PHYSICAL ACTVITY AND CARTILAGE HEALTH

THE EFFECT OF PHYSICAL ACTIVITY ON MEDIAL TIBIAL CARTILAGE HEALTH IN CLINICAL KNEE OSTEOARTHRITIS

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Abstract

Knee osteoarthritis (OA) is a common chronic disease that often occurs in older adults, affecting their quality of life. The purposes of this study were to examine 1) the relationship between physical activity and medial tibial cartilage volume and thickness in participants with clinical knee OA; and 2) the test-retest reliability of daily step counts produced by participants with knee OA.

The study included 34 participants (age 60.6 ± 6.5 years; body mass index 28.5 ± 5.4 kg/m^2). Dependent variables were medial tibial cartilage volume and thickness, measured from magnetic resonance images. Independent variables were average step counts and average time spent in light intensity activity, measured with an accelerometer. These data were then was analyzed using linear and second degree polynomial regression analyses to determine the relationship between dependent and independent variables along with age, sex and BMI as covariates. The test-retest reliability of step counts collected over 5 days was evaluated with an intraclass correlation coefficient (ICC).

Average time engaged in light intensity activity, average daily step counts, sex and age accounted for 56.3% of the variance in medial tibial cartilage volume. Age and average time in light intensity activity explained 33.2% of the variance in medial tibial cartilage thickness. Results from the second degree polynomial analyses were not significant. The ICC for the daily step counts over first 5 days of 10 hours wear time was 0.929 (95% [CI] =0.883, 0.961).

A weak linear relationship existed between physical activity and cartilage volume and thickness within the knee joint. The greatest medial tibial cartilage volume was found

in men who were engaged in longer durations of low intensity physical activity. The test-retest of step counts data by participants with knee OA was very reliable over the 5 days. Findings from this study augment current knowledge of knee OA.

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List of Abbreviations

1T	1-Tesla
ACL	Anterior Cruciate Ligament
ACSM	American College of Sports Medicine
ANOVA	Repeated Measures Analysis of Variance
BMI	Body Mass Index
CT-PAQ	Chasan-Taber Physical Activity Questionnaire
dGEMRIC	Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage
ECM	Extracellular matrix
GAG	Glycosaminoglycan
K/L	Kellgren and Lawrence
L-PAQ	Lifetime Physical Activity Questionnaire
LT-PAQ	Lifetime Total Physical Activity Questionnaire
MRI	Magnetic Resonance Imaging
MT.VC	Medial Tibial Cartilage Volume
MT.ThCtAB	Medial Tibial Cartilage Thickness
OA	Osteoarthritis
PASE	Physical Activity Scale for the Elderly
SEM	Standard Error of Measurement

Chapter One - Introduction

Osteoarthritis (OA) is one of the top three most common chronic diseases in Canada (Health Canada, 2003). In Canada, the prevalence of OA is 10.8% (Wong, Davis, Badley, Grewal, & Mohammed, 2001). On average, OA-related costs equal approximately $12,200 per person in Canada annually (Gupta, Hawker, Laporte, Croxford, & Coyte, 2005). There is no cure for OA, with few evidence-based therapies to slow the progression of the disease. The knee is the most commonly affected joint (Gupta *et al.*, 2005). Knee OA is a disease mainly defined by the degradation of the articular cartilage that lines the ends of the femur and tibia. For many people, chronic pain, inability to perform activities of daily living, and ultimately, decreased quality of life could be related to knee OA and degradation of cartilage (Buckwalter & Mankin, 1997).

People with knee OA demonstrate a decrease in tibial cartilage thickness and volume compare to individuals without knee OA (The arthritis society, 2011; A. E. Wluka, Wolfe, Davis, Stuckey, & Cicuttini, 2004), especially in the medial compartment of the knee, since it takes on 50% more load than the lateral compartment (Moskowitz, Altman, Hochberg, Buckwalter, & Goldberg, 2007). Thus, cartilage thickness and volume are often used as a measure of cartilage health in OA. The main function of the cartilage within a joint is to provide a smooth surface during movement, as well as evenly distribute loads across the joint surfaces during weight-bearing activities (Nordin & Frankel, 2001). Once the cartilage is damaged, its capacity to regenerate is very limited due to a lack of a direct supply of nutrients to rebuild this avascular tissue (Markenson,

2004). However, cartilage compression as a result of physical activity promotes diffusion of nutrients from perichondrium to cartilage via synovial fluid, which provides the necessary building blocks such as protein and sugar for the regeneration of cartilage (Chaudhari, Briant, Bevill, Koo, & Andriacchi, 2008). Not only is physical activity a modulator in nutrient flow that can promote cartilage health, physical activity may also be a risk factor for knee OA (Michaëlsson, Byberg, Ahlbom, Melhus, & Farahmand, 2011).

The etiology of knee OA is multifactorial and it is associated with many different risk factors (Dequeker, Aerssens, & Luyten, 2003). Factors that are important in knee OA include physical activity and body mass (Anderson & Felson, 1988; Lee & Kean, 2012; Verweij, van Schoor, Deeg, Dekker, & Visser, 2009). People with knee OA typically demonstrate low physical activity levels in comparison to non-OA group (Farr *et al.*, 2008). This reduction in physical activity has been suggested to be due to the pain or fear of progression in the disease (Campbell *et al.*, 2001). Conversely, physical activity has been linked with reductions in pain and improving cartilage health by promoting cartilage regeneration through compressive forces that encourage the passive flow of nutrients into the tissue (O'Reilly, Muir, & Doherty, 1999; Røgind *et al.*, 1998). Furthermore, engagement in physical activity can help in reducing body mass (another modifiable risk factor for OA), which, in turn, reduces the load placed on the knee. Therefore, physical activity is an important factor to consider when studying individuals with knee OA.

Previous literature has described physical activity as a factor that could both positively and negatively impact articular cartilage within the knee joint. As an example, Hanna and colleagues completed a cross-sectional study which looked at the effect of

physical activity on medial tibial cartilage volume (MT.VC) (Hanna *et al.*, 2007). This study collected data from 176 women aged 40-67 years, with no clinical knee OA or major injury. Magnetic resonance imaging (MRI) scans were acquired for all participants and the women were asked to complete a questionnaire to determine the frequency with which they participated in physical activities. The results showed that more physical activity was positively associated with higher MT.VC with a beta value of 0.12 (95% CI: 0.02-0.22), $P = 0.03$ (Hanna *et al.*, 2007). From the Framingham Study, McAlindon and colleagues published a study examining the association between physical activity and the modified Kellgren and Lawrence (K/L) scale from radiographs (McAlindon, Wilson, Aliabadi, Weissman, & Felson, 1999). The K/L scale is used to identify severity of radiographic joint damage, mainly by the presence of osteophytes and joint space narrowing (Brandt, Braunsteinm, & Katz, 2011) The study had 473 participants (295 women, 178 men) with a mean age at 70.1 $\pm$ 4.5 years. Results from the study showed that heavy physical activity was positively related to the incident risk of radiographic knee OA with an odds ratio of 1.3 per hour of heavy physical activity (95% confidence limits at 1.1-1.6, p= 0.006) (McAlindon *et al.*, 1999). By reviewing the results from previous two studies on effects of physical activity and knee joint health, the contradictory findings must be noted. These conflicting findings suggest that the relationship between physical activity and cartilage or knee joint health may not be a simple linear relationship. Other factors, such as disease status and the intensity of physical activity, likely influence this relationship. Thus, an observational study must first

be done to look at the whole spectrum of physical activities that people with knee OA engage in, as well as its effect on knee joint health.

In order to understand the effect of physical activity on knee joint health over the progression of knee OA, a baseline for this population must be obtained. To the best of our knowledge, no cohort study has been performed to examine the intensity and duration of physical activity and its effect on cartilage health. This information can be an important first step to prescribing the appropriate levels of intensity and duration of exercise for participants with clinical knee OA. Therefore, the purpose of this study was to investigate the relationship between the quantity and intensity of physical activity with cartilage health by the measure of MT.VC and medial tibial cartilage thickness (MT.ThCtAB) in participants with clinical knee OA (Altman *et al.*, 1986).

Chapter Two- Literature Review

2.1 Knee Osteoarthritis

One out of six Canadians will suffer from some form of arthritis in their lifetime. By 2026 there will be over six million Canadians affected by arthritis (Health Canada, 2003). Arthritis is one of the top three most common chronic diseases in Canada (Health Canada, 2003). Osteoarthritis (OA) is the most common type of arthritis, with the knee being the most frequently affected joint (Gupta *et al.,* 2005; Moskowitz *et al.,* 2007). In the United States, knee OA affects 16% of adults over 45 years of age (Jordan *et al.,* 2007) whereas in Canada, the prevalence is about 10.8 % (Wong *et al.,* 2001).

Knee OA is a disease that affects the whole knee joint in many aspects. One of the main features of this disease is the breakdown of the articular cartilage that normally permits smooth and frictionless movement between the femur and tibia. This disease leads to a decrease in cartilage thickness, which may be a consequence of frequent intensive loading or immobilization (The Arthritis Society, 2011). Due to the pain and immobility caused by the disease, the loss of productivity caused by knee OA and other arthritic conditions is estimated to cost the Canadian economy over $17.8 billion dollars annually (Perruccio, Badley, & Guan, 2004). People with OA must deal with much pain and immobility, and many activities of daily living are hampered (The Arthritis Society, 2011). In order to prevent the progression of knee OA and improve treatment outcomes, it is critical to first understand the contributing factors associated with disease progression.

Identifying and understanding the effects of these factors will help develop interventions that minimize disease progression, which will help improve quality of life.

2.1.2 Functions of Healthy Cartilage

Articular cartilage at the knee joint covers the end of the distal femur, proximal tibia as well the posterior aspect of the patella. Major roles of the cartilage are to prevent bone-on-bone contact, increase joint congruency and distribute loads evenly across joint surfaces (Nordin & Frankel, 2001). In the articular cartilage, water accounts for 65-80% of cartilage's wet weight and influences the mechanical and physiochemical behavior of cartilage (Mankin, Mow, Buckwalter, Iannotti, & Ratcliffe, 1999). Most of the water component is within the intrafibrillar space, bound by the collagen and proteoglycan matrix (extracellular matrix-ECM). The ECM accounts for 99% of the cartilage and 1% of chondrocytes within the matrix. The ECM is responsible for the structural support of the cells and it consists of mainly proteoglycans which is a combination of covalently bonded glycosaminoglycan (GAG), a large molecule containing protein and collagen. Chondrocytes within the matrix are responsible for producing collagen and proteoglycans, managing the components of ECM and maintaining its structure (refer to figure 2.1 for illustration of cartilage components). The surface of cartilage in the human body is covered by a substance called perichondrium. Perichondrium is important because it is the only blood supply to in the cartilage structure.

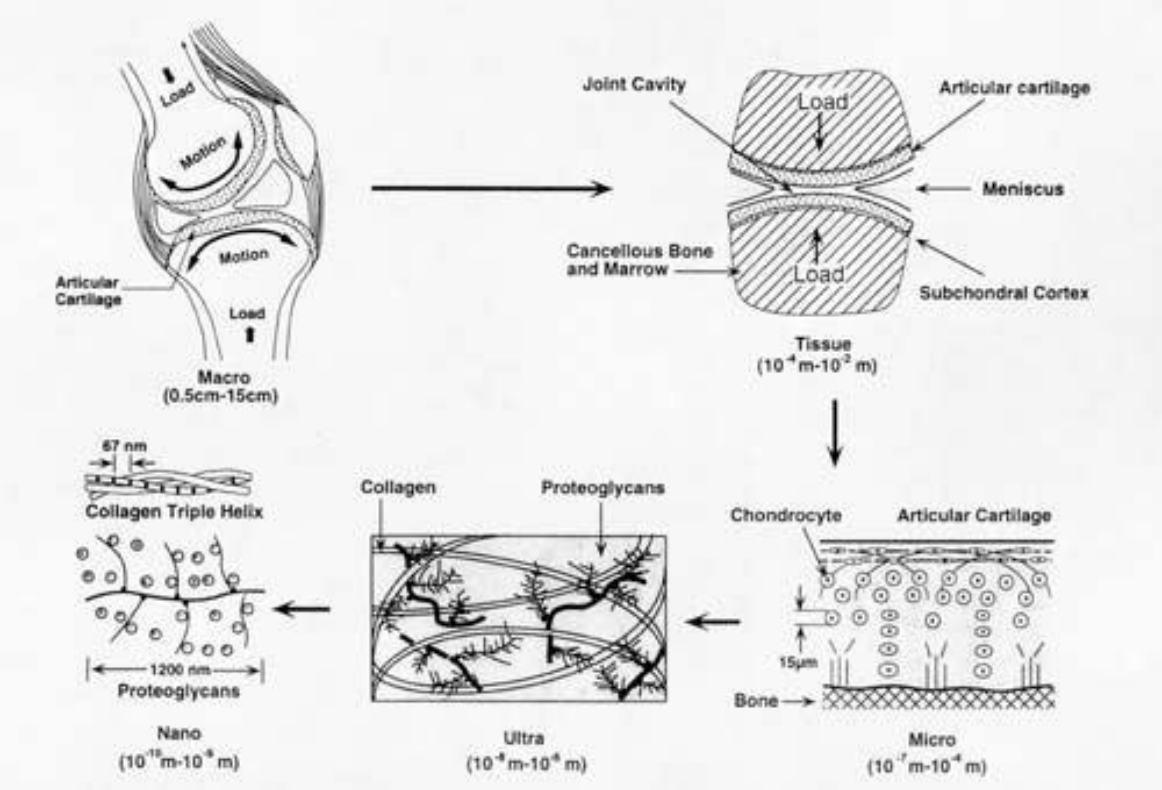

Figure 2.1 Cartilage components (Loren, 2012)

The cross-linking interaction between collagen, proteoglycans and water results in the biomechanical characteristics that manage the internal mechanical stress resulting from loading (Nordin & Frankel, 2001). In an aqueous environment, proteoglycans are polyanionic, which means the molecule's negatively charged sites arise from the carboxyl and sulfate groups. The repulsive force of the negative charges causes the proteoglycans to spread and occupy a large volume within the tissue. When cartilage is compressed, these proteoglycans are pushed even closer, which increases the repulsive force and therefore the stiffness of the cartilage when compressed. During compression, water also flows through the cartilage and across the articular surface. If the pressure difference is

applied across a section of the cartilage, water can also flow to tissues like a sponge (Oatis, 2004).

Unlike other connective tissues, cartilage is unable to regenerate itself efficiently due to a lack of direct blood supply. Because of this feature, nutrients and growth factors are unable to induce a fast healing process. Chondrocytes must derive nutrition from the blood supply of perichondrium, subchondral bone and synovial fluid (Markenson, 2004). To obtain this nutrition, there needs to be compression of the articular cartilage. Compression causes diffusion of the nutrients from the surrounding perichondrium to chondrocytes. This phenomenon was shown by studies that looked at cartilage physical adaptation to chronic loading (Chaudhari *et al.,* 2008).

2.1.3 Aging and changes to cartilage

Aging increases the rate of cartilage thinning (Ding *et al.,* 2006). In healthy men and women without knee OA, an annual reduction of tibial cartilage volume is on average 2.8% (Hanna *et al.,* 2005) and 2.4%, respectively (Wluka *et al.,* 2004). With aging, there is an alteration in the matrix composition of the cartilage and chondrocyte synthesis activity. Age-related alterations in cartilage composition include a decrease in cellularity, decrease in size and aggregation of proteoglycans and increase collagen cross-linking (Bonassar *et al.,* 1995; 1995; Magnussen, Guilak, & Vail, 2005; Meachim, 1969). The more aged cartilage has an increase in cross-linking which results in stiffer cartilage and thus it is unable to withstand impact as well compared to the young healthy cartilage (L'Hermette, Tourny-Chollet, Polle, & Dujardin, 2006). The decrease in chondrocyte

activity limits growth, repair, and maintenance of the tissue, which are strongly linked to cartilage thinning during aging (Buckwalter & Lane, 1997).

2.1.4 Osteoarthritis and changes to cartilage

In people with knee OA, cartilage undergoes a progressive degeneration in both quantity and quality at a rate that is faster than in healthy aging. Compared to age-matched healthy adults, the adult with knee OA will have a much higher rate of cartilage loss on average, which is between 4.4% and 6.3% annually for both men and women (Wluka *et al.,* 2006). This study assessed cartilage volume using magnetic resonance imaging (MRI) in participants with symptomatic knee OA over 4.5 years, with 78 subjects (44 women) completing the study.

Another form of cartilage damage involved in knee OA is the edema of the ECM. Edema is swelling within the ECM that results from proteolytic and proteoglycan degradation of the chondrocytes. The breakdown means there is a smaller amount of the proteoglycan in the ECM, creating more space between each molecule. Greater space leads to higher permeability within the cartilage (Pearle, Warren, & Rodeo, 2005). The reduction of the proteoglycan also leads to a decrease in stiffness when the joint is loaded due to the decrease in repulsive force between the proteoglycan molecules. Therefore, edema of the ECM causes the cartilage to become poorer in quality. The cartilage is now softer and more vulnerable to injury and other damage, even though its volume and thickness appears to be high (Altman *et al.*, 1984; Pritzker, 1998).

2.1.5 Knee osteoarthritis and associated risk factors

Knee OA has many risk factors that are associated with an increase in either incidence or progression rate. Incidence is defined as the number of new cases diagnosed. Progression represents the total burden of the disease, where it is the sum of all diagnosed cases, including the new diagnosed cases (National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health, 2011).

The risk factors for disease incidence and progression can be generalized into 2 subgroups: non-modifiable and modifiable factors. In the non-modifiable group, the most common risk factors for knee OA are sex, age, ligamentous injury and alignment of the joint. Statistically, over the age of 55 years, men have 45% lower incidence than women (Srikanth *et al.,* 2005). Therefore, women, on average, are more likely to develop knee OA than men as they age (Srikanth *et al.,* 2005). Knee OA has been known to be a disease of middle age because the age of 45 is the most common age for onset of this chronic disease defined by clinical criteria (Australian Government, Department of Health and Aging, 2010; Buckwalter, Saltzman, & Brown, 2004). One other important factor associated with the initiation of OA would be anterior cruciate ligament (ACL) injuries. Many studies have shown that ACL injuries act as an initiator of knee OA due to the many negative complications related to damage to this ligament, such as immobilization, joint laxity, and muscle atrophy (Andriacchi, Koo, & Scanlan, 2009). Finally, the alignment of the knee joint is also very important for the progression of the disease. For example, one study looked at the effects of alignment by observing participants over an 18 month period to look at disease progression by knee alignment,

joint space width and changes of physical functions (Sharma et al., 2001). Having varus alignment at baseline resulted in a 4 times greater odds of medial compartment OA progression. Valgus alignment at baseline had a 5 times greater odds of lateral OA progression. Both of these malalignments affected the joint space as well as mobility (Sharma *et al.,* 2001). These results showed that malalignment of the knee joint can have a dramatic effect on disease progression as well as changes in mobility performance.

Modifiable risk factors for the incidence and/or the progression of knee OA include physical activity level, obesity, manual labour and muscle dysfunction (Juhakoski *et al.,* 2009). Physical activity is likely one key in altering other modifiable risk factors. With adequate activity, weight loss or weight maintenance can be achieved, as well as improvement in muscle function. For example, moderate physical activity has positive effects on cartilage volume in comparison to the sedentary controls (Wacker, König, Felsenberg, & Wolf, 1994). On the other hand, absence of physical activity through immobilization has been shown to lead to the loss of cartilage proteoglycans, which, in turn, compromises cartilage health, promoting OA. (Säämänen, Tammi, Kiviranta, Jurvelin, & Helminen, 1987).

Obesity is also another important risk factor to consider in both the initiation and the progression of knee OA. Obesity is defined by abnormal accumulation of fat that impairs health. Greater body mass that one carries from day to day will increase the absolute load that each knee is bearing. The amount of total load bearing on each knee will influence cartilage health (Felson & Chaisson, 1997; Schouten, van den Ouweland, & Valkenburg, 1992). For each increase in body mass by one pound, the knee cartilage

would need to withstand 2 to 3 times more force (Teichtahl, Wang, Wluka, & Cicuttini, 2008). Obesity not only creates excess load for the joint but also facilitates an inflammatory response, which accentuates OA. Obesity is also related to excess adipose tissue, this tissue act like an endocrine organ which release hormone such as leptin. Leptin from previous study was associated with potential initiation of inflammation response in OA (Toussirot, Streit, & Wendling, 2007). Obese women are, on average, 4 times more likely to develop incident knee OA than non-obese women; obese men are 5 times more likely than non-obese men (Anderson & Felson, 1988). In a recent systematic review, Lee and Kean demonstrated that obesity was a strong determinant in developing knee OA (Lee & Kean, 2012). Obesity in middle age women resulted in a 2 fold increase in the risk for knee OA in comparison to young obese women (Hart, Doycle, & Spector, 1999). Obesity also has strong effect on the progression of knee OA. Study by Spector and colleagues showed that with an increase of body mass index (BMI) there is an increased progression of knee OA with a relative risk of 4.69 (Spector, Hart & Doyle, 1994).

Manual labour and working environment can also greatly influence the development of OA. Long periods of repetitive bending, kneeling and squatting are risk factors for cartilage damage (McWilliams, Leeb, Muthuri, Doherty, & Zhang, 2011) with an incidence rate of 2.5% and progression rate of 3.6% per year (Cooper, McAlindon, Coggon, Egger, & Dieppe, 1994). The presence of radiographic OA at the knee in participants between 55 and 64 years of age was three times more likely in people whose jobs required repetitive knee bending (Anderson & Felson, 1988). From the Framingham

study, the highest risk in radiographic knee OA was for those whose jobs were physically demanding and involved bending of the knee (Felson *et al.*, 1991). Evidence for the exact mechanisms that damage articular cartilage by squatting and bending is still unclear (Cooper *et al.*, 1994).

Muscle weakness has also been noted to influence the development of knee OA. The mechanism linking muscle weakness to knee OA includes the increase the load attributed to cartilage, and lower physical activity (Baker *et al.*, 2004). Muscles are theorized to decrease the joint contact force by facilitating the distribution of load across the cartilage. Also, if the physical activity level is lowered, the cartilage is no longer getting the compression to obtain the nutrients in order to maintain its healthy function (Chaudhari *et al.*, 2008). Studies have found that quadriceps weakness is strongly related to pain, and the ability to perform activities of daily living (O'Reilly, Jones, Muir, & Doherty, 1998). Potential causes of this muscle weakness could be due to atrophy and dysfunction, or lack of usage in fear of further progression of knee OA (Hurley, 1999; Ikeda, Tsumura, & Torisu, 2005). A randomized controlled trial with an intervention of strengthening the quadriceps muscle resulted in significant improvement in pain and functional tasks in both men and women with knee pain (O'Reilly *et al.*, 1999). Another study done in Denmark also shows a similar effect, where participants with severe OA were divided into control (n=12) and intervention (n=11) groups. The intervention was to attend an exercise training group twice a week for 3 months. Training included balance, lower extremity strengthening, stretching, coordination and a home exercise program. The findings from this study showed that the intervention group had a higher functional

level and less pain in comparison to the control group, even after 1 year follow up (Røgind *et al.,* 1998).

Physical activity, obesity and muscle dysfunction can all be grouped as modifiable risk factors. It is important to note that physical activity is a contributing factor that could alter the other two modifiable risk factors. With adequate physical activity, weight reduction can be possible, as well as an increase in muscle strength. Therefore the focus of this thesis is physical activity as a major risk factor for the progression of cartilage degradation in knee OA.

2.2 ***Physical Activity***

Physical activity can be both protective and detrimental to cartilage, however with adequate amount and intensity it showed a positive effect on cartilage health in both healthy adults and adults at risk for knee OA (Hanna *et al.,* 2007; Roos & Dahlberg, 2005). However, it remains relatively unclear how cartilage reacts with different intensities of physical activity in people prevalent with knee OA.

2.2.1 Physical activity and osteoarthritis

Physical activity includes any bodily movement produced by skeletal muscles which requires energy expenditure (World Health Organization, 2012). Physical activity is recommended by multiple health organizations; however the general population does not demonstrate that it is taking the advice seriously (Centers for Disease Control and Prevention, 2011; World Health Organization, 2010). Inactivity is still the 4th leading risk

factor of global mortality (World Health Organization, 2011). In the Canadian population, 48% of those over 12 years old were inactive during their leisure time in 2005, which is roughly less than 30 minutes of slow walking everyday (Statistics Canada, 2012). About 70% people with knee OA do not meet the recommended levels of physical activity (Farr *et al.,* 2008). People with knee OA often avoid exercises due to pain or fear of damaging the joint due to the belief that being physically active will "wear out" the remaining intact cartilage (Campbell *et al.,* 2001). However, being physically active has many benefits such as reducing risk for hypertension, cardiovascular disease, diabetes, obesity and improving bone health and joint function (Pate *et al.*, 1995; World Health Organization, 2011). Physical activity can be considered one of the most important influences on the risk for knee OA since it has the potential to stimulate cartilage repair and minimize obesity, an important risk factor for development of knee OA. However studies have showed that the effects of physical activity on cartilage can be both positive and negative.

2.2.2 Physical activity improves articular cartilage

Physical activity has many positive effects on joint health, especially in knees. Exercise can increase cartilage volume but not increasing the incidence or progression rate of OA (Hanna *et al.,* 2007). For example, the Framingham Study showed that the incidence rate of knee OA was not increased by regular recreational physical activity (Felson *et al.,* 2000). Radiographs and self-reported physical activity were collected from 1,279 healthy participants from the Framingham cohort at baseline and after 9 years. The incidence of OA was not related to the amount of physical activity performed (Felson *et al.*, 2007). Participants who exercised on a regular basis as a part of their lifestyle did not

increase their risk in progression of the disease. Regular exercises even helped reduce pain and improve physical function. Physically active children have 24.8% thicker articular cartilage compared to sedentary controls (Wacker *et al.,* 1994). In other words, cartilage thickness is proportional to exposures to physical activity loading up to a threshold. Cautions should also be taken when performing vigorous intensive sports or exercise (Bosomworth, 2009).

Many studies suggest that regular and moderate physical activity will increase cartilage health (Hanna *et al.*, 2007; Roos & Dahlberg, 2005). This idea has been presented in many different types of studies, including cross-sectional, longitudinal, randomised control trials, as well as animal models. In a cross-sectional study, healthy women without signs of OA, knee pain or knee injuries in the past 5 years, who exercised daily for at least 20 minutes, had higher medial tibial cartilage volume (MT.VC) in comparison to those who were sedentary (Hanna *et al.,* 2007). A cross-sectional study looked at MRIs of 297 participants (63% women and average age of 58 years at baseline) without knee injury or diseases. Activity questionnaires were completed at baseline and again at after 9 years. The study found that vigorous activities such as swimming and biking with an intensity that induces shortness of breath were associated with higher cartilage volume and no cartilage defects (Racunica *et al.,* 2007). In children, Jones and colleagues showed that physical activity is very important for children in gaining articular cartilage. Boys in vigorous sports had the highest accrual rates of cartilage volume, pointing to the importance of physical activity in early stages of life (Jones *et al.,* 2003).

In a randomised controlled trial, Roos and Dahlberg compared an experimental group who exercised 3 times a week (1 hour each session) for four months with a control group that received no intervention. The participants recruited for this study were men and women between 35 to 50 years of age who had partial medial meniscus reconstruction, which is considered a risk factor for developing knee OA. The primary outcome measure was the glycosaminoglycan (GAG) content in the cartilage. The GAG content is an important building block in cartilage and is measured using delayed gadolinium-enhanced MRI of cartilage, or dGEMRIC. The dGEMRIC method is used to estimate cartilage quality by measuring the fixed-charge density of tissue, comprising GAG content (Bashir *et al.,* 1997; Bashir, Gray, Boutin, & Burstein, 1997; Bashir, Gray, Hartke, & Burstein, 1999). The principle underlying this technique is that when the negatively charged contrast agent gadolinium is injected, it will avoid negatively charged GAGs in the cartilage. In other words, if there is a high GAG content in cartilage, there is a low content of the gadolinium (Bashir *et al.,* 1999). Both of the groups had MRIs at baseline and again at the end of the study. The results showed that GAG content improved in the moderate intensity exercise group but not the control group (Roos & Dahlberg, 2005). In other words, the quality of the cartilage improved after the intervention. Finally, a quantitative study of articular cartilage in knee joint of 20 beagle dogs (10 as control) showed that the running group had a thicker articular cartilage due to mechanical loading, which supports all of the studies described above (Oettmeier *et al.*, 1992). The mechanical loading accompanied by performing physical activity increases

the likelihood of articular cartilage getting nutrients from the perichondrium, subchondral bone and synovial fluid.

2.2.3 Physical activity causing destruction of cartilage

As opposed to the studies described earlier, some investigations link physical activity to cartilage damage, mainly under the conditions of overuse or underuse. Overuse of the knee joint will damage and diminish the cartilage thickness due to wear and tear. If the joint is immobilized low in physical load the lack of usage can also be cause of cartilage loss (McAlindon *et al.,* 1999; Michaëlsson *et al.,* 2011).

Three major subcategories of research evaluate over-usage leading to cartilage degradation. The subcategories are divided based on the type of the activity: recreational physical activity, occupational or industrial exposure to kneeling, squatting, heavy lifting, and professional sports. In 473 elderly participants with normal radiographs of their knees, an eight year follow up showed that heavy, intensive physical activity is, in fact, a risk factor for knee OA (McAlindon *et al.,* 1999). The study used the modified Kellgren and Lawrence score obtained at baseline and follow-up. Then participants' self-reported their physical activity to an interviewer who was familiarized with examples of physical activity in classifications of light, moderate and heavy. The interviewer then assigned a classification to each participant. The measure of physical activity was not done by a questionnaire instead just by taking the responses of participants verbally. The results of the study showed that those with heavy physical activity (more than 4 hours a day) had

3.5 greater odds of incident clinical knee OA, after adjusting for age, sex, body mass index, weight loss, knee injury, health status, current smoking, and total caloric intake.

Occupational physical activity has also been shown to be a risk factor for knee OA. In Coggon and colleagues' study, 518 participants scheduled for surgical treatment of knee OA were compared with controls who were matched in age and sex from the same community (Coggon *et al.,* 2000). Occupations with no heavy lifting, kneeling or squatting had an odds ratio of 1.0 for incident knee OA. Occupations with heavy lifting demonstrated an odds ratio of 1.5, and occupations with kneeling and squatting had an odds ratio of 1.7 for knee OA. Lastly, participants who reported frequent kneeling, squatting and heavy lifting at work had an odds ratio of 3.0 for developing knee OA after adjusting for BMI, previous knee injury and the presence of Heberden's nodes (Coggon *et al.,* 2000).

Professional sportsmen could also be at high risk for developing knee OA. A study of long-distance cross-country skiers showed that with high intensity physical performance, there is an increased risk of developing OA (Michaëlsson *et al.,* 2011). The study included 53,983 men and women, with a mean age of 38 years, who participated in the Vasaloppet 90km ski race at least once between 1989 and 1998. This 90 km ski race is very challenging, with some athletes unable to finish the race. With improvement of finish time, the odds ratio of developing knee OA increased; in another words, the better the athlete performed at the race, the higher their risk for developing OA. Compared to the participants who only finished one race between the years 1989 to 1998, participants who finished 5 or more races in those years had an 83% greater chance of developing

knee OA (Michaëlsson *et al.*, 2011). Another study done in Finland showed similar results in which they found athletes in competitive sports have increased risk of OA in the hip, knee and ankle (Kujala, Kaprio, & Sarno, 1994).

Other studies have supported that immobilization or lack of physical activity leads to loss of knee cartilage. Most studies in this field have used animal models. Long-term immobilization of an animal (such as rabbit and canines) joint is known to cause degradation of articular cartilage similar to those in human OA (Lane Smith *et al.*, 1992; Narmoneva, Cheung, Wang, Howell, & Setton, 2002; Salter & Field, 1960; Videman, 1982). For example, the dorsal right hind leg was immobilized into knee extension with a splint in 79 nine-month-old rabbits (Videman, 1982). Only four days of immobilization were required to produce the first signs of knee OA. With continuous immobilization for 4 to 6 weeks, these rabbits demonstrated progressive knee OA. One other very important study looked at the knee cartilage in participants with traumatic spinal cord injury 6 (n=9), 12 (n=11) and 24 (n=6) months post injury in comparison to 9 young men as healthy controls. After 6 months of immobilization after the injury, the medial tibial cartilage thickness (MT.ThCtAB) was 16% thinner than the control group. For those 12 and 24 months post injury, the thickness was 24% and 25% thinner than controls, respectively (Vanwanseele *et al*., 2010). The results of this study provide some compelling evidence that knee cartilage thinning can be caused by a lack of mechanical stimulation through immobilization.

Physical activity is crucial to cartilage health. When one is lacking physical activity, an important stimulus for cartilage growth is minimized. Or, when one is

performing too much physical activity, cartilage health can be compromised. Moderate amounts of load bearing appear to maintain the thickness of articular cartilage (Hanna *et al.*, 2007; Jones *et al.*, 2003; Roos & Dahlberg, 2005). No one has investigated whether objective measurements of physical activity, documenting both over- and under-use, relate to cartilage thinning in people with knee OA. The two extremes of doing and not doing physical activity are likely both detrimental to cartilage health. Regular, moderate exercise may not increase the risk of knee OA or accelerate the progression of the disease; in fact, moderate exercise might even have a protective effect on cartilage. As mentioned previously, Roos and Dahlberg's randomized control trial showed that with moderate intensity exercise, there was an improvement in the GAG content in the participants who are at high risk of developing knee OA (Roos & Dahlberg, 2005). Improvement in GAG content means an improvement in cartilage health; however it does not mean a change in cartilage volume or thickness. Carefully selected exercises at an adequate intensity such as walking, stationary biking may be beneficial to physical performance (Buckwalter & Lane, 1997) and perhaps even cartilage heath.

2.2.4 Measuring physical activity

Physical activity can be measured in many ways, both qualitatively and quantitatively. In many studies, qualitative interviews or self-reported physical activity levels have been used due to the convenience, efficiency in data collection, and low cost. One challenge of these qualitative measures is the ambiguity of the answers participants provide, as well as the interpretation of these answers. Each individual has their own perception of what is considered exercise.

Quantitative measures can include questionnaires. These physical activity questionnaires are generalized into two categories: one focuses on the current physical activity level and one goes back in history and to find out what the person has participated in across their lifetime. More questionnaires are designed to look at the current level of activity, such as the Physical Activity Scale for the Elderly (PASE) (Washburn, Smith, Jette, & Janney, 1993). The PASE, designed and validated for the elderly population (age 65 years and older), is a brief questionnaire regarding the activity level over the past week, including elements such as duration and intensity during leisure, work and household activities. Participants indicate a number from 0 to 3 to represent how often they were physically active, with 0 being never and 3 being often. The duration is indicated by a number from 1 to 4, 1 being less than an hour, 4 being more than 4 hours (Abete *et al.*, 2001; New England Research Institute, 2001). Scoring of this questionnaire is the product of the duration (hours per week) and an item weight, which was then summed across all PASE activity items to give a final score (Albertine, Schouten, Westerterp, & Saris, 1997; Washburn *et al.,* 1993). The item weight of this questionnaire was established by Washburn *et al.,* using objective data from a motion sensor and an activity diary. The end result of the PASE score is a numerical score to represent the activity level of the individual. The higher the score is, the higher the activity level.

Examples of questionnaires that document lifetime physical activity are the Lifetime Physical Activity Questionnaire (L-PAQ), Lifetime Total Physical Activity Questionnaire (LT-PAQ) and Chasan-Taber Physical Activity Questionnaire (CT-PAQ). The L-PAQ is set up in different life stages, and then split into 3 categories of recreational,

occupational, and household activities. Each category has questions regarding the duration and frequency of activity (De Vera, Ratzlaff, Doerfling, & Kopec, 2010). The total lifetime activity score is obtained by multiplying the duration and the frequency in each life stage, which is then divided by age. The LT-PAQ has the same 3 categories but it includes intensity of the activity in addition to the duration and frequency (Friedenreich, Courrneya, & Bryant, 1998). In another variation of the physical activity questionnaire, the CT-PAQ has only 2 categories: recreational and household activities. This lifelong questionnaire asks participants to recall their activity history and typically takes one to one and a half hours to complete (De Vera *et al.*, 2010). These questionnaires all have a potential bias of overestimation (Fillipas, Cicuttini, Holland, & Cherry, 2010).

Finally, objective measurements of physical activity can be obtained using devices such as pedometers or accelerometers, which measure the daily step count as a representation of physical activity level. These small instruments sense changes in the position of the centre of the device relative to gravity during stepping and record daily step counts performed by the individual in the total wear time period. Both pedometers and accelerometers have the ability to give objective measures of the current physical activity. Pedometers are reliable and suitable for representing physical activity levels in adults (Felton, Tudor-Locke, & Burkett, 2006). However, pedometers are not able to pick up low intensity, low force stepping which is characteristic of the frail older adults. In addition, pedometers are not as accurate as accelerometers (Le Masurier & Tudor-Locke, 2003; Tudor-Locke, Ainsworth, Thompson, & Matthews, 2002). Many studies that evaluate physical activity level use accelerometers instead of pedometers. Accelerometers

are more sensitive to non-ambulatory movements such as bending and shifting weight from one leg to the other (Le Masurier & Tudor-Locke, 2003). For older adults with knee OA, accelerometery is likely a better choice since this type of device will be more accurate at capturing lower intensity activities than a pedometer. To supplement the objective quantitative data captured by the accelerometer, a physical activity log is often used to track activities that may be erroneously recorded as physical activity, such as long durations of driving (Harris, Owen, Victor, Adams, & Cook, 2009). The log would also have information regarding the users' on and off time, activities the accelerometer was not worn for, such as swimming, and activities that should not be counted as physical activity, such as long distance driving. Previous studies that used accelerometry to measure physical activity have supplemented physical activity measures with the use of an activity log book to help augment the accuracy level from the readings on accelerometers (Hale, Pal, & Becker, 2008; Harris *et al.*, 2009).

A previous systematic review has compared self-report questionnaires (indirect measure) to accelerometry (direct measure) in quantifying physical activity (Adamo, Prince, Tricco, Connor-Gorber, & Tremblay, 2009). A total of 83 studies were included in the analysis looking at correlation between these two ways of measuring physical activity. Results showed that the correlations between two measures are low to moderate, with 72% of the studies using self-reported physical activity measures being higher than values measured by an accelerometer. Since each study may use a different outcome unit, the percentage is obtained by this equation: [(self-report – direct measure) / direct measure]*100% (Adamo *et al.*, 2009). This study concluded that questionnaires are a

good indicator in screening for physical activity, however these are not accurate measures. Using an accelerometer over a period of time will minimize this bias. It is important to note, though, that accelerometry requires a longer data collection time and is higher in cost compared to self-report questionnaires, but the accuracy and consistency is far more valuable.

2.2.5 Recommendations for Physical Activity

Physical activity is encouraged by numerous healthcare agencies around the world (Public Health Agency of Canada, 2011; US Department of Health and Services, 2012; World Health Organization, 2011). People with knee OA can benefit greatly from modified guidelines for arthritis because physical activity can reduce pain and improve function during daily activities (Penninx *et al.,* 2001). The general guideline for arthritic adults is to engage in at least 150 minutes per week of moderate intensity aerobic exercise, or 75 minutes of vigorous intensity aerobic exercise. This recommendation is a variation of the original American College of Sports Medicine (ACSM) physical activity guideline which evolved from a concern of cardiovascular disease and physical activity level in the 1950s by Morris and Crawford.

The most standard and frequently recommended exercises to manage OA are brisk walking, muscle strengthening, and water based activities (National Center for Health Promotion and Chronic Disease Prevention, Division of Adult and Community Health, 2011; Zhang *et al.,* 2008). The ACSM has recommended that individuals with OA take short bouts of interval exercise at lower impact or intensity (Minor & Kay, 1997). Some

examples of low impact, low intensity exercises are: swimming, aquatic walking, biking and walking which is safer on the weight bearing joints (Maes & Kravitz, 2004). However there are no data to define exercise intensity in knee OA participants. Low impact or intensity exercise is also recommended to reduce the chance of promoting pain in the knee (National Center for Health Promotion and Chronic Disease Prevention, Division of Adult and Community Health, 2011). Seventy percent of people with OA are not meeting the recommended level of physical activity level set out by the ACSM guideline (Farr *et al.,* 2008).

What is missing from the current literature are concrete guidelines regarding the duration, intensity and type of exercises that are adequate to promote health, without aggravating disease, for people with knee OA. Defining the duration, intensity and type of physical activity is a challenge, because such guidelines likely need to be specific to each individual since everyone would have a different combination of risk factors such as obesity, previous injuries and alignment. Before these guidelines can be created, observational studies are required to determine the duration, intensity and type of physical activity that is associated with worsening of OA disease. This work is necessary to identify the ideal "moderate" durations, intensities and types of activities for people with knee OA.

2.3 ***Significance of study and hypothesis***

The two main purposes of this study were the following: 1) to determine the association between physical activities with MT.VC and MT.ThCtAB, determined from

analyses of MRI scans, in participants who have clinical knee OA. 2) To determine if participants with clinical knee OA demonstrate reliable daily step count data over 5 days as measured by an accelerometer. The medial tibiofemoral compartment was chosen because it is the site where articular cartilage has the greatest load burden in comparison to the lateral compartment during activities of daily living (Schipplein & Andriacchi, 1991; R. H. Thomas, Resnick, Alazraki, Daniel, & Greenfield, 1975). The hypotheses were the following 1) the least and most active participants would have the least MT.VC and MT.ThCtAB and 2) participants with clinical knee OA will demonstrate reliable average step counts over the 5 days. In addition, a moderate number of steps each day will relate to the greatest values of cartilage thickness and volume.

This study will add to the literature regarding the relationship between the repetition of knee loading through physical activity and cartilage health in people with clinical knee OA. It can also provide evidence regarding the quantities and intensities of physical activity that appear to optimize the maintenance of cartilage integrity in adults who had been diagnosed with knee OA.

Chapter Three – Methods

3.1 Research Design

This study was part of larger three year knee osteoarthritis (OA) cohort study. The objective of this thesis was to perform a cross-sectional analysis from data and images collected at baseline. Participants underwent a knee magnetic resonance imaging (MRI) scan and were given an accelerometer to wear for the next seven consecutive days.

3.2 Participants

3.2.1 Recruitment

Participants were recruited at one rheumatology and two orthopedic surgery clinics located within St. Joseph's Healthcare, Hamilton, Ontario, Canada. Two different recruitment methods were utilized:

1. At the rheumatology clinic, a list of potential participants who signed a consent form authorizing contact regarding potential research studies, were contacted by mail or in clinic. A clinic receptionist provided potential participants a letter of information. This letter included a detailed description of the study and contact information for the research assistant to call if they were interested in participating. Also, a research assistant would sit in clinic to recruit participants approved by the rheumatologist in clinic when permitted.

2. Within the two orthopaedic surgery clinics, flyers were posted to inform and invite potential participants to the research study. Contact information for a

research assistant was included in this flyer. Potential participants called the research assistant if interested in the study.

From both recruitment techniques, a research assistant responded to potential participants by describing the purpose, protocol, risks and benefits of the study (see Appendix A for participant consent form). Potential participants who expressed an interest were then screened for the inclusion and exclusion criteria. All participants were from the same general geographical area which may not represent the Canadian population.

3.2.2 Inclusion and Exclusion Criteria

The study included men and women in an age range between 40 and 70 years old. This age range was selected because it captures the highest incidence of knee OA in Canada (Health Canada, 2003). Incidence rate is the measure of a person's probability of developing the disease, or in another words, the rate of new cases (National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health, 2011). The average onset age of clinical knee OA diagnosis is 45 years old (Australian Government, Department of Health and Aging, 2010). In order to capture the changes with early knee OA, the age range was extended to 40 years old.

Inclusion criteria also utilized the clinical criteria of diagnosing knee OA set out by the American College of Rheumatology (Altman *et al.*, 1986). To develop these criteria, Altman and colleagues separated 264 participants from 14 different centres into either a knee OA or comparison group. Consistent findings in the knee OA group included having knee pain, which varied in duration, intensity and frequency in

comparison to controls. Crepitus (crackling or granting feeling or sound inside the joint) was present with active range of motion and activities such as squatting in the knee OA group. In the OA group, palpable bony enlargement and periosteal joint margin bony tenderness were more frequent than in the comparison group. Inflammation in the knee joint was less frequent and less severe in the comparison group compared to participants with OA. All together these findings resulted in clinical criteria for knee OA diagnosis, which requires at least three out of the five following criteria: having knee pain most days of the week, crepitus with active range of motion, bony enlargement, bony tenderness to palpation, signs of inflammation, and age between 40 to 70 years (Hochberg *et al.*, 1995; Altman *et al.*, 1986) (See Table 3.1).

Eligibility for an MRI scan was also required for this study in order to obtain measures of cartilage thickness and volume. Therefore, individuals with metal implants such as a pacemaker, insulin pump, ear implant, artificial joint, metal pins/plates or aneurysm clip were excluded (see Appendix-C, the eligibility for MRI scan sheet for a full list) due to safety concerns. In addition to eligibility for MRI, previous surgery that altered the joint itself was an exclusion criterion to ensure data reflected the natural progression of OA in the knee. These surgeries included joint replacement, ligament repair, and high tibial osteotomy. Minor procedures such as arthroscopic debridement and hyaluronic acid injections were not exclusion criteria because these did not involve in changing the physical structure of the knee. Other types of arthritis, such as rheumatoid arthritis, were exclusion criteria since these conditions may become a cofactor to knee OA. Regular use of assistive walking devices was an exclusion criterion since other

aspects of the larger cohort study required participants to walk without assistance. Injuries to the hip, knee or ankle in the past three months were also exclusion criteria to ensure that the data reflected knee OA only. Lastly, potential participants with cancer, other major illness, or pregnancy were also excluded for health and safety considerations for MRI, X-ray and other performance tasks. If both legs were qualified, the most severe leg (usually more pain) would be chosen. A summary of the exclusion criteria includes the following: knee surgery (such as joint replacement, ligament repair, high tibial osteotomy), other types of arthritis, use of cane or other walking devices, injury to hip/knee/ankle in the past 3 months, cancer or other major illness and pregnancy. The study leg was chosen by the leg that meets the criteria the most. Finally, written informed consent was an inclusion criterion (see Appendix B for full participant screening form).

Table 3.1 Inclusion and Exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Age between 40-70 years old **3 of 5 in any of the following:** • Knee pain most days of the week • Crepitus with active range of motion • Body enlargement • Bony tenderness to palpation • Signs of inflammation	• Unable to perform a MRI scan • Knee surgery • Other types of arthritis • Pregnancy • Use cane/walking devices • Injury to hip/knee/ankle in past 3 months • Currently receiving cancer treatment

3.3 Data Collection

3.3.1 Procedure Overview

Data collection began with a baseline MRI scan performed at the Centre for Appendicular Magnetic Resonance Imaging Studies (CAMRIS), Hamilton, Ontario. At the end of this session, an accelerometer was given to the participants to wear for the next seven consecutive days.

3.3.2 Dependent Variable – Medial Tibial Cartilage Volume and Thickness

Cartilage thickness and volume are good representations of cartilage health in participants with knee OA. Many studies have used MR imaging for cartilage volume and thickness quantification as a representation of cartilage health (Eckstein, Cicuttini, Raynauld, Waterton, & Peterfy, 2006; Raynauld *et al.,* 2003). Wluka and colleagues showed that the measure of cartilage volume was sensitive to change in participants with knee OA. The research group examined cartilage volume using MRI in 123 participants with knee OA at baseline and 2 years follow-up and suggested that cartilage loss is rapid early in the disease (Wluka, Stuckey, Snaddon, & Cicuttini, 2002). Average cartilage thickness is a measure of cartilage health that is calculated by dividing the cartilage volume by the joint surface area. A study which looked at knee cartilage loss between men and women with knee OA used the measure of cartilage thickness as a measure of cartilage health (Amin *et al.,* 2005). However, thickness changes may be more difficult to detect due to the limited amount of colour coded grey scale by the output of MR images (Eckstein *et al.,* 2006). Also, since MT.ThCtAB is the MT.VC divided by the surface area,

the thickness value should represent the average thickness value in the medial tibial cartilage area. A focal defect in one area would likely be washed out in a measure of the average thickness.

Medial tibial cartilage volume (MT.VC) and medial tibial cartilage thickness (MT.ThCtAB) were obtained by analyzing the images from using a high resolution peripheral magnetic resonance system located at CAMRIS 610-25 Charlton Ave, E., Hamilton, Ontario. Magnetic resonance imaging was chosen as the primary imaging modality for investigating cartilage thickness rather than X-ray because MR images produced direct views of the cartilage in three-dimensional space and x-ray images do not capture soft tissues such as cartilage. A peripheral scanner was chosen instead of a whole body system for several reasons including improved accessibility and lower direct costs. Also, using a peripheral scanner minimizes potential issues of claustrophobia often encountered with a full body scanner (Peterfy, Roberts, & Genant, 1998). The peripheral MR (1-Tesla, 1T) scanner used in this study employed a 180 mm removable quadrature volume transmit-receive coil (GE Medical, Fairfield, CT). Data yielded from the images produced by MRI scans have been shown to be valid and reliable in showing cartilage in participants suggesting MR imaging is an effective non-invasive tool to quantitatively investigate cartilage health (Raynauld *et al.,* 2003; Inglis *et al.,* 2007). In addition, MR produces images that are sensitive for the analysis to detect changes in cartilage for longitudinal studies of the progression of knee OA (Eckstein, Mosher, & Hunter, 2007).

Procedures followed to obtain the MRI scans are described in this paragraph. Participants were scheduled for the MRI visit at CAMRIS. Self-reported body mass, sex

and age were entered into the software program used to acquire the MR images in advance for participant identification. Before entering the scanning room, participants were asked to remove any metal items or items with batteries or magnetic strips such as cell phones, hearing aids, watches, keys, credit cards, pocket knives, clips and coins. They were also asked to remove their shoes before they entered the imaging room.

Participants were asked to sit in the chair and place the study leg through the bore of the scanner. The chair was positioned so that the knee was at the centre of the bore of the magnet. If the knee was not at the centre, padding was used to adjust the position. To enhance comfort, a leg rest was placed under the other leg. Blankets were provided to cover the whole body and pillows were used to support the neck and lower back as needed. Careful attention was paid to positioning and comfort to minimize the potential that participants moved during the scanning procedure. After all of the set up was finished, the chair was locked into place, and the door to the scanning room was closed. Participants could communicate with the research staff through a window to report any discomfort or an emergency situation.

First a localizer scan was used to check the position of the knee. These images were in three planes including sagittal, axial and coronal. If the knee was not in the centre of the bore, positioning was adjusted by moving the participant in or out of the magnet as needed. The scanning sequence flow chart is presented in Figure 3.1. An axial fat spin-echo localizer scan took place just before the parameter setting scans to acknowledge the participant-specific fat content in knee region. This scan usually takes about 2-3 minutes. This was followed by three scan sequences. The first scan of the protocol was acquired in

the sagittal plane. Slices of the scan were positioned at the centre of the tibiofemoral joint space. This sequence formed the dimensions of the region of interest from anterior to posterior. The second scanning sequence was for the transverse plane to set the axial centre of the scan volume. The centre of the slices was set at midpoint of the distal end of the femur on the lateral side. This set of slices defined the medial to lateral dimensions of the region of interest. The third scanning sequence was to set the coronal slices and centre of scan volume. The centre of these slices was taken tangent to the posterior femoral condyles and defined the distal to proximal dimensions of the region of interest. In addition, a water peak scan was conducted to visualize the bone in the knee. All three setting scans together were completed in 10 minutes. Then the final volume scan took roughly 15-16 minutes. The scanning sequence used in this study was called the fat suppressed T1-weighted three-dimensional spoiled gradient echo sequence. This particular sequence was reported to result in the highest accuracy in reporting chondral abnormalities (Pedowitz, Chun & Resnick, 2008). This sequence is also important in highlighting the cartilage contrast in order to delineation between other tissue and cartilaginous tissue. The parameters for the scan were as follows: TR 60 ms; TE 12.4ms (or minimum); flip angle 40 º; bandwidth 30kHz; matrix 512 x 256 (frequency x phase); 1 excitation; field of view 150 mm; slice thickness 1.5 mm; 56 to 64 slices depending on the participant size. The whole MRI procedure including the pre-qualifying questions and the scan took approximately 40 minutes. The last sequence is the scan which is used in the image analysis. This last scan is determined by the parameters obtained from the

positional scans necessary to describe the knee in three dimensions. Images were archived and transferred to an external hard drive for storage and analysis.

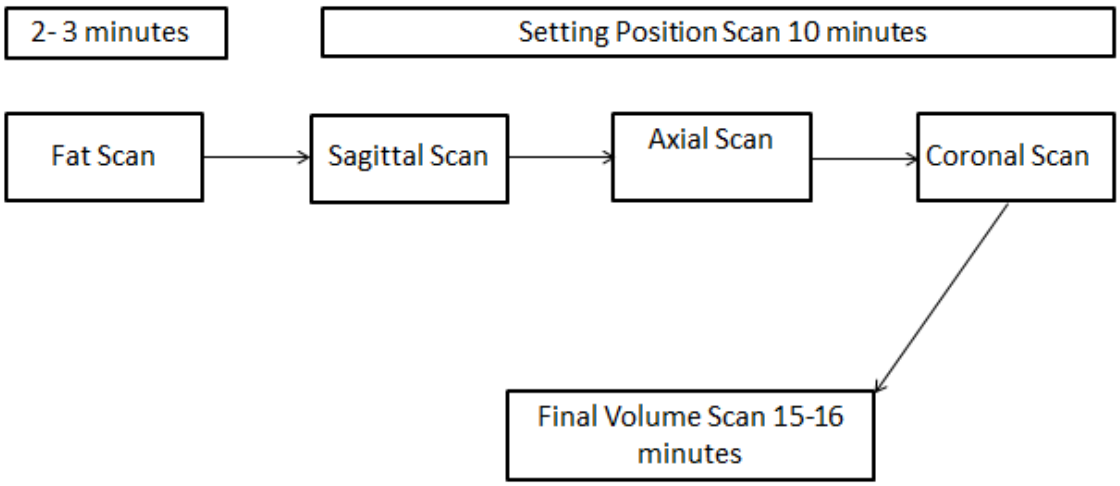

Figure 3.1 Series of scanning sequences implemented in the protocol

The overall goal of the analysis of the MRI scans was to outline the cartilage structure, and distinguish cartilage from non-cartilaginous structures (bone, meniscus, tendons, ligaments and soft tissue) from anterior to posterior and medial to lateral to quantify the total cartilage volume in the tibial joint. This process is known as segmentation. Options for segmentation include manual, semi-automated and automated techniques. Manual segmentation refers to drawing the outline of the cartilage free-handed. While manual segmentation results in highly precise and accurate data (Eckstein & Glaser, 2004), it requires many hours of segmentation and a high level of training (Eckstein *et al.,* 2006). Semi-automated segmentation is drawing free-hand, with the assistance of some computerized edge-tracking that spreads the contour identified on one image slice to the next. The benefit of this semi-automated method is that it allows for a

faster outlining process; however it still requires hours of segmentation and remains subject to the researcher's technique in outlining (Raynauld *et al.,* 2003).

Recently, a highly automatic segmentation technique was developed specifically to detect cartilage in the presence of knee OA (Tamez-Pena *et al.,* 2012). This fully automated segmentation technique implements the use of an atlas of a healthy set of knees for reference points. Data produced by this newly developed technique was shown to be accurate, repeatable and reproducible in longitudinal study (Tamez-Pena *et al.,* 2012). Pilot data from the study recruited 6 symptomatic OA subjects and 6 controls that were 40 years of age or older. Manual segmentation was used as a gold standard. Results from the pilot showed the thickness measure ranged between -2.2% to 10.4% in accuracy (% of mean) and 88% ± 4% in sensitivity for femoral cartilage; and 89% ± 6% in accuracy and 0.89 ± 0.06% in sensitivity for tibial cartilage (Tamez-Pena *et al.,* 2012). Specificity of the methodology is at >0.9999 which means the specificity is more than 99.99% correct in separating the non-cartilage tissue from cartilage tissue the images. The reproducibility variation is at 1.6% meaning that the outcome number can be reproduced with only 1.6% of error with a range between 0.7-2.1 percent (Tamez-Pena *et al.,* 2012). Thus this method was chosen for analysis of the cartilage in this study because of its objectivity, accuracy, consistency of image analysis, and efficiency. This procedure is currently available only at QMetrics Technologies LLC, for quantitative medical image analysis.

A summary of the automatic segmentation procedure created by QMetrics Technologies LLC is as follows. First, a set of images from 5 women and 4 men with

healthy knees were acquired using the same peripheral MRI scanner, sequence, and protocol from as the present study. These images were then manually traced by a radiologist with extensive experience in segmenting cartilage to identify bone and cartilage surfaces on femur, tibia, and patella. These images resulted in a knee atlas, with anatomical landmarks which represented areas of interest including the following: central medial tibial weight bearing region, central lateral tibial weight bearing region, posterior medial femoral condyle, posterior lateral femoral condyle, medial tibial plateau and lateral tibial plateau.

The fully automated image segmentation procedure was used to compare MRI scans obtained for each participant with the atlas of healthy knee joints. This procedure included the following steps (Tamez-Pena *et al.,* 2012):

1. Cartilage segmentation began with an affine registration, a technique that utilizes and preserves straight lines between registration points outlining articular cartilage, where similar structures were identified and registered.

2. Next, a mathematical technique used to interpolate points was used to adjust the registration. This cubic spline deformation is then used to fit the segmentation to the image. The cubic spline procedure used in this automated procedure used a 3x3x3 grid.

3. Next, the atlas was compared to the knee OA image. Full resolution free form boundary matching was used to match all registered atlas boundaries to input image. This procedure used all of the edges as control points.

4. Registered boundaries from the previous step may have been sharp and spiky. These edges then were smoothed.

5. The next step in the procedure was to automatically label regions of cartilage. Cartilage closer to the tibia than femur was labelled as tibial cartilage and vice versa.

6. Any voxels of articular cartilage that were three standard deviations above or below the mean cartilage signal were deemed outliers and removed.

7. Refine with voxel by voxel deterministic reclassification to match the MRI contrast information.

8. At the end, five segmentation classifications were fused together as one final image representing the articular cartilage present with the knee joint of each participant.

Finally, once segmentation was complete, the thickness (mm) and volume (mm^3) of cartilage within the medial compartment of the knee, for tibia was calculated.

3.3.3 Independent Variable - Physical Activity

The total number of steps taken daily was measured using a tri-axial accelerometer (ActiGraph, Pensacola, Florida, USA). Step counts produced by accelerometers are a valid, objective measure of physical activity (Feito, 2010; Preston, Baltzen, & Trost, 2011). The Actigraph GT3X+ model was chosen for this study because of its long battery life, large memory space and software (ActiGraph & DandSoftware Departments, 2011).

Prior to each participant's first visit, the accelerometer was programmed with ActiLife software. The setup of the accelerometer included sampling rate, starting and ending time and date, side of the study limb, and sex. The sampling rate was set at 30 Hz, which means it was sampling accelerations 30 times per second. The starting day was set one day after their initial MRI visit at 12:00 AM. The ending time was set at nine days at 11:59 PM after the initial wear day. This nine day collection period provided two extra days for data collection in case a participant missed up to two days.

Along with the accelerometer, a set of forms were also given to the participants, which included an instruction sheet with a diagram of correct position for accelerometer (Appendix-D) and an activity log book (Appendix-E). Participants were asked to complete an activity log book to record their regular activities, driving, water activity or any other time periods when they did not wear the accelerometer. Participants were asked to record the intensity of any activity they performed during the week with the duration. Participants were instructed to wear the accelerometer for seven consecutive days on their waist, on the same side as their study leg.

3.3.4 Step Counts

Upon return of the accelerometer, the data were downloaded and presented at 10 Hz to accommodate the capacity of Microsoft Excel. Another reason for selecting 10 Hz was to enable comparison with other similar studies (Belza *et al.,* 2000). These accelerometry data were then inspected to ensure quality of the data. The days where the accelerometer was worn for less than 10 hours were excluded (Matthews *et al.,* 2008;

Semanik *et al.*, 2010). Previous studies have used 12 hours as a cut-off (Robbins, 2010); however, the sample in this study was older and less active. The activity log was reviewed to eliminate days where participants did not wear the accelerometer, or participated in unusual activities not typical in their schedule. Accelerometry in elderly age groups requires a minimum of three days of wear time to estimate the daily physical activity (Kochersberger, McConnell, Kuchibhatla, & Pieper, 1996). Other studies have shown that five days is a sufficient time period to measure the physical activity level of adults (Gretebeck & Montoye, 1992; Trost, Mciver, & Pate, 2005). Therefore, the first five full days was averaged. Data from the participants who did not meet the wear time criteria were not included in the analysis. The final daily average from each participant was used as a representation of current physical activity level.

3.3.5 Activity Intensity

Another independent variable taken from the accelerometry data was the average daily time spent engaging in "moderate to vigorous activity." In addition to the step counts data, estimates of time spent in light, moderate and vigorous activity can be defined by the frequency at which large magnitude accelerations are recorded per minute (ActiGraph R&D and Software Departments, 2011). An activity count is a measurement of the change in voltage signal over a period of time (voltages times 60 seconds). Several cut-off frequencies defining light, moderate and vigorous activity for the accelerometer have been published. The cut points for the activity counts used in the study were as follows: 0 to 2224 activity counts defined light, 2225 to 5950 activity counts defined moderate and 5951 counts and above defined vigorous (Farr *et al.*, 2008). The cut points

were established by having participants wear the accelerometer to perform various intensity exercises on the treadmill in the laboratory with an open circuit spirometry to measure oxygen consumption, which represents the intensity of the exercise (Freedson, Melanson, & Sirard, 1998). These cut points were then modified and averaged from calibration studies (Matthews, 2005) of accelerometer output and were used in the study by Farr *et al.,* in which the participants were similar to those in this thesis study. Farr and colleagues' study measured the physical activity intensity in people with knee OA (mean age at 54.6 ± 7.1 years) using an Actigraph accelerometer (MTI) (Farr *et al.,* 2008). An average number from five days of collection will be calculated for the three categories (Tudor-Locke & Bassett, 2004; World Health Organization, 2008).

3.4 Covariates

A longitudinal study indicated that female sex, age and obesity were associated with cartilage defects (Ding *et al.,* 2006). This longitudinal study was one of the largest describing the natural history of knee cartilage depreciation. The study had 325 participants who completed initial and two-year follow-up MRI scans for cartilage volume measurements. Female sex had an odds ratio of 3.09 for reduced cartilage volume in the medial tibiofemoral compartment, which means that women are 3.09 times more likely than men to show worsening of cartilage defects (Ding *et al.,* 2006). In addition, women were shown to have a thinner cartilage and a different rate of cartilage loss compared to men. In comparison to men, women between the ages of 20 to 69 years (38.2 ± 13.2 years) only have an average cartilage thickness of 1.45 mm versus men who

have on average 1.71 mm (Beattie *et al.,* 2008). Therefore, sex is a very important covariate to analyze when studying physical activity and cartilage.

Felson *et al.,* showed that the rate of developing OA increased 2 to 10 fold from 30 to 65 years of age, with further increases after the age of 65 (Felson *et al.,* 2000; Oliveria, Felson, Reed, & Walker, 1996). With advancing age, cartilage thickness in the knee also decreases at a rate of 0.013 mm to 0.035 mm each year (Ding, Cicuttini, Scott, Cooley, & Jones, 2005). This loss is dramatic since, on average, women only have 1.45 mm (Beattie *et al.,* 2008) of cartilage; thus losing 0.035 mm means losing 2.4% of cartilage each year.

In 45 healthy men, mean age at 52.5 years, MT.VC was inversely associated with age and body mass index (BMI) (Cicuttini *et al.,* 2003). In 372 adults (158 men and 214 women) with a mean age at 45 years, BMI was positively related to knee cartilage defects (Ding, Cicuttini, Scott, Cooley, & Jones, 2005).

3.5 Data Analysis

Descriptive statistics, including means, standard deviations, and variances were calculated for the demographics as well as dependent and independent variables. Sex was coded as one to represent men and zero to represent women.

The relationships between variables were first analyzed with a linear regression analysis. The assumptions of this analysis were that the dataset must be normally distributed and that the covariates must be linearly related to each dependent variable.

Normality of each variable was evaluated by looking at the mean, median, kurtosis and skewness. In the linear regression analysis, MT.VC was the dependent variable, with the covariates and independent variables entered in two separate blocks. Variables entered in a stepwise fashion into block 1 of the regression were age, sex and BMI; and average step counts, average time in light intensity activity and average time in moderate-vigorous activity were entered in a stepwise fashion in block 2. Another regression was conducted with the dependent variable as MT.ThCtAB.

Second degree polynomial analyses were done by using linear regressions. First the age, step, and BMI terms were looked at to see if there was a quadratic relationship with MT.VC and MT.ThCtAB by scatter plots. The terms that were not significantly correlated with the quadratic relation were dropped from the analysis. The remaining terms were then squared and interaction terms were calculated. A linear regression analysis was conducted with the dependent variable as MT.VC, and the independent variables as the original non-squared terms, squared terms and the interaction terms (refer to Figure 3.2). Another regression was conducted with the dependent variable as MT.ThCtAB.

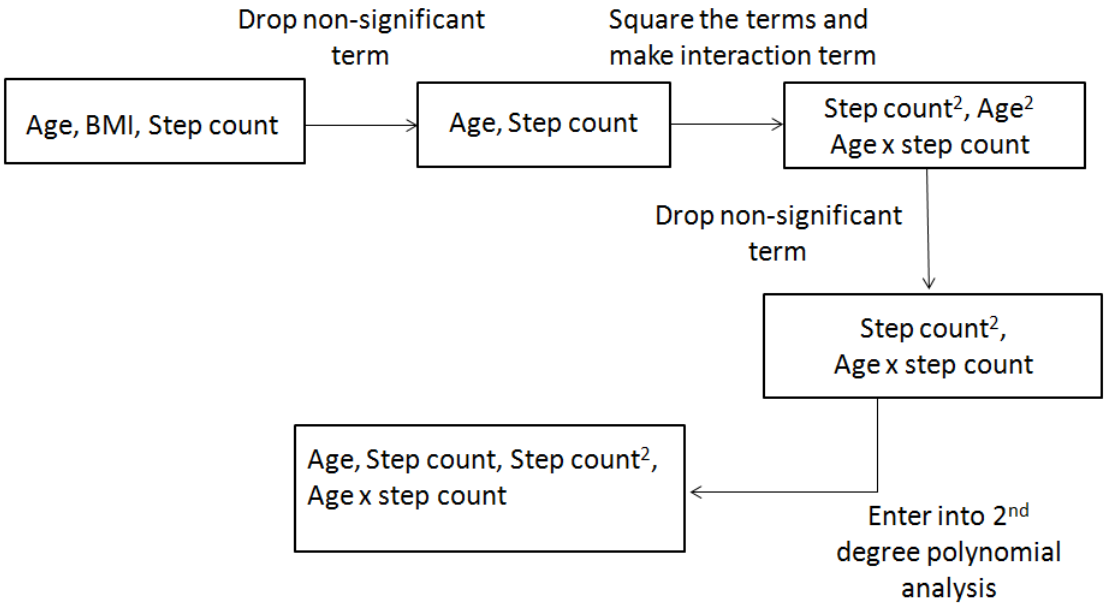

Figure 3.2 Quadratic analysis term incorporation chart in finding important independent quadratic terms the dependent variables would be MT.VC and MT.ThCtAB

The test-retest reliability of the step counts data from the accelerometer used in the study was examined over 5 days from each participant. The intraclass correlation coefficient (ICC) was determined by the reliability model set as two-way mixed type set as absolute agreement. The ICC with 95% confidence interval and the standard error of the device for 5 days of step counts were then calculated. A repeated measures analysis of variance (ANOVA) was performed to detect the differences in step count data between the five days of data collection.

Chapter Four- Results

4.1 Demographics

Data from 34 eligible participants were analyzed for this study, with 6 men and 28 women, aged 60.6 ± 6.5 years (See table 4.1 for complete descriptive statistics). The dependent variables for this sample were an average medial tibial cartilage thickness (MT.ThCtAB) of 1.89 ± 0.17 mm and medial tibial cartilage volume (MT.VC) of 1739.07 ± 416.97 mm^3 (Figure 4.1). Figure 4.1 depicts that an outlier in MT.VC was in the sample, who was 2.85 standard deviations away from the mean. The independent variable of average step counts per day ranged from 1,288.0 to 21,935.6 steps with an average of 9,074.3 ± 4,516.7 (Figure 4.2). Figure 4.2 demonstrated that Participant 006 was an outlier with an average step count of 21,935 steps per day, which were 2.85 standard deviations away from the mean. On average, each day participants spent 569.9 ± 66.7 minutes in sedentary activity, 209.1 ± 46.1 minutes engaged in light activities and only 36.7 ± 21.4 minutes engaged in moderate and vigorous activities combined.

The correlation coefficients between the independent and dependent variables are shown in Table 4.2. In the correlation table, MT.VC had strong correlations with age and sex. Men had more MT.VC than women. A negative relationship was present between age and MT.VC, where the older the participants had less MT.VC. These relationships were not significant in MT.ThCtAB.

Table 4.1 Descriptive statistics for variables (n=34, 28 women, 6 men)

Variable	Mean ± Standard Deviation	Median	Minimum-Maximum
Age (y)	60.6 ± 6.5	61.5	41-69
Mass (kg)	75.9 ± 16.4	74.6	51-117
BMI (kg/m^2)	28.5 ± 5.4	27.2	19.7-38.9
Steps per day	9074.3 ± 4516.7	8007.2	1288.0-21935.6
MT.ThCtAB (mm)	1.89 ± 0.17	1.87	1.60-2.26
MT.VC (mm^3)	1739.07 ± 416.97	1705.44	934.28-2929.40
Average time in light intensity activity (min)	779.0 ± 67.8	795.8	602.4-899.6
Average Moderate Vigorous Physical Activity Time (min)	36.7 ± 21.4	34.1	1.8-93.8

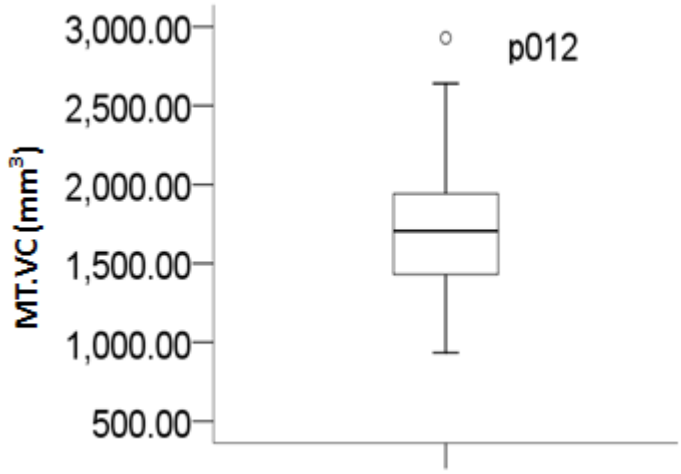

Figure 4.1 Boxplot of Medial Tibial Cartilage Volume (MT.VC) in mm^3. Note that data point 012 is an outlier.

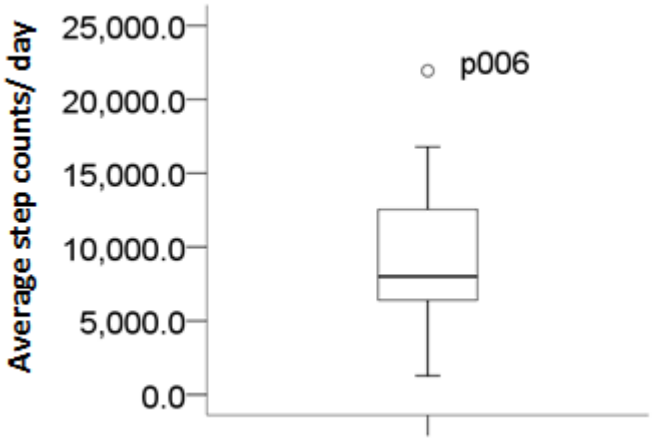

Figure 4.2 Boxplot of average step counts per day. Note the data point 006 is an outlier.

Table 4.2 Correlation table between variables. Note the direction of the correlations in age and average step counts per day, age and MT.VC and MT.ThCtAB, age and average moderate vigorous activity time, sex and MT.VC, average time in light intensity activity time and MT.VC. Significant relationships are bolded.

Variable	Step	Age	Sex	BMI	MT.ThCtAB	MT.VC	Avg Light	Avg MVPA
Step	-	**-0.452**	0.109	0.069	0.194	0.282	0.194	**0.599**
		(0.007)	(0.538)	(0.697)	(0.271)	(0.105)	(0.270)	(<0.001)
Age		-	-0.140	-0.098	**-0.488**	**-0.349**	0.109	**-0.544**
			(0.429)	(0.582)	(0.003)	(0.043)	(0.540)	(0.001)
Sex			-	0.171	0.210	**0.693**	0.070	0.043
				(0.333)	(0.234)	(<0.001)	(0.695)	(0.809)
BMI				-	-0.011	0.229	0.099	0.056
					(0.951)	(0.194)	(0.576)	(0.753)
MT.ThCtAB					-	**0.706**	0.284	0.091
						(<0.001)	(0.104)	(0.609)
MT.VC						-	**0.358**	0.047
							(0.038)	(0.794)
Avg Light							-	**-0.493**
								(0.003)
Avg MVPA								-

Step= average steps per day, Sex= men coded as 1, BMI=body mass index, MT.ThCtAB = medial tibial cartilage thickness, MT.VC= medial tibial cartilage volume, Avg Light= average time in light intensity activity, Avg MVPA= average time in moderate and vigorous intensity physical activity time

4.2 Linear Regression

4.2.1 Medial Tibial Cartilage Volume

The relationships of MT.VC and average step counts as well as average light activity time are illustrated in Figure 4.3 and Figure 4.4. The linear regression with MT.VC as the dependent variable demonstrated that the total adjusted R^2 was 0.628, with sex, age, and average time in light intensity activity as the explanatory variables (p=0.003) (refer to Table 4.3). This R^2 value implies that with the knowledge of sex, age and the average time spent in light activity, the regression equation would have accounted for 62.8% of the variances in MT.VC.

Descriptive statistics identified that participant 006 and participant 012 were potential outliers. From graphing the dependent and independent variables these two participants were suspicious since it was far off from the mean. The residual value is the difference between the measured value and predicted value. A residual and leverage analysis was then performed since these values are useful in detecting the influence towards a regression analysis (Barrett & Gray, 1997). The residual value was 1214.14 for participant 012 and 566.08 for participant 006. The residual value is the difference between the measured value and the predicted value. The leverage value was 21519.88 for participant 006 and 46758.63. Leverage value is a measure of how far an x vale falls from the mean x-value. Both the residuals and leverages from participant 012 and participant 006 were very high. Thus, the linear regressions with MT.VC as a dependent variable was repeated, with these two outliers removed (See Figure 4.5). The R^2 value

was 0.563, with sex, average time in light intensity activity and average step counts per day as the explanatory variables (p=0.017). This result implies that, with knowing sex, average time in light intensity activity as well as average step counts per day, the regression equation accounted for 56.3% of the variance in MT.VC.

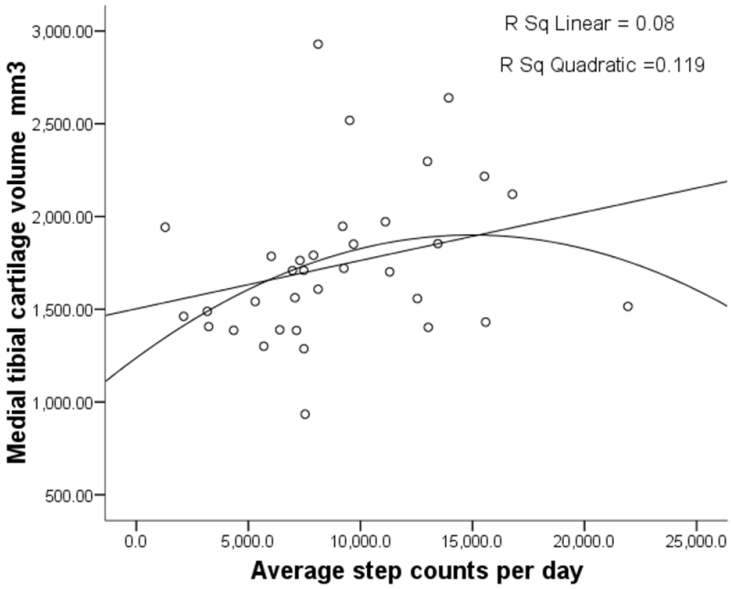

Figure 4.3 Average step counts per day versus MT.VC in mm^3.

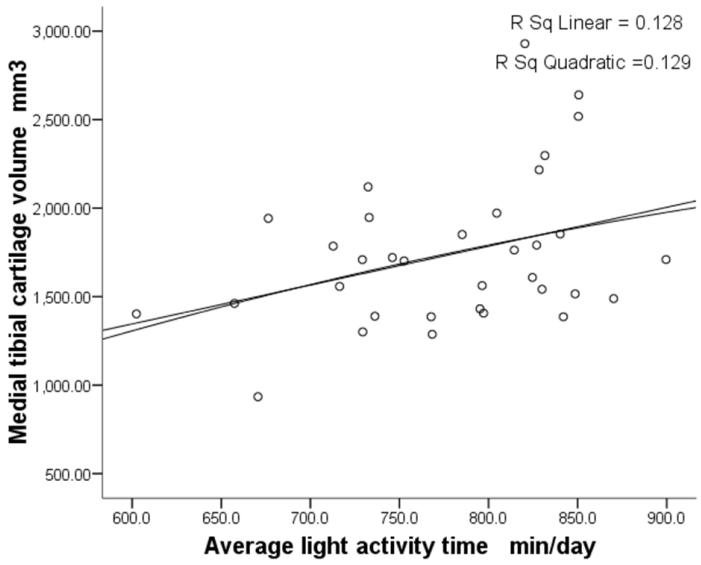

Figure 4.4 Average time in light intensity activity in minutes per day versus MT.VC in mm^3.

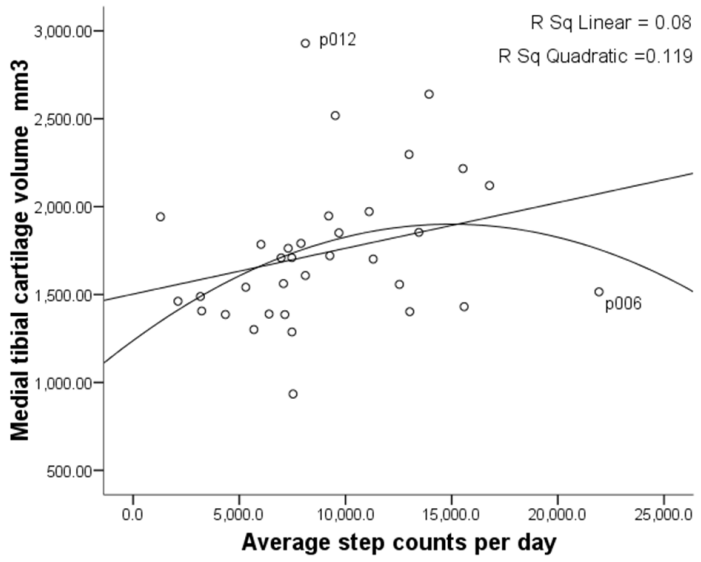

Figure 4.5 Average step counts per day versus MT.VC in mm^3. Note the outlier participant 006 and 012 and their influence towards the regression line.

Table 4.3 Linear regression analysis output of MT.VC.

	Total Adjusted R^2	Change in R^2	Standardized B coefficient	P
Sex	0.463	-	0.627	<0.001
Age	0.515	0.052	-0.298	0.010
Average time in light intensity activity	0.628	0.113	0.346	0.003

Table 4.4 Linear regression analysis output of MT.VC with participant 006 and 012 outliers removed.

	Total Adjusted R^2	Change in R^2	Standardized B coefficient	P
Sex	0.372	-	0.550	<0.001
Average time in light intensity activity	0.481	0.109	0.314	0.014
Step count	0.563	0.082	0.311	0.017

4.2.2 Medial Tibial Cartilage Thickness

Age and average time in light intensity activity explained 31.2% of the variance in MT.ThCtAB (p=0.026) (See Table 4.5). The relationships between MT.ThCtAB, step

counts and average sedentary time are illustrated in Figure 4.6 and 4.7. The same regression performed again with the outliers removed had illustrated same results, with only age and average time in light intensity activity involved in the regression (See table 4.6). With the two participants removed the R^2 value was 0.332 (p=0.018).

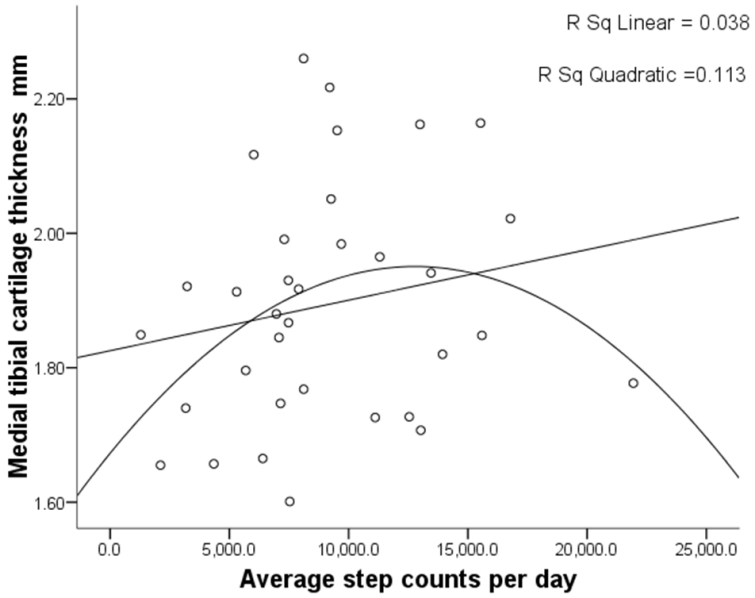

Figure 4.6 Average step counts per day versus MT.ThCtAB in mm.

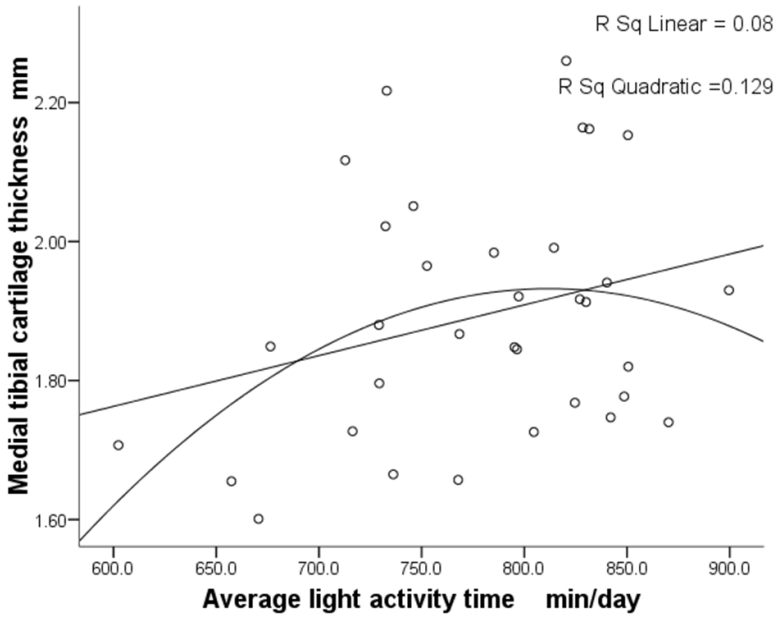

Figure 4.7 Average time in light intensity activity in minutes per day versus MT.ThCtAB in mm.

Table 4.5 Linear regression analysis output for MT.ThCtAB.

	Total Adjusted R^2	Change in R^2	Standardized B coefficient	P
Age	0.215	-	-0.525	0.001
Average time in light intensity activity	0.312	0.097	0.341	0.026

Table 4.6 Linear regression analysis output for MT.ThCtAB with participant 006 and 012 outliers removed.

	Total Adjusted R^2	Change in R^2	Standardized B coefficient	P
Age	0.213	-	-0.544	0.001
Average time in light intensity activity	0.332	0.119	0.374	0.018

4.3 Second degree polynomial analysis

Results from the 2nd degree polynomial analyses using linear regression demonstrated no significant results for MT.VC and MT.ThCtAB (See table 4.7 for MT.VC analysis and 4.8 for MT.ThCtAB analysis). This result indicates that there were no significant terms to build a quadratic equation representing the relationship between step and MT.VC or MT.ThCtAB with the consideration of age. Even when the outliers were removed, the results from this analysis remained the same (See table 4.9 for MT.VC and 4.10 for MT.ThCtAB).

Table 4.7 Second degree polynomial analysis using linear regression on MT.VC

Volume	Total Adjusted R^2	Standardized B coefficient	P
Step	0.077	2.990	0.282
Age		0.215	0.714
$Step^2$		-1.027	0.201
Step x age		-1.685	0.403

Table 4.8 Second degree polynomial analysis using linear regression on MT.ThCtAB

Thickness	Total Adjusted R^2	Standardized B coefficient	P
Step	0.204	-1.268	0.620
Age		-0.880	0.114
$Step^2$		-0.382	0.604
Step x age		1.482	0.428

Table 4.9 Second degree polynomial analysis using linear regression on MT.VC with removal of participants 006 and 012 as outliers

Volume	Total Adjusted R^2	Standardized B coefficient	P
Step	0.140	2.076	0.534
Age		0.300	0.669
$Step^2$		-0.113	0.920
Step x age		-1.429	0.513

Table 4.10 Second degree polynomial analysis using linear regression on MT.ThCtAB with removal of participants 006 and 012 as outliers

Thickness	Total Adjusted R^2	Standardized B coefficient	P
Step	0.176	-2.555	0.436
Age		-1.058	0.131
$Step^2$		0.458	0.679
Step x age		2.025	0.346

4.4 Test-retest reliability

Step count data were tested for the reliability between the 5 days during which participants wore the device for 10 or more hours (Refer to Figure 4.8 for boxplot over 5 days). Average wear time per day was 815.0 ± 69.1 minutes or 13.58 ± 1.15 hours per day. A high degree of reliability was found between the average step counts data from the 5 days. The F score obtained from the repeated measures analysis of variance (ANOVA) F (4, 33) was 1.301 with a *p* value at 0.273; therefore there was no difference between the 5 days of wearing the accelerometer. The intraclass correlation coefficient was 0.929 with a 95% confidence interval [0.883, 0.961] with standard error of the measurement (SEM) of 1199.4steps.

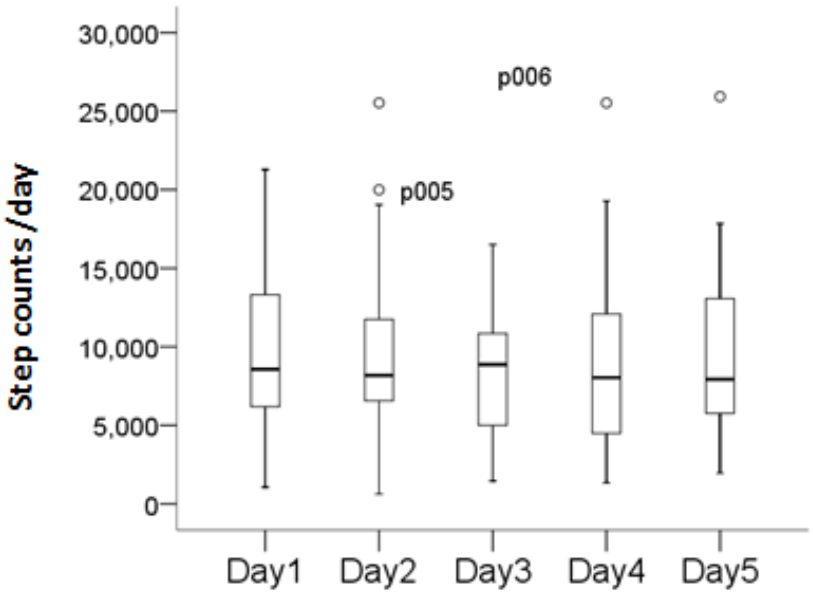

Figure 4.8 Boxplot of daily step counts over 5 days

Chapter Five- Discussion

This study aimed to examine the relationship between physical activity and medial tibial knee cartilage volume (MT.VC) in participants with clinical knee OA. Based on this study, though a relatively weak relationship, it was found that participants who engaged in a greater quantity of low intensity exercises had the most MT.VC when compared to rest of the participants in the study. Examples of low intensity activities include walking (less than 4 km/h), riding stationary bikes, tai chi and light aerobics (Buckwalter & Lane, 1997; Fransen, Nairn, Winstanley, Lam, & Edmonds, 2007). In the current study, only a few participants were engaged in high intensity physical activity; as a result, the findings were not conclusive regarding the impact of high intensity exercise, or a large quantity of intense exercise, on MT.VC or medial tibial cartilage thickness (MT.ThCtAB). The clinical relevance of the study findings would be that adults with relatively mild, clinical knee OA likely benefit from engaging in moderate amount of low intensity physical activities.

5.1 Amount and intensity of physical activity and knee cartilage health

The current study demonstrated a weak linear relationship between activity level, measured by step counts, and MT.VC. A previous study by Hanna and colleagues showed similar results, suggesting that engagement in physical activity was associated with greater MT.VC (Hanna *et al.,* 2007). The study enrolled 176 women with no clinical knee OA or history of knee injury, between the ages of 40-67 years. The assessment of the cartilage volume included automated segmentation from magnetic resonance images

(MRI) of the knee cartilage. The physical activity measure included questions such as "On how many days during the last 14 days did you spent at least 20 minutes doing strenuous exercise, e.g., bicycling, brisk walking, jogging, aerobics, etc. that was severe enough to raise your pulse rate or cause you to breathe faster?" The responses were given in the number of days that participants were engaged in those exercises during the last 14 days. Those who answered at least 1 or more days were considered as participating in physical activity (Hanna *et al.*, 2007). Of the entire sample, 138 met the criteria for being physically active, and the remaining 38 were sedentary. The study results were that women who were physically active at least once in 14 days showed slightly greater MT.VC than the sedentary group (β=0.12, p=0.02) (Hanna *et al.*, 2007). There are some differences between the Hanna *et al.*,'s study versus the current study. Hanna and colleagues' study enrolled participants with no clinical knee OA; whereas the current study had participants who have clinical knee OA. Also this previous study used a questionnaire to measure of physical activity, while the current study used an objective measure. Despite these differences, the current study results still showed a similar relationship between physical activity and cartilage volume.

On the other hand, the current study results were different than those studies that showed an inverse relationship between cartilage volume and the quantity of physical activity. For example Cicuttini and colleagues recruited 45 men with a mean age of 52.5 ± 13.2 years with no previous significant knee injuries. The goal of this study was to determine the factors associated with knee cartilage volume in men (Cicuttini *et al.*, 2003). Physical activity was assessed by a survey that assigned units to time spent engaging in

physical activity. Each unit of activity consisted of either 15 minutes vigorous weight bearing exercise or 30 minutes of moderate weight bearing exercise. Examples of vigorous categories include jogging, squash, tennis, hockey, badminton and aerobics. Moderate categories included table tennis, golf, stretching, and social dancing. Walking and bowling were not considered sports and swimming and cycling were excluded since these are non-weight bearing activities. A score of 1 or fewer units per week was considered low, 1-3 units moderate and 4 units or more active (Spector *et al.*, 1996). The result from Cicuttini *et al.*'s study showed that there was a negative relationship between physical activity and MT.VC. The β value (coefficient in a regression) was -0.07 (p=0.017) between physical activity and MT.VC in a multivariate regression analysis (Cicuttini *et al.*, 2003). There are several differences between this study and the current study which may explain the discrepancy in results. Cicuttini and colleagues recruited healthy men whereas the current study had a sample of clinical knee OA, mostly women. The physical activity measurement was also very different. The previous study used a categorical scoring system and the current study used an accelerometer. An important factor to note is that, in the current study, many participants reported walking, cycling and swimming as exercise in the given activity logs; not many were engaged in more intense sporting activities. Thus the scaling of intensity in physical activity may be different between the two studies resulting in different findings.

Many studies in the past suggest that moderate intensity exercises are beneficial to pain and physical function (Ettinger *et al.*, 1997; Martin *et al.*, 2001; K. S. Thomas *et al.*, 2002) however, in those studies, intensity was not measured objectively. Roos and

Dalberg's randomized control trial found participants with a partial medial meniscus reconstruction had an improvement in cartilage glycosaminoglycan (GAG) content, measured using the delayed gadolinium-enhanced MRI (dGEMRIC), after engaging in "moderate intensity" exercises for 4 months (Roos & Dahlberg, 2005). The "moderate intensity" exercises were chosen by one physical therapist who then trained 5 other therapists to lead the exercise group. The exercise program consisted of a warm up (e.g. cycling, rope skipping, jogging on trampoline), strengthening exercises (e.g. squats, lunges) and neuromuscular exercises (e.g. single leg stance on step). The changes of dGEMRIC T1 (Gd) were 15 ± 54 msec in intervention group, whereas the control was -15 ± 32 msec (p=0.036). Results from this study showed that the exercise intervention improved the GAG content of knee cartilage. Differences between this study and the current study lie in several places. First the cartilage health in the current study was measured from MRI which only quantifies features of cartilage such as cartilage thickness and volume. In comparison, Roos and Dalberg investigated the GAG content, which was the measure of the quality in the cartilage. Second, the participant demographics were different. None of the participants in the current study had a history of surgery or injury whereas the randomized control trial had participants who went through partial medial meniscus reconstruction. Age was also different in the two studies. Participants in the Roos and Dalberg study were younger, with a mean age of 45.8 ± 3.3 years old, where the current study participants' mean age was 60.6 ± 6.5 years. The intervention study sample was 66.7% men; whereas current study was 83% women. Most importantly, the

intervention study's definition of moderate intensity was a subjective perception on the intensity and not measured like the current study with a standard tool, it.

The original hypothesis of the current study was based on the literature which stated being extremely active (McAlindon *et al.*, 1999; Michaëlsson *et al.*, 2011) or having a very sedentary lifestyle (akin to immobilization) would have negative effects on knee cartilage (Vanwanseele *et al.*, 2010; Vanwanseele, Eckstein, Stüssi, & Spaepen, 2002). None of the studies of the relationship between physical activity and knee cartilage morphology had connected the trends together to look at this inverted U relationship. Instead, the data from the current study demonstrated a weak linear relationship between the two variables. This result may be due to the fact that there were not enough participants to perform this analysis. The current study only had 34 participants due to limited recruitment in this study. Another reason may because the participants in the current study scored between 6,000 steps to 12,000 steps per day on average. What was missing from the spectrum of activity levels were participants who were very sedentary (fewer than 5,000 steps a day) or those who are extremely active scoring over 15,000 steps a day. Thus these participants may only be representing the medium quantities of physical activity and therefore only the middle half of the hypothesized curve.

Another reason why the study did not show the quadratic relationship could be the fact that the cartilage quality in knee OA participant can be poor, yet the quantity of the cartilage may be observed to be large (Chen *et al.*, 2005). Edema of cartilage may explain this discrepancy. Edema can be caused by the lack of proteoglycan GAG content, which leads to higher permeability to water within the cartilage (Pearle *et al.*, 2005). By

using the MRI in the current study, only the quantitative MT.VC and MT.ThCtAB could be assessed (Cohen *et al.,* 1999). This limitation meant the study can only comment on the quantity of the cartilage in the knee and not the quality inside the cartilage. Other items that could be used to define knee OA from radiographs include joint space narrowing and osteophytes, detection of bone spurs, and knee alignment (Moskowitz *et al.,* 2007). Magnetic resonance imaging broadens the tissues that can be evaluated to include subchondral bone marrow, synovium, ligaments and other joint tissues.

5.2 Test-retest Reliability of step counts data over five days

Accelerometry data collected over the 5 days were very reliable from the current sample of participants. The current study participants stepped an average of 9,074 steps per day (range 1,288.0-21,936 steps per day). While study participants differ from each other, each participant demonstrated relatively consistent step counts over the 5 days yielding a high intraclass correlation coefficient. The accelerometer device (ActiGraph GT3X+) used in the current study was a fairly new model by this company. Reliability of this model in human participants with knee OA has not been reported. Previous studies looked at the reliability of older models by ActiGraph and showed that these older models such as the GT1M and 7164 were comparably reliable with other accelerometers (such as Actical and RT3) (Bassett & John, 2010). A reliability study done by Robbins and colleagues used the GT1M model on 30 healthy adults also demonstrated high reliability by the accelerometer. The intraclass correlation coefficient was 0.85 with a 95% confidence interval from 0.71 to 0.92 (Robbins, Birmingham, Jones, Callaghan, & Maly, 2009). Nichols *et al.,* evaluated the TriTrac-R3D accelerometer in young adults (n=20)

during walking and running tasks on a treadmill at two occasions. The accelerometer had a reliability coefficient ranging from 0.87 to 0.92 (Nichols, Morgan, Sarkin, Sallis, & Calfas, 1999). One previous study which looked at the reliability of the output by the same accelerometer on canines found it to be highly reliable over 3 days, and even higher reliability over 7 days (Yam *et al.*, 2011). The result from the current study added to the literature about the step counts measured by accelerometers from participants with knee OA over five days to be reliable.

Additionally, the participants in the current study demonstrated average step counts that were similar to the recommended amount of physical activity, which is 10,000 steps per day for a healthy adults (Krucoff, 1999; Lindberg, 2000) or the recommendation for older adult 6,000-8,500 steps/day and 3,500-5,500 steps for older adults with chronic illness (Tudor-Locke & Myers, 2001). This comparison suggests that most of the participants in the current study were moderately active. A recent study done by Tudor-Locke and colleagues suggested that an average of 8,000 steps per day translates to about 30 minutes of MVPA (Tudor-Locke, Leonardi, Johnson, Katzmarzyk, & Church, 2011). This finding agrees with the current study result where, on average, study participants had 36.7 minutes of MVPA a day.

5.3 Relations between independent and dependent variables

5.3.1 Medial Tibial Cartilage Volume and Thickness

Medial tibial cartilage thickness is a mean value calculated by dividing the total medial tibial cartilage volume by the surface area of the underlying subchondral bone.

The results from analyses of MT.ThCtAB did not add more information to previous literature. The poor utility of MT.ThCtAB may be attributed to a smaller range in this variable, compared to MT.VC, where the coefficient of variation for MT.ThCtAB was about 9% and MT.VC was at 24% from the current study. In another words, the variation and ability to distinguish between thicknesses is lower than volume. Further, the measure of MT.ThCtAB as reported in the current study "washed out" the potential to find variations in different subregions within the joint by averaging (Reichenbach *et al.*, 2010).

5.3.2 Relationship between covariates

In the literature, age and sex were strongly correlated with cartilage volume and thickness (Beattie *et al.*, 2008; Meachim, 1969). In the current study, age was negatively correlated with MT.VC and MT.ThCtAB, which means with an increase of age, there was a decrease in cartilage volume and thickness. With aging, the number of proteoglycans decreases which leads to a reduction in cartilage quantity (Bonassar *et al.*, 1995; Magnussen *et al.*, 2005; Meachim, 1969). A cross-sectional study of 372 participants (214 women, 158 men) aged 26 to 61 years examined the relationship of age on knee cartilage morphology. In this large sample, there was a negative relationship $\beta = -0.014$ with a 95% CI of (-0.025, -0.004) $p < 0.05$ between MT.ThCtAB and age (Ding *et al.*, 2005). Another cross sectional study with 45 men found age to be negatively associated $\beta = -0.01$ with a 95% CI of (-0.02,-0.003) $p = 0.004$ with MT.VC (Cicuttini *et al.*, 2003). The negative beta value in both cases means that with age there will be a loss of MT.VC and MT.ThCtAB however the effect is not overly strong but statistically significant.

Men had higher MT.VC and MT.ThCtAB than women in the current study. This result corresponds to previous literature. For example, a cross sectional study looked at 119 healthy participants (73 women, 47 men) between 20-69 years of age. Beattie and colleagues found that, in healthy participants, men had greater MT.VC and MT.ThCtAB through the different age groups in comparison to women. On average women's cartilage volume was at 1l.50 ±0.19 μL/mm^2, thickness at 1.45 ± 0.19 mm whereas for men, cartilage volume and thickness average was at 1.77 ± 0.24 μL/mm^2 and 1.71 ± 0.24 mm respectively (Beattie *et al.,* 2008). A similar result was concluded in children where boys had higher cartilage volume and thickness in comparison to girls. This was a cross-sectional study examining the difference in cartilage volume and thickness in all the sites within the knee in 92 children (49 boys, 43 girls) from 9 to 18 years old. Boys had significantly more knee cartilage volume and thickness at all sites (Jones *et al.,* 2000).

Body mass index was negatively correlated with MT.ThCtAB and positively correlated with MT.VC in the current sample. This opposing relationship may be explained by the subchondral bone size. Previous work has shown that MT.VC was slightly higher in those with higher BMI (Ding *et al.,* 2005). This previous study investigated 372 conveniently sampled participants (from offspring of participants who had a knee replacement) also found that the higher the BMI, the greater medial tibial total bone surface area. The larger bone surface area results in a smaller thickness value since it is calculated by dividing the cartilage volume by the joint surface area. In this current study, BMI demonstrated a slight negative correlation with MT.ThCtAB, however it was not significant enough to be included as a factor in the linear regression analysis.

5.4 Study limitations

The recruitment of participants for this study was done in a rheumatology clinic that specializes in osteoporosis and an orthopedic clinic. This potentially can be an issue where some of participants may also be osteoporotic since this condition was not set as an exclusion criterion. An animal model suggested that there was a relationship between osteoporosis (OP) and OA (Calvo *et al.,* 2007). A previous study found that OA patients actually have a lower subchondral bone density in comparison to healthy controls (Verstraeten *et al.,* 2001). Also it has been published that bone cyst is a common symptom of both knee OA and OP although the link between the diseases is unclear. Therefore with the possibility of co-existing OP, the relationship between physical activity and cartilage health may be slightly different. Also due to this recruitment site, the majority of study participants were women. Moreover the timeline of the recruitment would also be a potential limitation. The recruitment started in winter 2010 and the last participant included in this study finished the data collection in spring 2012. There was a 1.5 year difference in the beginning and end of the data collection. Thus, there might be some seasonal influence on the participants' physical activity level. Also physical activity level was measured at one point in their life; perhaps the accumulated physical activities in the past may have an effect on cartilage health.

The small sample size at 34 participants was another limitation for the current study. The sample size determination for this study was based upon the rule of 10 participants per item of interest (Linarcre, 1999). This study had 3 variables of interest including independent variables in physical activity measure which are the step counts,

times spent in light intensity activity and time spent in moderate/vigorous activity thus a number of 30 were used as a guide. However, by including the covariates into the analysis, 30 participants may not have been enough. Thus, one of the limitations was the limited power for the regression analysis with the number of covariates involved in the analysis. If more participants were included, potential covariates can be added to the analysis in order to obtain a higher strength in the analysis. These covariates may include knee alignment angle (Cicuttini, Wluka, Hankin, & Wang, 2004) since it was found negative relationship between knee angle and cartilage volume loss. Height is also an important factor which influences the cartilage volume since taller people may have higher surface area of the bone for cartilage. Therefore chances of having higher cartilage volume for tall people are greater (Wluka *et al.*, 2002). Previous occupational related physical activities are also a very important factor. Since previous activity was not captured and was still accumulated over the year prior to the study period. This potential long term effect of the accumulated physical activity may be important in affecting the knee cartilage volume. Which bring another limitation of the study would be the effect of physical activity on medial tibial cartilage was only at one time point during the progression of knee OA. The MT.VC and its relationship with physical activity may change along the development of the disease.

Medial tibial cartilage volume and MT.ThCtAB were used as the measure of cartilage health in this study. There are other ways in measuring cartilage health such as the dGEMRIC method, which examines GAG content within cartilage. This method would be more invasive. Participants require an injection of dye agent first into the vein

follow by a saline flush for the contrast of GAG content (Van Ginckel *et al.*, 2010). Risks for performing the dGEMRIC scan would be a potential allergic reaction to the dye agent. It would be essential for a physician to be present.

The measurement of physical activity was based on accelerometry. However, the accelerometer cannot be worn during water activities such as swimming or water aerobics, which some of the participants did perform. On top of the aquatic activities, the accelerometer may not be able to capture the time during cycling, stationary biking, yoga and Pilates (Colbert & Schoeller, 2011). Although a log was used for participants to record other activities, there are some suggested conversions from swimming or cycling time into step counts. From the current sample about 47% of the participants were involved in some swimming, biking, yoga or Pilates. However these conversions needed the amount of time and intensity and those values would also be a subjective recording without the accelerometer.

The amount of vigorous activity from current participant group was quite low. The average time spent a day was at 0.7 ± 1.0 minutes a day. Farr and colleagues used this cut point previously and found a similar number of 0.95 minutes a day (Farr *et al.*, 2008). Compared to the current study, Farr and colleagues' sample was very similar, with 255 participants (76% women) with early knee OA (Kellgren/Lawrence grade II or lower) and a mean age of 54.6 ± 7.1 years. There might be a potential limitation where the cut off points for the accelerometer were inappropriate for both the current study and Farr *et al.*'s study. Perhaps the cut points set out for knee OA participants were too high for the participants to reach as moderate levels. Based on the results, the intervals between light

and moderate intensity may be too wide. Smaller increment for the cut off points for the intensities may be easier to capture the difference in intensity. To address this limitation a study must be first performed to find the more suitable cut points for this set of participant.

The outliers removed for data analysis would be another limitation. Removing the data from two participants reduces the power of the analysis. These two participants were removed due to the high residual and leverage values. If participants that demonstrated extremes of sedentary and vigorous activity were recruited in to this study, it may not have been necessary to have these two participants removed.

5.5 Future Directions

The current study showed the relationship between physical activity and MT.VC at one single time point. It would be valuable to determine potential long-term effects of physical activity in the future as the cohort study continues. Also as the cohort study continues, a bigger sample size would be stronger in power to demonstrate the relationships between variables. Moreover, expanding the participant recruitment to include extreme high and low physical activity levels would be ideal to further test the original hypothesis for the current study.

5.6 Conclusion

Physical activity is important and beneficial to MT.VC in participants with clinical knee OA. The main study results showed a slight linear relationship between physical activity and MT.VC. Participants with larger quantity of low intensity physical

activities have higher MT.VC than those that do not exercise at that amount and intensity. Age as a non-modifiable risk factor was also important in predicting the amount of MT.VC that remains in participant's knee. In order to maintain the highest quantity of MT.VC remaining, participants with knee OA should be encouraged to perform more low intensity exercises.

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Appendix A: Participant Consent Form

McMaster University

Letter of Information and Consent

Clinical Outcomes and Tissue Changes in Knee Osteoarthritis: A Novel Approach Using Cumulative Knee Load

Principal Investigator: Dr. Monica Maly
Assistant Professor, Rehabilitation Sciences
McMaster University
(905) 525-9140 ext. 27823
mmaly@mcmaster.ca

Co-Investigators: Dr. Kristina Calder, Post-Doctoral Fellow
Dr. Rick Adachi, Rheumatologist
Dr. Karen Beattie, Assistant Professor
Dr. Paul Stratford, Professor
McMaster University

Dr. Stacey Acker, Assistant Professor
University of Waterloo

Dr. Jack Callaghan, Associate Professor
University of Waterloo

Study Sponsor: Canadian Institutes of Health Research (CIHR)

Introduction

You are being asked to take part in a 3 year study that investigates the effect of exposure of daily activity on your pain, mobility and knee joint health.

Before agreeing to participate, it is important that you read and understand the proposed study procedures. The information provided describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at

any time. To decide whether you wish to participate, you should understand enough about its risks and benefits to be able to make an informed decision. This is part of the informed consent process. Make sure all of your questions have been answered to your satisfaction before signing this document.

Background and Purpose

Knee osteoarthritis causes chronic pain, limits mobility and reduces quality of life for thousands of Canadians. The magnitude and repetition of mechanical loads placed on the knee during daily activities are very important to understanding why knee osteoarthritis worsens over time. Unfortunately, studying the loads in a laboratory setting does not provide a complete understanding of the pain and mobility limitations people with this condition experience. **The purpose of this study is to determine whether the loads you place on your knees during your daily activities can predict the health of your knee over 3 years.**

To participate in this study, you will need to be between the ages of 40 and 70 years, with diagnosed knee osteoarthritis. We cannot include anyone who has metal anywhere in their body. We cannot include anyone who has medical restrictions to physical activity, may be pregnant, or has a history of other forms of arthritis, injury or surgery in their legs. We expect that 80 people will participate.

Procedure

If you meet the above criteria, we welcome you to enroll. We will ask if we can contact you via telephone, mail or email over the course of 3 years to answer any questions that may arise, and book appointments for these visits. We will ask if we can retain contact information for a friend or family member in case we cannot contact you.

First, we will ask that you visit 25 Charlton Ave. E., Hamilton at the Centre for Appendicular Magnetic Resonance Imaging Studies (CAMRIS). This centre is next door to Dr. J.D. Adachi's office. We ask that you visit this office 2 times: once at the beginning of the study and again after 3 years. Each of these visits will take no longer than 1 hour. Your parking and transportation costs will be covered. You will be asked to complete the following:

- A brief interview of your general health to ensure you do not have metal anywhere in your body.
- A scan of your most painful knee joint in our magnetic resonance imaging (MRI) scanner to assess the cartilage and bone inside your knee. This scan will take no longer 10 minutes.

- An X-ray of your most painful knee joint in standing, to assess the osteoarthritis and alignment of your knee. This X-ray will take no longer than 10 minutes.

Second, we will ask you to visit the Human Movement Laboratory, located at the 1400 Main Street entrance to McMaster University, every 3 months, for 3 years. Each of these visits will take approximately 2.5 hours. Your parking and transportation costs will be covered. At these visits, we will ask you to complete the following:

- An interview to describe your general health. We will measure your body weight and height.
- Brief questionnaires about your general health, pain, physical abilities, emotional health and confidence completing physical tasks.
- Walk for 6 minutes in an indoor corridor. You may set the pace and stop at any time.
- Measure your strength/power of your leg muscles.
- Walk up a set of stairs and back down. You may set the pace and stop at any time.
- Walk along a 10 meter indoor walkway, 10 times. For this walk, reflective markers will be placed on the skin of your legs using tape.
- Bend and straighten your leg at your maximal effort approximately 10 times. We will seat you in a machine that measures the strength of your knee muscles for this test.
- Wear a device like a pedometer that measures the number of steps you take in a day at your waist for the following 7 days. This device is smaller than a pager and will not record your activities, other than your steps. You may call or email us if you have questions about the device. You may send the device back to us, in a pre-paid envelope or drop the device off at McMaster.

Risks and Benefits

There is a minimal risk associated with participation in this study. As long as you have no metal in your body, this is no risk associated with the MRI. You will receive no radiation from this test. The X-ray of your knee will involve very short-term exposure to low-level radiation and therefore involves some risk, but the long-term effects are minimal provided you have not previously been exposed to large amounts of radiation.

You may experience some muscle soreness around your knee, typical of the discomfort felt with physical activity. Any muscle soreness should settle after 24-

48 hours. There is a risk to that, in extreme cases, you may experience a skin allergy to medical tape used to keep the markers in place. If you experience any serious discomfort following a study visit, please contact the Principal Investigator, **Dr. Monica Maly at (905) 525-9140 ext 27823**.

There are minimal benefits to you. You will learn about the health of your knee, pain and physical activity over 3 years. Your participation will help us better understand how loads placed on your knee during daily activity affects knee joint health.

Confidentiality

All information obtained during the study will be held in strict confidence. You will be identified in the study by a code only. No names or identifying information will be used in any publication or presentation. No information identifying you will be available outside the investigators. The information we collect will be secured in a locked filing cabinet in room 435 in the Institute of Applied Heath Sciences at McMaster University to which only the researchers will have direct access. This research space is also locked. Following completion of the study, the information we collect will be destroyed. Representatives of the McMaster University Health Sciences Research Board may require access to your study-related records or may follow up with you to monitor the conduct of the research.

Participation

Your participation in this study is voluntary. If you decide to participate, you can decide to stop at any time, even after signing the consent form or part-way through the study. If you drop out of the study your data will only be used with your explicit consent. You can withdraw from the study at any time, for any reason without any negative consequences. If you do not want to answer some of the questions, you do not have to, but you can still be in the study.

Questions

If you have any general questions, please call the principal investigator in charge of this study, Dr. Monica Maly at (905) 525-9140 ext. 27823. If you have any questions about your rights as a research participant or the conduct of the study, you may contact the Office of the Chair of the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board at (905) 521-2100 ext 42013. This person is not involved with the research project in any way and calling him will not affect your participation in this study. This letter is yours to keep for future reference.

Clinical Outcomes and Tissue Changes in Knee Osteoarthritis: A Novel Approach Using Cumulative Knee Load

Consent

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I will receive a *signed* copy of this form.

Participant Name (please print)	Participant Signature	Date

I confirm that I have explained the nature and purpose of this study to the participant named above. I have answered all questions.

Person Obtaining Consent	Signature	Date

Principal Investigator	Signature	Date

Appendix-B: Participant screening and information

CIHR CUMULATIVE LOAD STUDY

PARTICIPANT ID: _____ DATE: _____ (MMM/DD/YYYY)

Participant Screening and Tracking

Inclusion Criteria (American College of Rheumatology Clinical Criteria):		
Age between 45 and 70 years of age?	**Yes**	**No**
Knee pain on most days of the week?	**Yes**	**No**
Less than 30 minutes of morning stiffness?	**Yes**	**No**
Crepitus with active range of motion?	**Yes**	**No**
Bony enlargement?	**Yes**	**No**
Bony tenderness to palpation?	**Yes**	**No**
Signs of inflammation (warmth, swelling)?	**Yes**	**No**

Exclusion Criteria:

Any other forms of arthritis (rheumatoid, psoriatic)?	**Yes**	**No**
Knee surgery? Excluded: high tibial osteotomy, joint replacement, ligament repair Included: unrepaired lax ligament, arthroscopic debridement (or "clean up"), hyaluronic acid injections including "synvisc"	**Yes**	**No**
Do you use a cane or other helping aid to get around? Excluded: unable to ambulate 20' without an aid	**Yes**	**No**
Do you have an unstable heart condition? Excluded: physician-advised restrictions to physical activity	**Yes**	**No**
Have you injured your hip, knee, or ankle in the past three months? If so, which leg?: _____	**Yes**	**No**
Are you currently receiving cancer treatment?	**Yes**	**No**
Are you/could you be pregnant?	**Yes**	**No**

Notes:

Which knee will be studied (circle)? LEFT RIGHT

CIHR CUMULATIVE LOAD STUDY

PARTICIPANT ID: _____ DATE: _____ (MMM/DD/YYYY)

Identification:

Last Name		First Name	
Sex		Birthdate	(MM/DD/YYYY)
Phone Numbers	Home		
	Office		
	Mobile		
Email		Alternate Email	

Home Address:

Mailing Address (if different from Home Address)

***Please put an asterisk beside preferred mode of communication.**

CIHR CUMULATIVE LOAD STUDY

PARTICIPANT ID: _____ DATE: _____ (MMM/DD/YYYY)

Emergency Contact:

This person will be contacted in the unlikely event of an emergency

Name		
Relationship to You		
Phone Numbers	Home	
	Office	
	Mobile	
Email		

Alternate Contact:

This person will be contacted if we are unable to reach you by phone at your residence for two weeks.

Name		
Relationship to You		
Phone Numbers	Home	
	Office	
	Mobile	
Email		

Appendix-C: Request for MRI form

REQUEST FOR ORTHONE MRI SCAN & X-RAY FOR RESEARCH

Study Title: "Clinical Outcomes and Tissue Changes in Knee OA: A Novel Approach Using Cumulative Load"

MRI system ownership:
CAMRIS
610-25 Charlton Ave. E.
Hamilton, ON L8N 1Y2

Principal Investigators:
Dr. Monica Maly
Stacey Acker
Dr. Rick Adachi
Dr. Karen Beattie
Dr. Paul Stratford
Dr. Jack Callaghan

Date: _____/_____/_____ (d/m/y)

Study ID: _____

Year of birth: _____ Month of birth:_____

Weight: _____ (kg) Height: _____ (m)

** the year and month of birth are necessary for software operation

Is there any possibility that you may be pregnant? YES ☐ NO ☐
Have you ever worked with metal (hobby/occupation)? YES ☐ NO ☐

Please check if you <u>have</u> any of the following:

Pacemaker, defibrillator, pace wires	Yes ☐	No ☐
Prosthetic heart valve	Yes ☐	No ☐
Electrodes, shunts, plates, aneurysm clips	Yes ☐	No ☐
Vascular access port or cathe er	Yes ☐	No ☐
Intravascular coils, filters or stents	Yes ☐	No ☐
Insulin pump or infusion pump	Yes ☐	No ☐
Cochlear, stapes or orbit/ear implants	Yes ☐	No ☐
Bone growth/fusion stimulator	Yes ☐	No ☐
Implanted neur stimulator	Yes ☐	No ☐
Metal or wire mesh implants	Yes ☐	No ☐
Artificial limb or joint	Yes ☐	No ☐
Metal rods, pins or plates in a joint or bone	Yes ☐	No ☐
Bullets or shrapnel in your body	Yes ☐	No ☐
Metal fragme ts in your eye(s)	Yes ☐	No ☐
Tattoos, tattooed makeup, body piercing	Yes ☐	No ☐
Any other implanted device	Yes ☐	No ☐

Please check if you <u>have ever had</u> any of the following:

Brain, ear, eye or head surgery	Yes ☐	No ☐
Vascular (vein) surgery	Yes ☐	No ☐
Bone or joint surgery	Yes ☐	No ☐

Before your MRI, please REMOVE shoes and ALL metal objects, including:

-hearing aid	-barrettes/hair pins	-safety pins/clips	-jewelry/keys
-credit cards	-pocket knife	-coins/change	-pens/pencils
-watch	-cellular phone/pager	-clothing/undergarments containing metal	

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Appendix-D: Device Instructions

CIHR CUMULATIVE LOAD STUDY

PARTICIPANT ID: _____ DATE: _____ (MMM/DD/YYYY)

VISIT:

Year 1	Visit 01a ☐	Visit 01b ☐	Visit 01c ☐	Visit 01d ☐	
Year 2	Visit 02a ☐	Visit 02b ☐	Visit 02c ☐	Visit 02d ☐	
Year 3	Visit 03a ☐	Visit 03b ☐	Visit 03c ☐	Visit 03d ☐	Visit 04a ☐

Device Instructions

The device measures the amount of activity you undertake each day. When you receive the device, the green light will be flashing. On the first day you wear the device, the green light should stop flashing. If the green light turns on or starts flashing again after the first day you wear the device, record it in the activity log. If a red light turns on, **please contact Kristina Calder at (905) 525-9140, ext. 20748 or email** kcalder@mcmaster.ca

Wear the device for 1 week. Begin wearing the device on _____ when you wake up. The last day to wear the device is _____ until you go to bed.

Place the device on the front of your _____ hip at your waist using the belt.

- Wear during waking hours.
- Remove when sleeping.
- Do not get the device wet. Do not wear in the shower or when swimming.
- Please be careful not to drop the device.
- You may wear the device over or under your pants.

If you have any questions, please contact Kristina Calder at (905) 525-9140, ext. 20748 or email kcalder@mcmaster.ca.

Please bring the device with you to your next McMaster visit.

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CIHR CUMULATIVE LOAD STUDY

PARTICIPANT ID: _____ DATES: _____ (MMM/DD/YYYY)

VISIT:

Year 1	Visit 01a ☐	Visit 01b ☐	Visit 01c ☐	Visit 01d ☐	
Year 2	Visit 02a ☐	Visit 02b ☐	Visit 02c ☐	Visit 02d ☐	
Year 3	Visit 03a ☐	Visit 03b ☐	Visit 03c ☐	Visit 03d ☐	Visit 04a ☐

Activity Log Book

Over the next 7-consecutive days please report any physical activity that you would consider significant, such as attending an exercise class, going for a walk, doing heavy outdoor work, recreational activities, and any seasonal activities. Indicate the approximate time you started and ended the activity and **indicate the intensity of the activity as easy (E), moderate (M), or hard (H)**. Please indicate the time you put the monitor on and took the monitor off each day.

Report any irregularities to your typical physical activity pattern. For example, you may not have felt well one day and decided to rest rather than work outside or attend exercise class. Also report if you had any difficulties with the devices (e.g. the belt clip would not stay on, the light was flashing, etc.) **Please accurately record any time spent riding in a vehicle.**

If you have any questions please contact Kristina Calder at (905) 525-9140 extension 20748.

Example:

	Sunday
Time On	735am
Time Off	1030pm
Problems	Device worked well.
Activity AM	Did the dishes(E) 9-920am Walked the dog (M) 930-1000am Gardened (M) 1015-1115 Drove to Toronto (E) 1130am-1245pm

Date							
	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Time On							
Time Off							
Problems							
Activity AM							
Activity PM							
Activity After 6pm							