169. Jungmann PM, Kraus MS, Alizai H, et al. Association of metabolic risk factors with cartilage degradation assessed by T2 relaxation time at the knee: data from the osteoarthritis initiative. *Arthritis care & research.* 2013;65(12):1942-1950.
170. Hoeven TA, Kavousi M, Clockaerts S, et al. Association of atherosclerosis with presence and progression of osteoarthritis: the Rotterdam Study. *Annals of the rheumatic diseases.* 2013;72(5):646-651.
171. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes research and clinical practice.* 2005;69(1):29-35.
172. Livshits G, Zhai G, Hart DJ, et al. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford Study. *Arthritis and rheumatism.* 2009;60(7):2037-2045.
173. Dumond H, Presle N, Terlain B, et al. Evidence for a key role of leptin in osteoarthritis. *Arthritis and rheumatism.* 2003;48(11):3118-3129.
174. Simopoulou T, Malizos KN, Iliopoulos D, et al. Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2007;15(8):872-883.
175. Karvonen-Gutierrez CA, Harlow SD, Mancuso P, Jacobson J, Mendes de Leon CF, Nan B. Association of leptin levels with radiographic knee osteoarthritis among a cohort of midlife women. *Arthritis care & research.* 2013;65(6):936-944.
176. Karvonen-Gutierrez CA, Harlow SD, Jacobson J, Mancuso P, Jiang Y. The relationship between longitudinal serum leptin measures and measures of magnetic resonance imaging-assessed knee joint damage in a population of mid-life women. *Annals of the rheumatic diseases.* 2014;73(5):883-889.
177. Ding C, Parameswaran V, Cicuttini F, et al. Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. *Annals of the rheumatic diseases.* 2008;67(9):1256-1261.
178. Berry PA, Jones SW, Cicuttini FM, Wluka AE, Maciewicz RA. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage

volume loss in a population with clinical knee osteoarthritis. *Arthritis and rheumatism.* 2011;63(3):700-707.

179. Zhang Q, Li H, Zhang Z, Yang F, Chen J. Serum metabolites as potential biomarkers for diagnosis of knee osteoarthritis. *Disease markers.* 2015;2015:684794.
180. Mao Y, Xu W, Xie Z, Dong Q. Association of Irisin and CRP Levels with the Radiographic Severity of Knee Osteoarthritis. *Genetic testing and molecular biomarkers.* 2016;20(2):86-89.
181. Hochberg MC, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin JD. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. *The Journal of rheumatology.* 1995;22(3):488-493.
182. Abbate LM, Stevens J, Schwartz TA, Renner JB, Helmick CG, Jordan JM. Anthropometric measures, body composition, body fat distribution, and knee osteoarthritis in women. *Obesity.* 2006;14(7):1274-1281.
183. Sowers MF, Yosef M, Jamadar D, Jacobson J, Karvonen-Gutierrez C, Jaffe M. BMI vs. body composition and radiographically defined osteoarthritis of the knee in women: a 4-year follow-up study. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2008;16(3):367-372.
184. Blumenfeld O, Williams FM, Hart DJ, Arden NK, Spector TD, Livshits G. Lower limbs composition and radiographic knee osteoarthritis (RKOA) in Chingford sample--a longitudinal study. *Archives of gerontology and geriatrics.* 2013;56(1):148-154.
185. Lee S, Kim TN, Kim SH. Sarcopenic obesity is more closely associated with knee osteoarthritis than is nonsarcopenic obesity: a cross-sectional study. *Arthritis and rheumatism.* 2012;64(12):3947-3954.
186. Berry PA, Wluka AE, Davies-Tuck ML, et al. The relationship between body composition and structural changes at the knee. *Rheumatology.* 2010;49(12):2362-2369.
187. Ding C, Garnero P, Cicuttini F, Scott F, Cooley H, Jones G. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2005;13(3):198-205.
188. Wang Y, Wluka AE, English DR, et al. Body composition and knee cartilage properties in healthy, community-based adults. *Annals of the rheumatic diseases.* 2007;66(9):1244-1248.
189. Teichtahl AJ, Wang Y, Wluka AE, et al. The longitudinal relationship between body composition and patella cartilage in healthy adults. *Obesity.* 2008;16(2):421-427.
190. Visser AW, de Mutsert R, Loef M, et al. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2014;22(2):197-202.
191. Cicuttini FM, Teichtahl AJ, Wluka AE, Davis S, Strauss BJ, Ebeling PR. The relationship between body composition and knee cartilage volume in healthy, middle-aged subjects. *Arthritis and rheumatism.* 2005;52(2):461-467.
192. Ding C, Stannus O, Cicuttini F, Antony B, Jones G. Body fat is associated with increased and lean mass with decreased knee cartilage loss in older adults: a prospective cohort study. *International journal of obesity.* 2013;37(6):822-827.

193. Wang Y, Simpson JA, Wluka AE, et al. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. *Arthritis research & therapy.* 2009;11(2):R31.
194. Runhaar J, Luijsterburg P, Dekker J, Bierma-Zeinstra SM. Identifying potential working mechanisms behind the positive effects of exercise therapy on pain and function in osteoarthritis; a systematic review. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2015;23(7):1071-1082.
195. Lange AK, Vanwanseele B, Fiatarone Singh MA. Strength training for treatment of osteoarthritis of the knee: a systematic review. *Arthritis and rheumatism.* 2008;59(10):1488-1494.
196. Reid KF, Price LL, Harvey WF, et al. Muscle Power Is an Independent Determinant of Pain and Quality of Life in Knee Osteoarthritis. *Arthritis & rheumatology (Hoboken, N.J.).* 2015;67(12):3166-3173.
197. Berger MJ, McKenzie CA, Chess DG, Goela A, Doherty TJ. Quadriceps neuromuscular function and self-reported functional ability in knee osteoarthritis. *Journal of applied physiology (Bethesda, Md. : 1985).* 2012;113(2):255-262.
198. Accettura AJ, Brenneman EC, Stratford PW, Maly MR. Knee Extensor Power Relates to Mobility Performance in People With Knee Osteoarthritis: Cross-Sectional Analysis. *Physical therapy.* 2015;95(7):989-995.
199. Pelletier D, Gingras-Hill C, Boissy P. Power training in patients with knee osteoarthritis: a pilot study on feasibility and efficacy. *Physiotherapy Canada. Physiotherapie Canada.* 2013;65(2):176-182.
200. Sayers SP, Gibson K, Cook CR. Effect of high-speed power training on muscle performance, function, and pain in older adults with knee osteoarthritis: a pilot investigation. *Arthritis care & research.* 2012;64(1):46-53.
201. Calder KM, Acker SM, Arora N, et al. Knee power is an important parameter in understanding medial knee joint load in knee osteoarthritis. *Arthritis care & research.* 2014;66(5):687-694.
202. Murray AM, Thomas AC, Armstrong CW, Pietrosimone BG, Tevald MA. The associations between quadriceps muscle strength, power, and knee joint mechanics in knee osteoarthritis: A cross-sectional study. *Clinical biomechanics (Bristol, Avon).* 2015;30(10):1140-1145.
203. Slemenda C, Brandt KD, Heilman DK, et al. Quadriceps weakness and osteoarthritis of the knee. *Annals of internal medicine.* 1997;127(2):97-104.
204. Slemenda C, Heilman DK, Brandt KD, et al. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? *Arthritis & Rheumatism.* 1998;41(11):1951-1959.
205. Eckstein F, Hitzl W, Duryea J, Kent Kwoh C, Wirth W, investigators OAI. Baseline and longitudinal change in isometric muscle strength prior to radiographic progression in osteoarthritic and pre-osteoarthritic knees--data from the Osteoarthritis Initiative. *Osteoarthritis & Cartilage.* 2013;21(5):682-690.
206. Segal NA, Torner JC, Felson D, et al. Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. *Arthritis & Rheumatism.* 2009;61(9):1210-1217.

207. Segal NA, Glass NA, Torner J, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. *Osteoarthritis & Cartilage.* 2010;18(6):769-775.
208. Segal NA, Findlay C, Wang K, Torner JC, Nevitt MC. The longitudinal relationship between thigh muscle mass and the development of knee osteoarthritis. *Osteoarthritis & Cartilage.* 2012;20(12):1534-1540.
209. Amin S, Baker K, Niu J, et al. Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis. *Arthritis and rheumatism.* 2009;60(1):189-198.
210. Pan J, Stehling C, Muller-Hocker C, et al. Vastus lateralis/vastus medialis cross-sectional area ratio impacts presence and degree of knee joint abnormalities and cartilage T2 determined with 3T MRI - an analysis from the incidence cohort of the Osteoarthritis Initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2011;19(1):65-73.
211. Beattie KA, MacIntyre NJ, Ramadan K, Inglis D, Maly MR. Longitudinal changes in intermuscular fat volume and quadriceps muscle volume in the thighs of women with knee osteoarthritis. *Arthritis care & research.* 2012;64(1):22-29.
212. Kumar D, Karampinos DC, MacLeod TD, et al. Quadriceps intramuscular fat fraction rather than muscle size is associated with knee osteoarthritis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2014;22(2):226-234.
213. Conroy MB, Kwoh CK, Krishnan E, et al. Muscle strength, mass, and quality in older men and women with knee osteoarthritis. *Arthritis care & research.* 2012;64(1):15-21.
214. Standards of medical care in diabetes--2014. *Diabetes care.* 2014;37 Suppl 1:S14-80.
215. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *Jama.* 2002;287(3):356-359.
216. Chumanov ES, Wall-Scheffler C, Heiderscheit BC. Gender differences in walking and running on level and inclined surfaces. *Clinical biomechanics (Bristol, Avon).* 2008;23(10):1260-1268.
217. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology (Cambridge, Mass.).* 2003;14(3):300-306.
218. Zhang Y, Niu J, Felson DT, Choi HK, Nevitt M, Neogi T. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. *Arthritis care & research.* 2010;62(11):1527-1532.
219. Seidell JC, Bakker CJ, van der Kooy K. Imaging techniques for measuring adipose-tissue distribution--a comparison between computed tomography and 1.5-T magnetic resonance. *The American journal of clinical nutrition.* 1990;51(6):953-957.
220. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28(7):412-419.
221. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical chemistry.* 1972;18(6):499-502.
222. Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? *Diabetes care.* 2009;32(6):1068-1075.

223. Yang X, Smith U. Adipose tissue distribution and risk of metabolic disease: does thiazolidinedione-induced adipose tissue redistribution provide a clue to the answer? *Diabetologia.* 2007;50(6):1127-1139.
224. Markman B, Barton FE, Jr. Anatomy of the subcutaneous tissue of the trunk and lower extremity. *Plastic and reconstructive surgery.* 1987;80(2):248-254.
225. Miljkovic I, Kuipers AL, Cvejkus R, et al. Myosteatosis increases with aging and is associated with incident diabetes in African ancestry men. *Obesity.* 2016;24(2):476-482.
226. Baratta R, Solomonow M, Zhou BH, Letson D, Chuinard R, D'Ambrosia R. Muscular coactivation. The role of the antagonist musculature in maintaining knee stability. *The American journal of sports medicine.* 1988;16(2):113-122.
227. Segal NA, Glass NA, Torner J, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society.* 2010;18(6):769-775.
228. Harput G, Soylu AR, Ertan H, Ergun N, Mattacola CG. Effect of gender on the quadriceps-to-hamstrings coactivation ratio during different exercises. *Journal of sport rehabilitation.* 2014;23(1):36-43.
229. Malinzak RA, Colby SM, Kirkendall DT, Yu B, Garrett WE. A comparison of knee joint motion patterns between men and women in selected athletic tasks. *Clinical biomechanics (Bristol, Avon).* 2001;16(5):438-445.
230. Polgar J, Johnson MA, Weightman D, Appleton D. Data on fibre size in thirty-six human muscles. An autopsy study. *Journal of the neurological sciences.* 1973;19(3):307-318.
231. Schantz P, Randall-Fox E, Hutchison W, Tyden A, Astrand PO. Muscle fibre type distribution, muscle cross-sectional area and maximal voluntary strength in humans. *Acta physiologica Scandinavica.* 1983;117(2):219-226.
232. Jennekens FG, Tomlinson BE, Walton JN. Data on the distribution of fibre types in five human limb muscles. An autopsy study. *Journal of the neurological sciences.* 1971;14(3):245-257.
233. Essen B, Jansson E, Henriksson J, Taylor AW, Saltin B. Metabolic characteristics of fibre types in human skeletal muscle. *Acta physiologica Scandinavica.* 1975;95(2):153-165.
234. Lexell J. Human aging, muscle mass, and fiber type composition. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 1995;50 Spec No:11-16.
235. Coen PM, Goodpaster BH. Role of intramyocelluar lipids in human health. *Trends in endocrinology and metabolism: TEM.* 2012;23(8):391-398.
236. Taaffe DR, Henwood TR, Nalls MA, Walker DG, Lang TF, Harris TB. Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults. *Gerontology.* 2009;55(2):217-223.
237. Aubrey J, Esfandiari N, Baracos VE, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta physiologica (Oxford, England).* 2014;210(3):489-497.
238. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *Jama.* 2014;311(8):806-814.