The Effect of Running on the Onset and Development of Osteoarthritis

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Abstract

Osteoarthritis is a prominent and debilitating form of joint disease characterized by pain and deterioration of the articular cartilage and other tissues in the affected joint. Research has identified a variety of risk factors for osteoarthritis, including age, obesity, gender, previous injury, and occupation. The relationship between running and osteoarthritis is a topic of particular interest because of the prevalence of running as a simple and physiologically beneficial form of exercise. Increasing evidence suggests that recreational running has at worst no effect and at best a protective effect on joint and articular cartilage health in contrast to high-intensity professional/elite-level running and sedentary behaviors which are characterized by a relatively higher risk of osteoarthritis.

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Introduction

The purpose of this thesis is to examine the consensus among literature about the relationship between running and risk of knee and hip osteoarthritis (OA) development. Although OA can affect a variety of joints, this thesis will focus exclusively on knee and hip OA because running primarily affects lower extremity joints. A discussion of ankle OA will not be included because the prevalence of knee and hip OA is significantly higher than ankle OA, and few studies have been published detailing the risk factors for ankle OA specifically (Murray et al., 2018). This thesis will begin with an overview of OA as a disease, examining what research has revealed about its pathophysiology, epidemiology, burden, and known risk factors. Understanding these aspects of OA will better inform an investigation of the effect of running on the risk of OA development and progression. Following this overview of OA will be a discussion of various aspects of running as a physical activity. Research has confirmed for decades that moderate to vigorous intensity exercise, including running, generally yields many beneficial physiological changes in the body that improve health outcomes (Piercy et al., 2018). Understanding how running affects the body, and especially the joints, will also better inform an investigation of the effect of running on the risk of OA development. The final section of this thesis will include an analysis of current literature that directly addresses the question of how running affects an individual's risk of developing or worsening knee and/or hip OA.

Osteoarthritis

Osteoarthritis (OA) is a chronic degenerative joint disease and one of the most prevalent joint diseases in the world (Mobasheri & Batt, 2016; Palazzo et al., 2016). OA predominantly

affects synovial and/or articular joints, most commonly the spine and peripheral joints such as the hips, knees, hands, and feet (Cope et al., 2019). OA is characterized by the damage and loss of the affected joint's articular cartilage – the strong but flexible lubricating tissue found between the articulating bone surfaces of joints. OA is most prevalent in older populations (Mobasheri & Batt, 2016; Vina & Kwoh, 2018). Aside from age, studies have shown that obesity and metabolic disease, previous injury, and highly physical occupations (ex: farming, construction, etc.) are prominent risk factors for OA (Mobasheri & Batt, 2016). In addition to pain and loss of joint function, depression (Sacitharan, 2019) and decreased quality of life (Coaccioli et al., 2022) are common resultant symptoms of OA as the disease progresses. The pain and subsequent loss of pain-free joint function of OA makes activities of daily living (walking, standing, lifting groceries, climbing stairs, etc.) substantially more difficult and less pleasant. This contributes to OA being a leading cause of disability in the world (Vina & Kwoh, 2018).

Two methods are commonly used to clinically diagnose OA: joint symptoms and radiographic observations of joint abnormalities. Joint symptoms include pain, stiffness, and weakness in the muscles surrounding the joint, with pain being the most common complaint (Ashkavand et al., 2013). Objective measures of OA through radiographic imaging include narrowing of the joint space, osteophytosis (bone spurs), subchondral sclerosis (hardening of bone tissue beneath articular cartilage), cyst formation, and abnormalities in the articulating bones' shape at the joint (Arden & Nevitt, 2006). Symptomatic and radiographic methods of diagnosing OA do not always agree. Palazzo et al. (2016) found that only 40% and 60% of individuals with moderate and severe diagnosed radiographic knee OA reported experiencing

symptoms, respectively. The causes of OA are not exhaustively understood, but research has revealed much about its pathophysiology/pathogenesis, epidemiology, and risk factors.

Pathophysiology

Pathophysiology is the study of how a disease progresses and what effects it has on the body (Witthöft, 2013). To understand the pathophysiology of OA, it is helpful to know the various tissues/components that make up the osteochondral unit. The main components of a synovial joint affected by OA include the articular cartilage, synovium, subchondral bone, and surrounding muscles (Coaccioli et al., 2022). All these tissues of an arthritic joint are affected negatively during the progression of OA, making it akin to the gradual failure of the joint organ as a whole – similar to cardiac or renal failure (Arden & Nevitt, 2006). However, much of the research performed on OA has focused on understanding articular cartilage deterioration specifically (Mobasheri & Batt, 2016).

Articular Cartilage

Articular cartilage is a sturdy and smooth tissue covering the ends of a joint's articulating bones. It provides a lubricated surface on which the articulating bones can more readily slide during joint movement. Cartilage is composed of primarily water (65-80%), 20-40% extracellular matrix, and a small percentage of chondrocytes (1-5%) (Coaccioli et al., 2022). Like many other tissues of the body, cartilage is repeatedly remodeled by specialized cells (called chondrocytes) as it naturally degrades through normal wear and tear. This process, however, is remarkably slow (Mobasheri & Batt, 2016). Articular cartilage is also aneural and avascular, meaning it has no neural input or output and no direct blood flow from the cardiovascular system (Coaccioli et al., 2022). The avascularity of cartilage is primarily to blame

for its slow rebuilding process which contributes to it being one of the least resilient tissues in the body in response to injury; although it can withstand significant and repetitive forces before inducing an injury, its lack of direct blood supply prevents the body from rebuilding it quickly once damaged (Mobasheri & Batt, 2016). Instead, nutritional support from the blood comes to cartilage through the underlying vascularized subchondral bone (Coaccioli et al., 2022). In a healthy joint, this rebuilding process occurs at the same rate or faster than the degenerative effects of joint stress.

It is believed that OA develops when the rate of cartilage degradation exceeds the rate of its repair process (Cope et al., 2019). This indicates that OA occurs as the result of a lack of homeostasis in the joint's remodeling process, favoring catabolism. The exact sequence of events that lead to this, however, remains uncertain (Cope et al., 2019). A few possibilities exist with varying levels of research to support them. Multiple studies support the hypothesis that pro-inflammatory cytokines secreted into the synovial joint cause cartilage degeneration resulting in structural bone damage and synovitis (Cope et al., 2019). However, other studies have found evidence that bone remodeling happens prior to cartilage degeneration (Cope et al., 2019).

The Role of Inflammation

The role of inflammation in OA is becoming an increasingly highlighted topic in research. Historically, OA has been viewed as a non-inflammatory disease caused by the biomechanical stress on the joint from various systemic and/or environmental factors (Griffin & Scanzello, 2019). Rheumatoid arthritis, by comparison, has a well-understood inflammatory factor in its development and progression (Griffin & Scanzello, 2019; Sacitharan, 2019; Woodell-May & Sommerfeld, 2020). However, recent research has revealed inflammatory

factors in the pathophysiology of OA as well (Griffin & Scanzello, 2019; Mobasheri & Batt, 2016). Chronic inflammation, in general, is known to worsen the process of tissue degradation which contributes to the progression of OA (Sacitharan, 2019). Additionally, certain pro-inflammatory cytokines are known to influence chondrocytes. The pathway of inflammation in OA begins with the release of pro-inflammatory cytokines triggering the production of matrix metalloproteinase (MMPs) that results in cartilage matrix degradation (Woodell-May & Sommerfeld, 2020). The term "cytokines" is a broad term referring to chemical messengers secreted by cells to communicate with other cells throughout the body (Sacitharan, 2019). Cytokines can have catabolic, anabolic, or inhibitory effects on the body (Sacitharan, 2019). The roles of the cytokines Interleukin 1 (IL-1) and Tumor Necrosis Factor-alpha (TNFα), for example, are well-understood to contribute to the progression of rheumatoid arthritis (Sacitharan, 2019). These same cytokines have been found to be upregulated in patients with OA, although to a lesser extent (Sacitharan, 2019). In light of this, some animal studies injected IL-1 receptor antagonists which resulted in less cartilage loss (Sacitharan, 2019).

Epidemiology of OA

Epidemiology is the study of a disease's prevalence and distribution across various populations (Rothman, 2012). Many studies on the epidemiology of OA have been conducted resulting in a well-developed understanding of the disease's impact around the world (Allen et al., 2022; Arden & Nevitt, 2006; Vina & Kwoh, 2018). OA is well-established as the most common joint disease in the world and is expected to increase in prevalence due to increasing population age and obesity (Coaccioli et al., 2022). Based on data from the World Health Organization (WHO), osteoarthritis was the 15th leading cause of disability in 1990 but increased

to the 11th leading cause of disability in 2010 (Vos et al., 2012). In developing countries, OA is more prevalent while in less developed countries OA prevalence is reduced (Vina & Kwoh, 2018). This is likely because the life expectancy in developed countries is longer and individuals are more likely to develop OA as they age (Palazzo et al., 2016). Globally, it is estimated that 9.6% of men and 18% of women, approximately 240 million individuals, 60 years or older experience symptomatic OA of some kind (Pereira et al., 2015). Global estimates of OA prevalence, however, vary depending on the joint in consideration, how OA is defined, and the breadth or specificity of the population being studied (Vina & Kwoh, 2018). To investigate the effects of running on osteoarthritis, examining the prevalence of lower extremity osteoarthritis specifically is more relevant.

Knee OA is the most commonly studied form of OA but reports of its prevalence vary (Vina & Kwoh, 2018). Knee and hip OA defined by radiographic imaging is estimated to be at 3.8% and 0.85%, respectively (Palazzo et al., 2016). In the United States, 14 million people have symptomatic knee OA, half of whom are above 65 years old (Vina & Kwoh, 2018). Other reports generated percentages of knee OA prevalence of 7%, 17%, and 14.6% in adults over the age of 45 (Allen et al., 2022). Regarding hip OA, several studies report prevalence estimates of 5.1% in Spain (adults 40 years or older), 19.6% (adults 50 or older), and 10% (adults 45 or older) (Allen et al., 2022). Knee and hip OA prevalence are higher in more developed regions such as North America (5,924 per 100,000), North Africa, the Middle East (4,610 per 100,000), and Australasia (4,595 per 100,000) but lower in regions such as Western Sub-Saharan Africa (2,678 per 100,000), Central Sub-Saharan Africa (2,633 per 100,000), and Eastern Sub-Saharan Africa (2,568 per 100,00) (Leifer et al., 2022). Additionally, the United States has the highest incidence

of knee and hip OA of any country at 6,128 per 100,000, over 30 million individuals (Leifer et al., 2022).

Economic Burden of OA

The economic burden of OA is high and likely to worsen as the prevalence of OA risk factors such as age and obesity increases (Coaccioli et al., 2022). Understanding of the role of various activities such as running in either contributing to or protecting against osteoarthritis offers economic benefits. The cost of OA is influenced by expensive treatment modalities currently used to alleviate symptoms of the disease. Primary treatments for OA include total joint replacement, non-steroid injections, and corticosteroid injections (Leifer et al., 2022). Direct costs of OA in more developed countries are substantially higher than in less economically developed countries because of the increased prevalence of the disease and longer average life expectancy (Palazzo et al., 2016). For example, in countries such as the US, the UK, Canada, and Australia, the direct costs of OA ranged within 1-2.5% of the country's gross national product (GDP) (Leifer et al., 2022). In the US, direct costs for OA amounted to just over $72 billion (Leifer et al., 2022). A major contributor is high-priced total joint replacements which are more accessible in economically developed countries (Leifer et al., 2022).

Risk Factors

Understanding risk factors for OA is an important step in helping avoid the onset of the disease. Various OA risk factors have been identified and can be separated into two categories: person-level risk factors and joint-level risk factors.

Person-Level Risk Factors

Person-level risk factors are factors that have to do with the behaviors and characteristics of the individual. These include factors such as age, sex, race/ethnicity, genetics, obesity, and nutrition. Each of these risk factors is explored below.

Age and Sex. Age and sex are two of the most well-established person-level risk factors, with OA risk increasing with age and female gender (Allen et al., 2022; Vina & Kwoh, 2018). Additionally, gender differences in OA prevalence become more pronounced as age increases (Allen et al., 2022), especially around menopause (Vina & Kwoh, 2018). Although the apparent relationship between increased risk of post-menopausal OA has led some researchers to hypothesize a protective role of estrogen, research has not confirmed this to be the case (Gessel & Harrast, 2019). Another possibility is that female sex may indirectly increase OA risk due to the higher occurrences of knee injuries, particularly ACL tears, in females (Voskanian, 2013).

Race/Ethnicity and Genetics. Race/ethnicity is also a known risk factor for OA, as various studies have revealed correlations between specific ethnic groups and OA prevalence. Multiple studies indicate black Americans have a higher prevalence and severity of lower extremity OA compared to white Americans (Allen et al., 2022). Additionally, several studies report that Chinese women are 45% more susceptible to hip OA compared to white women (Allen et al., 2022). However, this difference in susceptibility is unique to females; Chinese men and white men are equally susceptible (Allen et al., 2022). Additionally, research has revealed that genetics account for approximately 60% of hip and hand OA and 10-40% of knee OA (Palazzo et al., 2016; Sacitharan, 2019).

Obesity. Obesity has become a topic of heightened interest in OA research, and a strong direct relationship between excessive weight and OA prevalence has been well documented,

especially in knee OA (Allen et al., 2022; Vina & Kwoh, 2018). Studies have shown that individuals with obesity are at a three-fold increased risk for developing knee OA (Leifer et al., 2022). While the mechanism by which obesity contributes to OA was initially thought to be purely mechanical (heightened bodyweight increases loading and stress on weight-bearing joints), recent evidence points to other factors as well (Francisco et al., 2018). Obesity is known to cause chronic low-level inflammation in the body, which may contribute to the inflammatory component of OA's pathophysiology (Francisco et al., 2018). This is further supported by studies showing an increased prevalence of OA in non-weight-bearing joints, such as the hand, in obese individuals (Francisco et al., 2018). In light of these findings, obesity is thought to contribute to OA in two ways: by increasing the mechanical load on the joint (likely exceeding the joint's remodeling abilities) and by increasing chronic low-level inflammation throughout the body (Francisco et al., 2018). It is unclear which mechanism contributes more to the disease or if both mechanisms contribute equally.

Nutrition. In light of evidence indicating an inflammatory role in OA (Griffin & Scanzello, 2019), it has been hypothesized that inflammatory diets contribute to OA development and onset (Veronese et al., 2019). More research is merited, but recent studies consistently confirm this hypothesis. One study (Veronese et al., 2019), using data from subjects ($n = 4358$) from the Osteoarthritis Initiative, found a significant direct correlation between Dietary Inflammatory Index (DII) scores (a measure of the inflammatory potential of one's diet) and knee OA prevalence. After accounting for eleven potentially confounding variables, Veronese et al. (2019) found a 40% increased likelihood (OR 1.40; 95% CI 1.14–1.72; $p = 0.002$) of radiographic symptomatic knee OA in subjects with the highest DII scores. The relationship

between these variables was linear; each standard deviation increase in DII score was associated with an approximately 13% increase in knee OA prevalence (Veronese et al., 2019). Studies have also found that lower inflammatory diets (such as a Mediterranean diet) can be a positive risk factor for OA. An earlier study by Veronese et al. (2017) used the same data from the Osteoarthritis Initiative and found that adherence to a Mediterranean diet lowered the prevalence of knee OA by up to 17%.

Although not described in detail in the 2019 study by Veronese et al., other studies have identified various diets and specific food items associated with higher levels of inflammatory biomarkers. For example, diets high in sugars (Della Corte et al., 2018), sugar-sweetened beverages (Lin et al., 2020; Norde et al., 2021), and red/processed meats (Norde et al., 2021) have especially high inflammatory potential. Norde et al. (2021) investigated the association between various dietary patterns and chronic low-grade inflammation and found a moderate direct relationship between a "western" dietary pattern – characterized by high intakes of refined grains, red and processed meat, pizza, fast food, potatoes, sweets, sugar, and high-energy beverages (sodas, alcohol, energy drinks, etc.) – and inflammation. These findings were contrasted by a moderate inverse relationship between healthier diets – characterized by higher intakes of fruits, vegetables, and cereals and lower intakes of foods typical of a western diet – and inflammation (Norde et al., 2021). This may add further insight as to why the incidence of knee and hip OA is higher in the United States than any other country (Leifer et al., 2022). Considering that a poor diet also increases the likelihood of obesity, nutritional counseling is an important option for health providers to consider prescribing when offering preventative treatment for OA. Additional studies investigating the role of nutrition in OA risk reveal possible

evidence that diets low in vitamins D, C, and K increase OA risk (Allen et al., 2022; Vina & Kwoh, 2018). However, more evidence is needed to confirm the role of these specific vitamins (Allen et al., 2022; Vina & Kwoh, 2018).

Joint-Level Risk Factors

Joint-level risk factors have to do with the forces present around and within the joint itself. Examples include joint injury, shape, malalignment, and loading.

Prior Injury. Perhaps the most well-established joint-level risk factor is previous injury, particularly injury to the knee (Allen et al., 2022; Palazzo et al., 2016; Sacitharan, 2019). Knee injuries such as meniscus tears or damage to the anterior cruciate ligament (ACL) are well-correlated to a higher risk of knee OA and an earlier onset of the disease (Palazzo et al., 2016). An individual's risk for developing knee OA is 4-6 times higher following an ACL and/or meniscus injury compared to individuals with no comparable knee injuries (Allen et al., 2022). These findings are in agreement with earlier studies that found the risk of grade III or IV radiologic changes according to the Kellgren-Lawrence grading system (an objective rating of knee OA progression based on radiographic imaging) to be 4.71 times higher following ACL injury compared to the uninjured limb (Ajuied et al., 2014). Additionally, evidence suggests that individuals with prior ACL injuries are at an increased risk for an earlier onset of OA (10-20 years following the injury) compared to the uninjured knee (Palazzo et al., 2016; Sacitharan, 2019).

Bone/Joint Shape. Bone and/or joint shape also play a role in an individual's risk for developing OA. Abnormalities in hip bone/joint shape have been found in association with hip OA (Allen et al., 2022; Vina & Kwoh, 2018). Specifically, cam morphology (an abnormal shape

in the femoral head at the hip joint) and protrusion acetabuli (an overcovering of the acetabulum around the femoral head) are hip bone/joint shape abnormalities that increase the risk for hip OA.

Malalignment, Loading, and Sports. Other joint-level risk factors include joint alignment and loading. Occupations involving repetitive loading of the knee joint such as farming or construction show increased risk for knee OA (Coaccioli et al., 2022). The same is true of high-impact sports (Coaccioli et al., 2022). One recent systematic review (Migliorini et al., 2022) condensed data from 32 studies (n = 20,288) to investigate the prevalence of OA across a variety of sports. Specifically, soccer, handball, ice-hockey, football, rugby, track & field, dance/ballet, and triathlon athletes were included. The researchers found a higher probability of premature lower extremity OA in soccer, handball, ice-hockey, and rugby athletes while no significant increase in OA was detected for runners and dancers (Migliorini et al., 2022). The mechanism by which high-intensity sport participation increases the risk of OA is unclear in the literature, but some possible explanations exist (Driban et al., 2017). Similar to the heightened risk of OA in highly physical occupations, OA risk may be increased because of the repetitive high-impact loading on the joints in certain sports such as soccer or rugby (Driban et al., 2017; Migliorini et al., 2022). An athlete's risk of OA may also be indirectly influenced by participation in high-impact sports because of an increased risk of injury (Driban et al., 2017). These two joint-level risk factors – occupations and sports involving repetitive high-intensity loading – are of primary interest in investigating the relationship between running and OA. Running may induce similar excessive mechanical stress on the joint and therefore cause OA by overworking the cartilage remodeling process (Gessel & Harrast, 2019).

Running

Although the health benefits of regular exercise are well established in the literature (Piercy et al., 2018), there has been a diminishing trend of participation in appropriate amounts of regular physical activity (Swinburn et al., 2013). This has resulted in a growing epidemic of physical inactivity, contributing significantly to the global burden of non-communicable diseases such as obesity, diabetes, and numerous cancers (Swinburn et al., 2013). The estimated financial burden of health complications caused by physical inactivity is upwards of $117 billion in the United States alone (Piercy et al., 2018). Data from the World Health Organization in 2009 suggested that 6% of all premature mortality was related to physical inactivity, which was ranked as the 4th leading global risk factor for death (as cited in Lee et al., 2017). Additionally, a 2012 article suggested that 9% of all-cause mortality is caused by physical inactivity (as cited in Lee et al., 2017). In light of the growing epidemic of physical inactivity, running is an ideal form of physical activity for populations without contraindications because of its simplicity; participation in regular running for exercise requires minimal equipment and little to no prior training exposure. Even regular jogging has been shown to induce numerous health benefits (Lee et al., 2017).

As a form of exercise, running yields many of the beneficial physiological adaptions in the body necessary to improve general health outcomes and prevent non-communicable diseases. Endurance running improves body mass, body fat, resting heart rate, maximal oxygen uptake, triglycerides, and high-density lipoprotein cholesterol measures in previously inactive adults (Hespanhol Junior et al., 2015). Additionally, a longer history of running is associated with stronger positive effects on the same health measures (Hespanhol Junior et al., 2015). Because of these positive physiological adaptations, running is well-documented as preventative of

cardiovascular disease (CVD) and various cancers (Lee et al., 2017). There is also a growing body of evidence demonstrating positive mental health outcomes resulting from running as a form of physical activity (Oswald et al., 2020). Of interest for this investigation are the running-induced physiological adaptations to the body's musculoskeletal system, cardiovascular system, and articular cartilage.

Effects of Running on Musculoskeletal Health

The relationship between running and musculoskeletal health is generally positive. There is a substantial body of evidence indicating that high-intensity and high-impact sports (lacrosse, basketball, gymnastics, etc.) improve bone mineral density (BMD) (Gessel & Harrast, 2019). Running, although not as high-impact as jumping and ball sports, is also generally associated with improvements in BMD (Gessel & Harrast, 2019; McCormack et al., 2019). However, there is a direct dose-dependent relationship between running intensity and improved BMD but an indirect dose-dependent relationship between running mileage and BMD (Gessel & Harrast, 2019). Long-distance runners typically do not see as much improvement in BMD compared to sprinters and/or shorter-distance runners. Wolff's Law, which theorizes that bone tissues will adapt to increased repetitive loading stimulus by increasing BMD, is a widely accepted explanation for this relationship (Teichtahl et al., 2015). Although it is an explanation of physiological adaptations to bone tissue specifically, Wolff's Law offers insight into how the human body typically responds to increased stimulus. In the case of BMD, increased joint loading and stimulus cause a physiological response in the body that results in improved bone health if given proper nutrition and rest. Perhaps increased loading of joints during running could also trigger a physiological response in the body to improve articular cartilage health if the

degenerative stress of the stimulus does not exceed the rate at which chondrocytes can remodel joint cartilage.

Comparing the Effects of Running on Cardiovascular and Cartilage Health

Studies investigating the physiological effects of high-intensity exercise on the cardiovascular system, including ultra-endurance running, have revealed a reverse-J curve relationship (Sharma et al., 2015). A reverse-J curve relationship describes a primarily direct relationship between two variables (as one increases, so does the other) but an indirect relationship between the same variables at near maximal values of the dependent variable. This reverse-J curve is potentially insightful in understanding how joint cartilage responds to moderate strain compared to excessive strain. In the overwhelming majority of scenarios, running – like any form of consistent physical activity – improves cardiovascular health significantly and reduces the risk of CVD (Lavie et al., 2015; Lee et al., 2014). Habitual running results in physiological changes to the heart neurologically/electrically and structurally, resulting in a lower resting heartrate (Gessel & Harrast, 2019) and increased ventricular and stroke volume (Sharma et al., 2015). These factors indicate that active individuals have healthier and more efficient hearts. However, the reverse J-curve with regard to the dose-relationship between running and cardiovascular health benefits shows that more running is not always beneficial for the cardiovascular system (Sharma et al., 2015). Excessive running has been shown to increase the risk of atrial fibrillation (Sharma et al., 2015). Sharma et al. (2015) report that the mechanism by which this association is true is not clear, but some evidence suggests that excessive aerobic exercise adversely affects atrial remodeling. This reverse J-curve is comparable to the detrimental health effects of overtraining – too much of an otherwise healthy activity can become

harmful. Therefore, it is possible that there could be a similar reverse J-curve characterizing the relationship between articular cartilage health and running volume.

Effects of Running on Articular Cartilage Health

Understanding the effects of running on articular cartilage health is especially important in a discussion of running and OA. Directly studying the cartilage of live human populations engaged in running programs is difficult. Some studies have used animals to investigate the same question. For example, Ni et al. (2013) investigated the extent to which running intensity affected knee articular cartilage in male Wistar rats (n=24). Rats were subdivided into groups of sedentary, low-intensity running (15.2 m/min at no incline for 1 hour, 5d/w), medium-intensity running (19.3 m/min at a 5° incline for 1 hour, 5d/w), and high-intensity running (26.8 m/min at a 10° incline for 1 hour, 5d/w) (Ni et al., 2013). After an 8-week treadmill running program, rats that engaged in light to moderate levels of running throughout their lifetime had significantly healthier articular cartilage compared to sedentary rats (Ni et al., 2013). Conversely, rats in the sedentary and high-intensity groups saw a decrease in cartilage thickness, number of chondrocytes, and glycosaminoglycans indicating cartilage degradation (Ni et al., 2013).

Recently, Khan et al. (2022) examined the effect of running on cartilage in human subjects. Data from 43 studies was used measuring lower extremity cartilage quality at different times following an endurance run – immediately after, within the same day, within the same week, over one month later, and after repeated exposure (Khan et al., 2022). Results from studies examining cartilage immediately following a single running bout showed strong evidence of reductions in cartilage volume and thickness within the knee joint (Khan et al., 2022). These findings were in agreement with another study (Coburn et al., 2023) that found decreases in

cartilage morphology and composition immediately (within 20 minutes) following a single running bout. However, as the time between the running bout and the measurement of the runner's articular cartilage increases, cartilage volume and thickness measurements return to normal (Khan et al., 2022). This brief change in volume and thickness reflects the typical transfer of fluids in the cartilage responding to load. When cartilage induces a significant load (as in each step while running), water is forced out of the cellular matrix resulting and lower cartilage volume and thickness (Khan et al., 2022). However, because of the porous nature of articular cartilage, this change is only temporary; when joint-loading forces are removed water naturally reenters the intrachondral matrix and restores cartilage volume and thickness (Khan et al., 2022). This process is relatively quick and can restore cartilage water content within 24 hours (Khan et al., 2022). Furthermore, in all four timeframes there was no evidence that running induced or worsened the progression of existing bone lesions (Khan et al., 2022). This finding is noteworthy in light of recent research on the pathophysiology of OA suggesting that subchondral bone lesions precede articular cartilage degeneration (Coaccioli et al., 2022). Although many additional studies investigating the effects of running on articular cartilage health have been published, more relevant to the current discussion of running and OA are published studies that deal directly with running and the incidence of developing OA in the lower extremities.

Running and Osteoarthritis

The ideal study design for examining the relationship between running and OA risk compared to sedentary behaviors is remarkably difficult to produce. An ideal study would be prospective, randomized, and double-blind involving a large sample of individuals while controlling for important confounding variables known to influence OA risk (sex, age, BMI,

occupation, prior injury, etc.) (Alentorn-Geli et al., 2017). Because OA develops and progresses over the course of several years, any prospective study would present a significant time commitment for both the subjects and researcher(s). Additionally, the ethics of requiring a group of individuals to remain sedentary to maintain a control group is questionable in light of the significant health complications associated with sedentary behaviors (Lee et al., 2017; Swinburn et al., 2013). To date, no study meets all these criteria. However, many studies have investigated the role of running in OA using retrospective designs or relatively smaller sample sizes. Several systematic reviews have been published to condense the findings of many of these smaller studies.

Studies attempting to directly examine the relationship between running and OA are mildly conflicting, but a growing body of evidence suggests that running in moderation is protective of joint health compared to sedentary individuals but becomes an OA risk factor in excess. Perhaps one of the most extensive recent investigation of the effects of running on the risk of OA development was a 2017 study by Alentorn-Geli et al. Alentorn-Geli et al.'s (2017) review condensed data from 25 studies (18 case-control studies and 7 prospective cohort studies) to include a total of 125,810 individuals. Based on running volume data, individuals were organized into one of three categories: sedentary, recreational runner, or competitive runner (Alentorn-Geli et al., 2017). Among individuals in each category, data on OA prevalence was used to determine how the activities of each category affected the risk of OA development (Alentorn-Geli et al., 2017). Results showed a 3.66% (95% CI: 3.54%, 3.79%) prevalence of hip and/or knee OA in runners overall (both the recreational and competitive runner categories) compared to a 10.23% (95% CI: 11.62%, 15.20%) prevalence of hip and/or knee OA in control

individuals (Alentorn-Geli et al., 2017). The prevalence of OA in competitive runners was 13.3% (95% CI: 11.62%, 15.20%) compared to 3.5% (95% CI: 3.38%, 3.63%) in recreational runners (Alentorn-Geli et al., 2017). Results from this study provide evidence that moderate levels of running is protective against lower extremity OA compared to sedentary behaviors and the high-intensity training regimes of elite/competitive runners.

A few flaws in the study are worth noting. Gessel & Harrast (2019) point out that nearly all 25 studies included in Alentorn-Geli et al.'s (2017) report contained high levels of selection, performance, detection, attrition, and/or reporting bias. Despite this, Gessel & Harrast (2019) still agreed that the study offered strong evidence supporting the idea that running is generally protective of joint health compared to sedentary behaviors while being detrimental to joint health in excess. An additional concern is the lack of a clear definition of "recreational" as compared to "elite" levels of running. This is largely due to the inconsistent metrics used to quantify running volume/intensity across the various studies included. The authors report that they grouped the subjects from each study to recreational or elite categories on a case-by-case basis (Alentorn-Geli et al., 2017). While this ambiguity does not diminish the strength of the authors' basic conclusion, it leaves an important question unanswered: how much running is too much or too little?

Two older studies discussed by Alentorn-Geli et al. (2017) offer insight to this question, but the evidence they provide is outdated and far from conclusive. The first study (Konradsen et al., 1990) found no increase in hip or knee OA prevalence with a weekly running volume between 21 and 42 kilometers/week. This mileage may approximately represent the running volume of a recreational runner. The second study (Marti et al., 1989) found an increased

prevalence of hip OA in athletes running an average of 92 kilometers/week. Because the athletes in Marti et al.'s (1989) study were ex-elite athletes and 92 kilometers/week is a substantial distance, this weekly mileage may approximately represent an elite runner's running volume. These two studies are both over three decades old, use small sample sizes, and therefore do not offer conclusive data on what specific running volumes fit into the category of recreational or elite. Determining what running volume and intensity is appropriate to avoid tissue damage and produce beneficial joint adaptations may be a highly individualistic process and requires further attention in future studies. Additionally, the higher risk for injury when athletes rapidly progress running volume and/or intensity suggests that gradual progression (no more than 10% weekly mileage increases) may be a key aspect of a joint-protective running program (NSCA, 2015).

In contrast to Alentorn-Geli et al.'s (2017) study, Timmins et al. (2016) did not find sufficient evidence to make any confident conclusion regarding the role of running in knee OA. Data from 15 studies (6 retrospective cohort studies, 5 prospective cohort studies, and 4 case-control studies published from 1977 to 2010) were collected (Timmins et al., 2016). Although a qualitative analysis of included studies was inconclusive, the meta-analysis found that runners had a 50% reduced odds of undergoing surgery as a result of OA (Timmins et al., 2016). However, there were inconsistencies within the 15 included studies concerning the definition of OA and the level of running exposure in subjects (Timmins et al., 2016). In their discussion, they wrote "Only 4 studies were prospective (or ambispective) in design, and only one of these[10] was a large, well-designed, prospective study" (Timmins et al., 2016). In light of the lower quality of studies, the authors concluded there was not enough evidence to make any substantial conclusions regarding the role of running in OA. While their study does offer counterevidence

against the conclusions of Alentorn-Geli et al. (2017), the lower quality and coherency of the studies lessen the strength of its conclusions.

Further evidence suggests that running may be preventative (Lo et al., 2018) or at least neutral (Voinier & White, 2022) in the progression of symptomatic OA. Lo et al. (2018) performed an observational nested cohort study using data from the Osteoarthritis Initiative to determine if a history of self-selected running was associated with worsening knee OA pain and/or joint space narrowing. Subjects (n = 1,203 including 138 runners) were required to be ≥ 50 years old and have radiographic evidence of knee OA at the baseline of the Osteoarthritis Initiative (Lo et al., 2018). Lo et al. (2018) adjusted for baseline characteristics of age, sex, BMI, Kellgren Lawrence (KL) score (an objective rating of knee OA progression based on radiographic imaging), contralateral KL score, contralateral knee pain, and injury between the runner and non-runner control groups. The only noteworthy difference between groups was a higher prevalence of males in the runner group (69.6%) compared to the non-runner control (42.4%). Information about running duration, frequency, and competitive participation from the runner group was collected via a retrospective survey (Lo et al., 2018). The majority of runners included in the study had been running for more than six years of their life (74.6%), five or more months in the year (92.7%), and four or more times per month (88.4%). Statistical analysis of the subject's KL grades revealed that runners did not have an increased odds of worsening KL grades, medial joint space narrowing worsening, or new knee pain. Odds ratios were calculated for worsening KL grade (0.9; 0.6-1.3), new frequent knee pain (0.9; 0.6-1.6), and resolution of frequent knee pain (1.7; 1.0-2.8). These data indicate that runners were slightly more likely than not to not experience worsening OA and were more likely than not to experience a lessening of

frequent knee pain. As noted by Gessel & Harrast (2019), the strength of these results is lessened by the presence of a significant risk of recall bias due to the retrospective nature of data collection. In addition to the study by Lo et al. (2018), a literature review (Voinier & White, 2022) found consistent evidence across 32 studies (20 reviews and 12 original studies) that participation in common modes of physical activity such as walking and running did not worsen symptoms in subjects with, or at risk of, OA. These studies indicate that physical activities such as running will – at best – reduce painful symptoms of OA or – at worst – have no effect at worsening the disease's progression.

Theoretical Considerations

Running at moderate/recreational levels is not associated with an increased risk of OA development or progressions as is fairly evident in existing literature (Alentorn-Geli et al., 2017; Gessel & Harrast, 2019; Lo et al., 2018). Of further interest, however, is understanding why this is the case. Osteoarthritis risk factors such as obesity, malalignment, highly physical occupational workloads, high-intensity sport participation, and previous injury all increase mechanical stress on lower extremity joints. Although research has unveiled the presence of a non-mechanical inflammatory role in OA development (Griffin & Scanzello, 2019; Woodell-May & Sommerfeld, 2020), there is still strong evidence that OA develops and worsens as the result of mechanical stress as well (Francisco et al., 2018). This poses the question: why does running not contribute to this mechanical stress and overwhelm the cartilage remodeling processes of chondrocytes? Miller (2017) offered two possible explanations. Firstly, Miller (2017) suggested that cumulative load is more indicative of OA risk than peak load when running. Compared to walking, running produces an equivalent cumulative load on the involved

joints but a much higher peak load (eight times the load of standing) (Miller 2017). Biomechanical analysis and computer modeling has been used to examine this hypothesis further (Miller & Krupenevich, 2020). Miller & Krupenevich (2020) found that cumulative load of running compared to walking placed about twice the amount of strain on knee cartilage, leading them to reject Miller's (2017) first hypothesis. Miller's (2017) second hypothesis was that running may condition articular cartilage over time to endure the increased joint loading of running. Miller & Krupenevich (2020) also tested this hypothesis using computer modeling by predicting the timespan of cartilage failure if no adaptive increase in cartilage resilience occurred. They found a 95-98% likelihood of cartilage failure by the age of 55 when maintaining a running and walking program of 3km/day each (Miller & Krupenevich, 2020). In light of evidence that recreational running does not increase the prevalence of OA (Alentorn-Geli et al., 2017; Gessel & Harrast, 2019), Miller & Krupenevich (2020) concluded that cartilage must be capable of adapting to maintain homeostasis in response to the increased stress of running. This conclusion seems likely considering the body's innate ability to develop specific adaptations to imposed demands (also known as the 'SAID' principle) which forms the baseline of exercise physiology and exercise training. Similarly, the increased prevalence of OA in elite-level runners compared to recreational runners indicates that OA develops as a result of the healing processes of the joint being overwhelmed by excessive stress (Gessel & Harrast, 2019).

Practical Applications

In general, running is a highly beneficial and simple form of exercise proven to improve multiple aspects of physical (Hespanhol Junior et al., 2015) and even mental (Oswald et al., 2020) health. Although a growing pool of evidence suggests that running in moderation is

protective of lower extremity joints against the onset and progression of OA (Alentorn-Geli et al., 2017; Gessel & Harrast, 2019), many additional factors play into an individual's OA risk that must be considered before drawing practical conclusions. OA develops in runners when the cumulative exposure to running (accounting for intensity and volume) produces more mechanical strain on the joints than their innate healing abilities can keep up with (Gessel & Harrast, 2019). In this case, individuals with existing OA risk factors such as obesity or previous injury will have a lower threshold of running exposure their joints can tolerate compared to other runners with less or no risk factors. This means that determining the appropriate amount of running to ensure an individual reaps the protective benefits of recreational running without inducing the harmful effects of excessive running is a highly individual question. Individuals interested in participating in a regular running program must consider their unique predispositions for or against OA to determine what level of running is appropriate for them. Ideally, this should be determined with guidance from a clinician (Gessel & Harrast, 2019).

Several general guidelines can be given to help direct individuals interested in running without increasing the risk of OA. Knowing that OA risk is increased in individuals with improper gait mechanics, cross-training to strengthen supportive muscles – especially the core, hip abductors & adductors, and hip & ankle stabilizers – is recommendable for runners to encourage healthy running gait mechanics (Gessel & Harrast, 2019). Additionally, obese and elderly individuals should consider themselves at a significantly greater risk of OA than the general population and therefore begin a running program extremely gradually. Because obesity is a modifiable risk factor for OA, nutritional counseling for weight management emphasizing a low-inflammation diet (low in refined carbs and sugars, higher quantities of quality fruits,

vegetables, legumes, etc.) is important for obese individuals interested in running. Elderly individuals should schedule significant periods of rest between running bouts in addition to beginning a running program very gradually. Recommended guidelines for running progression to avoid overuse injury from the National Strength and Conditioning Association (NCSA) include no more than a 10% weekly increase in running volume (Gessel & Harrast, 2019; NSCA, 2015). Considering that previous injury is a risk factor for OA, these guidelines may be especially relevant to avoiding OA.

Conclusion

Osteoarthritis (OA) is a prevalent, debilitating, and costly degenerative joint disease (Allen et al., 2022; Coaccioli et al., 2022). Although current research offers significant insight into the disease's pathophysiology, epidemiology, and risk factors, much remains unknown about exactly how to prevent and/or treat the disease. Running, like most forms of physical activity, has been shown to induce many health benefits and offers an ideal form of exercise for an increasingly inactive culture because of its simplicity (Lee et al., 2017). However, there has been concern as to whether the repetitive joint loading of running is damaging to lower extremity joints and possibly accelerates the development and/or worsening of OA. While further research on this topic is warranted, a growing body of evidence suggests that running in moderation does not increase OA risk and may even be protective of the joints against OA development (Alentorn-Geli et al., 2017; Gessel & Harrast, 2019) and progression (Lo et al., 2018). Healthcare providers can be confident that encouraging patients to engage in appropriate amounts of recreational running will improve patient health outcomes and not increase the risk of OA development.

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