Joint Loading in Runners Does Not Initiate Knee Osteoarthritis

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Abstract and Introduction

Abstract

Runners do not have a greater prevalence of knee osteoarthritis (OA) than nonrunners. The hypothesis that joint loads in running do not cause OA is forwarded. Two mechanisms are proposed: 1) cumulative load, which is surprisingly low in running, is more important for OA risk than peak load, and 2) running conditions cartilage to withstand the mechanical stresses of running.

Introduction

The etiology of osteoarthritis (OA) involves a complex balance of anabolic and catabolic cellular metabolism mediated by local mechanical, as well as systemic inflammatory factors. However, the notion that cartilage loss is driven by the accumulation of excessive or abnormal joint loading remains a prominent component of many theories on the disease process.[2,16,17] *In vitro* mechanical testing of human articular cartilage indicates its fatigue life (number of loading cycles until fracture) decreases exponentially as the peak stress per loading cycle increases,[48] suggesting a wear-and-tear explanation for the initiation of OA. This suggestion is supported indirectly by the prevalence of knee OA in populations who ostensibly overload their joints[12,16,26] and more directly by longitudinal studies where greater joint loads during walking were associated with the initiation and/or progression of knee OA.[1,31,36] Cartilage failure from mechanical fatigue is particularly relevant given recent findings that the collagen matrix undergoes little if any turnover on reaching adulthood, suggesting OA likely results from mechanical or biochemical breakdown of joint structures rather than an imbalance in collagen turnover rates.[18] However, if repeated application of relatively high loads reduces the fatigue life of cartilage, it is paradoxical that long-distance runners do not have a high risk of developing knee OA[29] even though peak knee joint loads per stride in running are quite high, approximately three times the load in walking and 8 times the load in standing,[34,35] and even though runners may take several million strides of running per year depending on their training volume. It, therefore, seems reasonable to consider the hypothesis that joint loads in running do not initiate knee osteoarthritis and to consider potential mechanisms for this phenomenon.

After arguing that the low prevalence of knee OA in runners is not explained fully by selection bias, this article then introduces joint loading in running as it relates to cartilage mechanics and outlines two potential mechanisms for explaining how peak joint loads in running may not initiate knee OA (cumulative load, cartilage conditioning). The mechanisms are discussed in the context of the material properties of cartilage and relationships between applied superficial loads and internal stress/strain. The reader should be mindful that OA in general is a complex disease that afflicts a wide range of populations and can occur in any joint of the body, with causal mechanisms that remain poorly understood. The present article, its hypothesis, and suggested mechanisms relate to OA of a specific joint (the knee) in a specific population (distance runners) and may not generalize to OA in other joints of other populations. However, an attempt is made to place these mechanisms within the larger picture of knee OA etiology. The premise is that much can be learned about preventing knee OA in high-risk populations from further study of low-risk populations such as runners.

Mechanics, Structural Damage, and Pain in OA

The relationship between running and knee OA can depend on how the presence of the disease is established. For example, runners often have knee lesions or aberrations, but no pain.[42,44] In biomechanics and orthopedic research, it is common to describe OA by its evident severity of structural damage and/or pain. *Radiographic OA* is characterized by evidence of structural deterioration, and *symptomatic OA* is characterized by pain during activities of daily living, particularly when loading the joint. An advantage of these definitions is that they do not assume a specific causal event (*e.g.,* traumatic injury) or lifestyle (*e.g.,* wear and tear) led to the disease.

Knee OA is not typically diagnosed until the disease is already symptomatic, and it is generally unknown how or if the natural histories of radiographic and symptomatic knee OA are related. Articular cartilage itself is aneural in a healthy state and is thus not considered a direct source of knee pain, but its structural deterioration may play a secondary role in pain through the exposure of underlying bone, development of bone marrow lesions and synovitis, and the innervation of normally aneural tissues.[24] Knee OA patients in the seminal longitudinal study by Miyazaki *et al.*[37] who had greater pain at baseline also had greater risk of radiographic disease progression. Pharmaceutical pain relief increased walking speed and knee joint moments in knee OA patients,[7] suggesting increased loads on the knee and, potentially, a return to gait mechanics that may have played a

role in the development of pain. In the only longitudinal study to date on joint loading and the initiation of symptomatic knee OA, older adults who developed knee pain had greater peak knee adduction moments during activities of daily living at baseline.[1] Therefore, although the present hypothesis and mechanisms speak more directly to the risk for radiographic knee OA, they also are relevant for symptomatic knee OA. The related topics of the neurology and psychology of pain in knee OA are relevant to running but are beyond the scope of this review and the expertise of the author. Interested readers are referred to the review by Hunter *et al.*[24]

Running and OA: Selection Bias?

Most studies agree that long-distance running at recreational volumes and intensities does not increase the risk of developing knee OA.[29] *Recreational* here means an individual who is not an elite competitive runner. Elites are distinguished more by their ability and lifestyle than by any particular training parameters, but will commonly run 100 plus miles·wk^{-1} including several intensive workouts, whereas most recreational runners will run perhaps 10–20 miles·wk^{-1} and may not include any workouts. A recent meta-analysis concluded that the quality of the evidence on running and knee OA is moderate at best because of the scarcity of longitudinal data.[46] A key issue is to determine if the conclusion that running does not increase OA risk is unique to runners as a population, or if it can be extended to other populations. For example, perhaps runners who never develop OA had a very low baseline risk, and their running increased this risk up to normal levels. This argument is feasible and important. However, it is unlikely to fully explain the low risk of OA in most runners. First, although there are no prospective studies to date on running and joint health over the lifespan, in training periods of up to 6 months by individuals who have not previously run on a frequent basis, the cartilage loss incurred has been deemed clinically irrelevant: too small to rule out measurement error and/or similar to controls who did not perform the training.[20,47] Relatedly, runners and nonrunners have similar changes in cartilage thickness and collagen matrix integrity after a bout of running.[38]

Second, although transgenic animal models have suggested particular human phenotypes can affect the ability of cartilage to withstand mechanical loading,[6,28,40] there is no evidence to the knowledge of the author that the associated genes differ systematically in human runners versus nonrunners. In addition, transgenic mice who develop radiographic OA lesions from running continue to voluntarily run long distances on a daily basis, suggesting they may not have symptomatic OA,[28] similar to human runners with knee lesions.[42,44]

Third, if runners are inherently resistant to OA, we would expect similar resistance in other populations who frequently load their joints. However, individuals with physically demanding occupations such as miners, farmers, and jackhammer operators have a greater risk of OA than the general population,[15,16] and athletes in other weight-bearing sports (*e.g.,* soccer, weight lifting) have a greater risk of OA than runners even after controlling for traumatic knee injury.[12,27]

Lastly, a strong capability for endurance running is a defining feature of humans as a species.[8] Assuming the common position from evolutionary biology that modern humans evolved from a *common ancestor* more similar to modern chimpanzees, who are poor runners,[8] it is contradictory that humans would have become good runners if running was simultaneously causing joint damage that impaired the ability to run. It is possible that early humans did not live long enough to develop OA from running, but this theory is inconsistent with the modern observation that older adults are among the fastest-growing age groups at many marathons (*e.g.,*[25]). The human knee seems to be well suited to sustaining the joint loads of running because of the enlarged joint surface area compared with chimpanzees, the shape of the articulating surfaces increasing contact area (and reducing stress) as load increases, and structures such as menisci reducing the stress transmitted to cartilage by external forces.[8,22,30] The anatomy of the human knee in general (not just in runners specifically) thus seems to be well suited to safely sustaining the loads and stresses of distance running.

Therefore, although it cannot be ruled out that runners as a population have a disproportionately high fraction of individuals who would not develop OA regardless of their exercise habits, it seems reasonable to pursue the possibility that many runners may be resistant to OA because of their running, and not in spite of it.

Joint Loads in Running

Loading of the body in biomechanics is assessed using a wide range of variables. In structural mechanics, a load is specifically a force that causes stress and deformation within the loaded structure. By this definition, the reaction forces between articulating joint surfaces (*i.e.,* joint contact forces) are the most direct variables for examining *joint loading*, with the acknowledgement that joint loading can be affected or indirectly reflected by other variables such as resultant joint moments (*e.g.,*[36]).

The actual loads on the tibiofemoral cartilage during running are unknown. Two studies have reported compressive loads on the tibial plateau measured *in vivo* from older adults (aged 62–83 yr) with instrumented knee replacements, with average peaks of approximately 4 times bodyweight (BW) when jogging at relatively slow speeds of 1.4–1.7 m·s^{-1}.[4,11] Greater knee joint loads in younger subjects running at faster speeds have been estimated from gait analysis data and a variety of musculoskeletal modeling approaches (Fig. 1), although the range between studies at similar speeds is quite high (*e.g.,* 6–14 BW at ~ 3.5 m·s^{-1}). It is unknown to what extent this range reflects normal biological variance versus differences in modeling approaches.
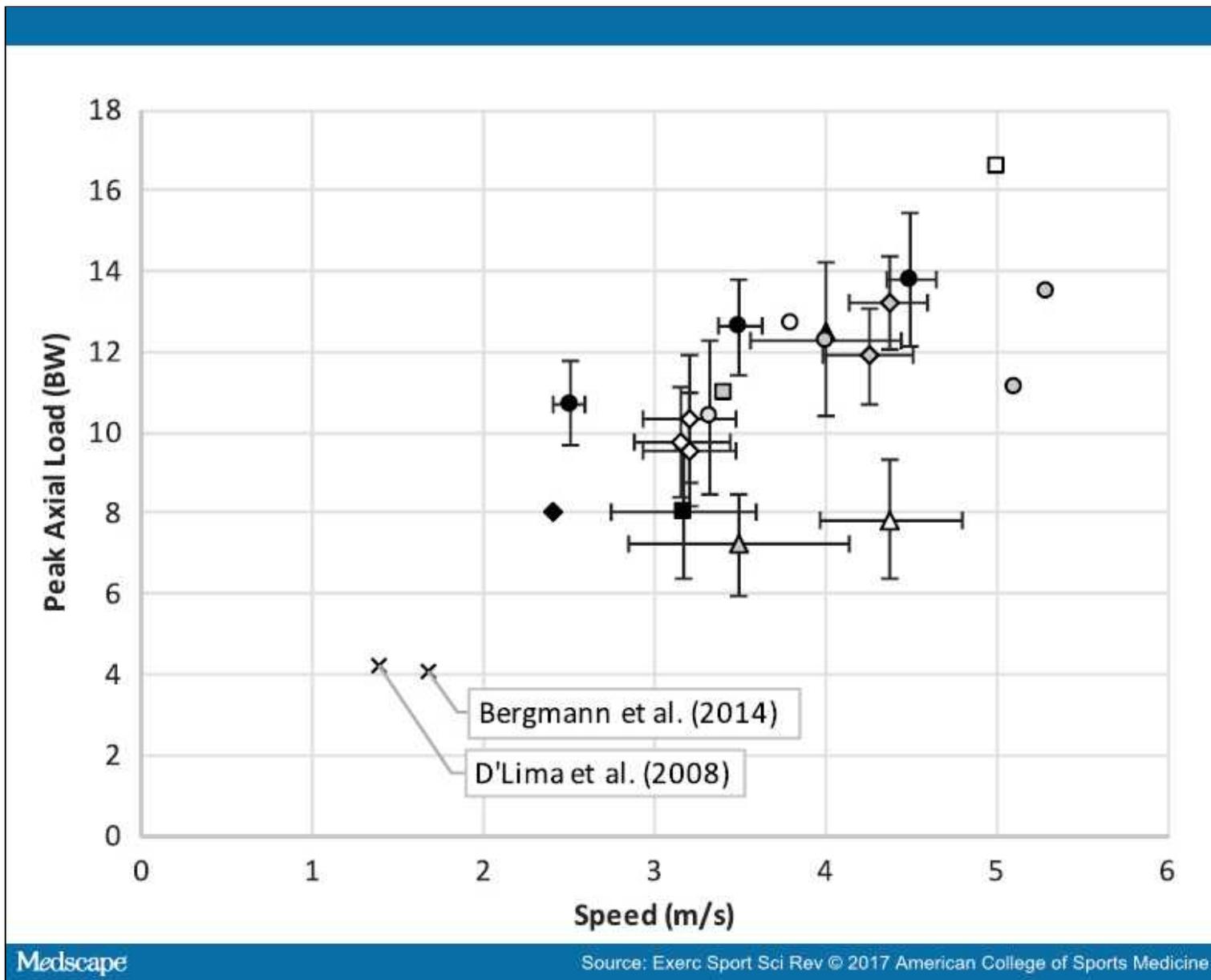
Figure 1.

Scatterplot of peak axial knee loads during running in multiples of bodyweight (BW) from 13 studies on healthy young adults using various musculoskeletal modeling methods. Different symbol/shading combinations are means from different studies. Error bars are standard deviations when available. The data points labeled "X" are in vivo instrumented knee replacement data.

Figure 1 presents data on running speed and peak compressive load, which is only one of the many features of a loading cycle that can potentially influence joint health. Relatedly, discussions of joint loading in relation to OA are incomplete without considering the mechanical properties of cartilage and its response to different types of loads. The compressive stiffness of cartilage (elastic modulus) is greater in dynamic loading than in static loading and increases with increasing loading rate.[33] The detailed mechanisms of these phenomena are outside the scope of this review, but many of them can be explained by the popular biphasic poroviscoelastic model of cartilage. The interested reader is referred to Mansour[32] for details. Thus, an increase in peak joint load (say, by increasing running speed) does not necessarily imply an increase in cartilage strain; changes in loading rate, the duration of loading, and the mechanical properties of cartilage also must be considered.

Potential Mechanism I: Cumulative Load is Low in Running

One potential explanation for the phenomenon that runners have a low risk for OA is that the peak load per stride may be less important for OA risk than the total load accumulated over many strides. This pathway for the tolerance of knee joint loads in runners is summarized in Figure 2. Whereas peak knee joint loads are much greater in running than in walking, the average load per unit distance traveled ($F/\Delta x$):

$$\bar{F}/\Delta x = \frac{\int_0^T F(t)dt}{LT} \qquad [\text{Eq. 1}]$$
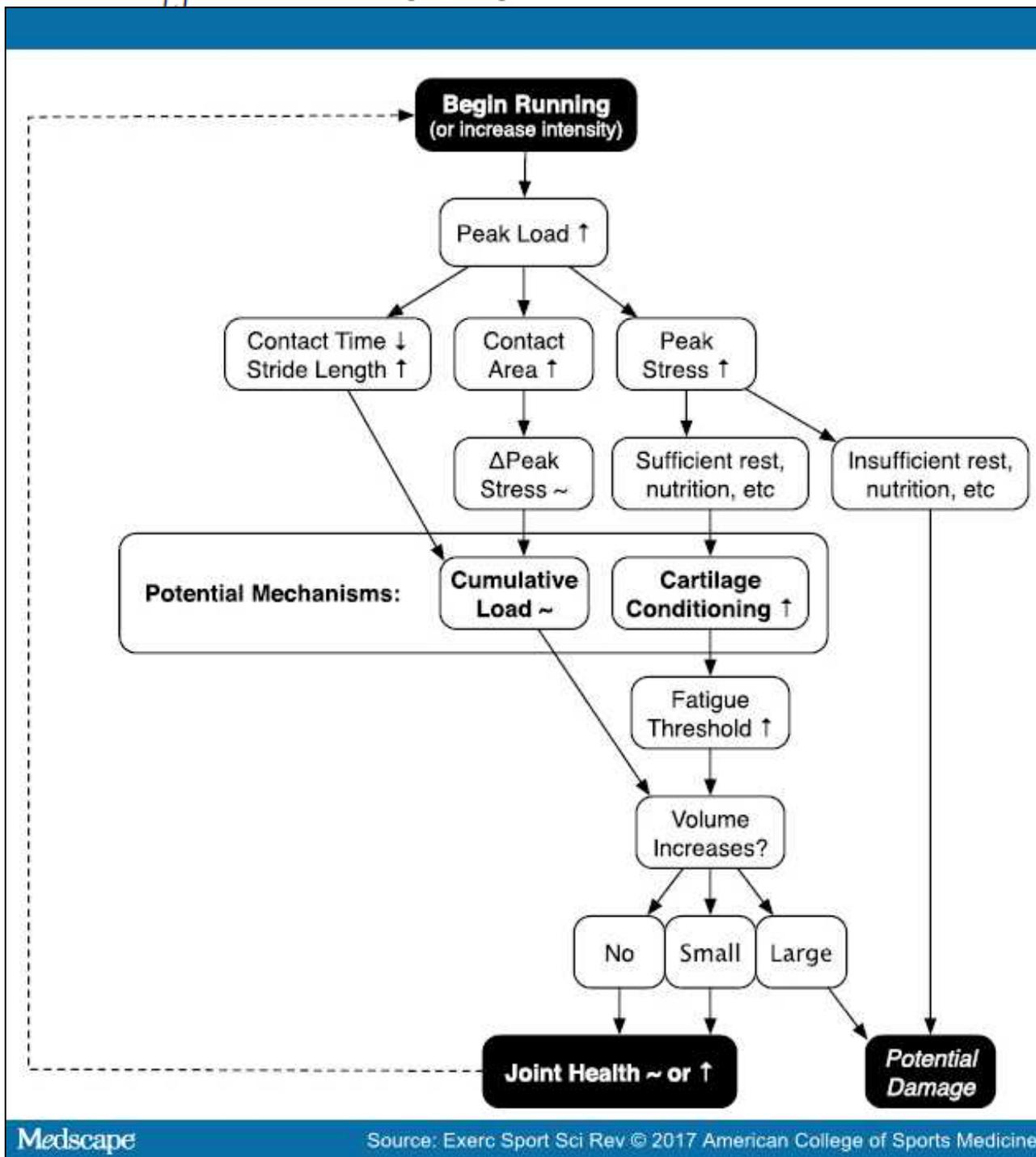
Figure 2.

Schematic of potential mechanisms for maintaining knee joint health when initiating running or increasing the intensity of training. Arrows indicate the expected direction of meaningful change of the variable in the box in response to input from the previous box; a "~" symbol indicates an expected trivial change. Initiating running or increasing the intensity of training increases the peak loads placed on their joints. These loads will not necessarily incur a high cumulative load (relative to an equivalent volume of walking or other exercise) because of the mechanics of running and the anatomy of the knee joint (cumulative load pathway). If peak load increases peak cartilage stress, cartilage adapts to withstand this new stress given sufficient rest, nutrition, and the absence of comorbidities. Both mechanisms can potentially be overridden by extreme volumes of running. The dashed arrow completes a feedback loop allowing for incremental changes in the volume and intensity of running to be well tolerated.

where *F(t)* is the time-varying joint load, *L* is stride length, and *T* is stride duration, is similar in walking and running at self-selected speeds (Fig. 3) because of shorter ground contact time and longer stride length in running.[34] The total load accumulated by all activities of daily living may be more relevant for forecasting joint health than the peak load in one particular activity, and the load accumulated by running alone may not be especially high (no higher than walking the same distance) unless extreme volumes of running are performed (Fig. 2).
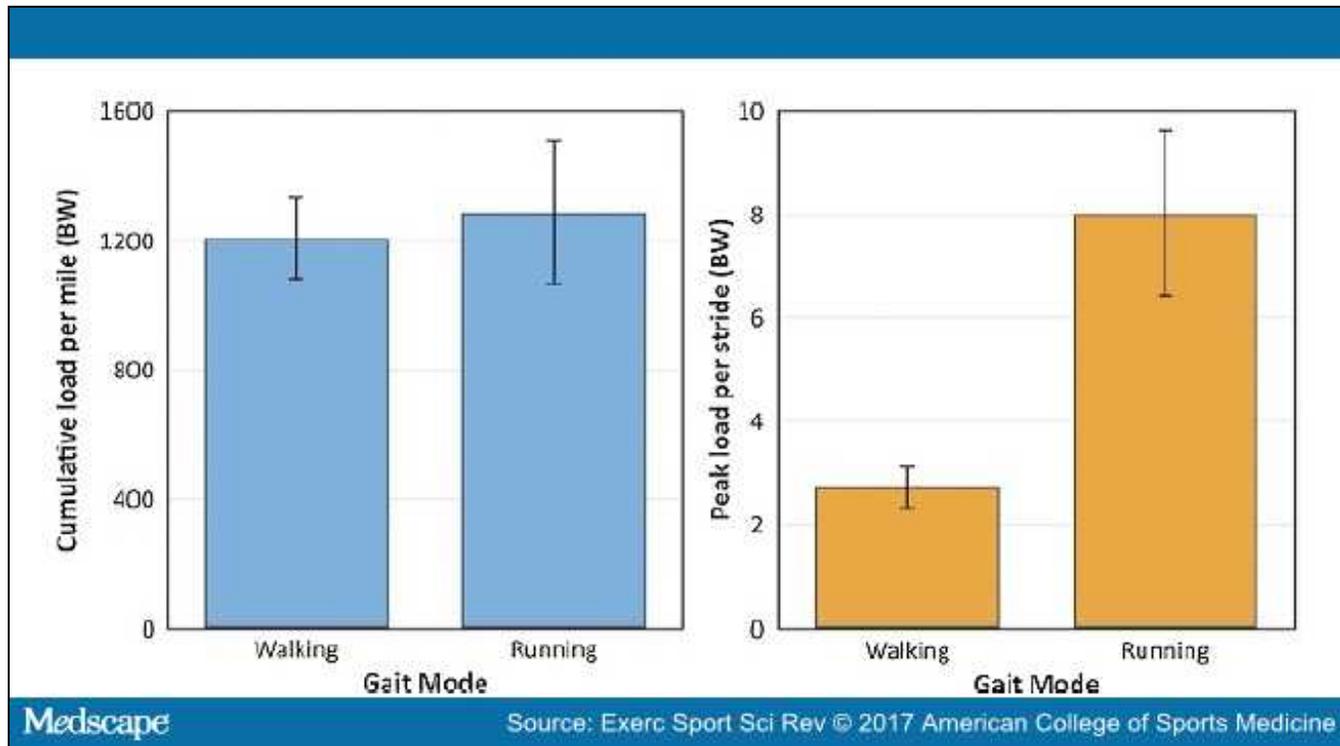

Figure 3.

Compressive knee joint loads in multiples of BW at self-selected speeds of walking (1.45 ± 0.12 m·s⁻¹) and running (3.17 ± 0.43m·s⁻¹) expressed as the load accumulated over 1 mile (left panel, *P* = 0.10) and the peak load per stride (right panel, *P* < 0.001). Loads were estimated from inverse dynamics modeling and static optimization with a sum of squared muscle stresses cost function; error bars are +/− one standard deviation around the mean for 14 healthy adults. [Adapted from (34). Copyright © 2014 Wolters Kluwer Health, Inc. Used with permission].

Most of the evidence for the fatigue life of cartilage comes from *in vitro* tests where peak stress was the independent variable.[3,48] Stress is proportional to load, so it is tempting to assume that peak load is the most relevant variable for assessing fatigue life. However, even if peak load is known accurately and is an appropriate surrogate for peak stress, estimates of the risk for fatigue are incomplete without knowledge of how many times that load is applied. A complete assessment for fatigue life in running requires load-related metrics that consider running volume and the number of loading cycles needed to complete a particular volume, which some studies have recently included (*e.g.,*[13,34,35]).

Even with knowledge of both load magnitude and loading cycles, load is an appropriate surrogate for stress only in cases where the stressed area can be assumed constant. This assumption is obviously difficult to verify for between-subjects study designs and may not be a good assumption even for within-subjects designs. The anatomy of the knee is such that greater joint loads increase the contact area of the articular surfaces[30] (Fig. 4). The stress reduction afforded by this mechanism could potentially be compromised by running mechanics that feature a high amount of knee flexion, which decreases contact area.[19] However, largely because of its biphasic composition that includes a liquid phase and a porous, viscoelastic solid phase, cartilage stiffness is lowest under static loading and increases with increasing loading rates of dynamic loading,[33] which would reduce the strain produced by greater peak loads if they are accompanied by greater loading rates as would be expected with faster running speeds. It is therefore possible that the peak cartilage stress and strain in running are not particularly high, regardless of peak load or running speed. Relatedly, an individual could accumulate more total strain by standing for 30 min than by running for 30 min, even though running accumulates more compressive loading than standing during this time.[35] The relatively high strains from static loading could play a role in relatively high risk for knee OA among physically demanding occupations that involve long periods of standing and/or kneeling, compared with the relatively low risk for knee OA in running where loading is dynamic with high loading rates. A similar hypothesis could be posed to explain why walking with excess body weight could accumulate greater cartilage strain than running at a healthy body weight, even if peak and/or cumulative loads were similar between these cases, or why athletes who heavily load their joints but do so with longer durations of static

compression than runners (*e.g.,* weight lifters) seem to have a greater risk of knee OA.[12,27] These possibilities could be investigated with cadaver models, finite element models, or a combination of musculoskeletal modeling and imaging.
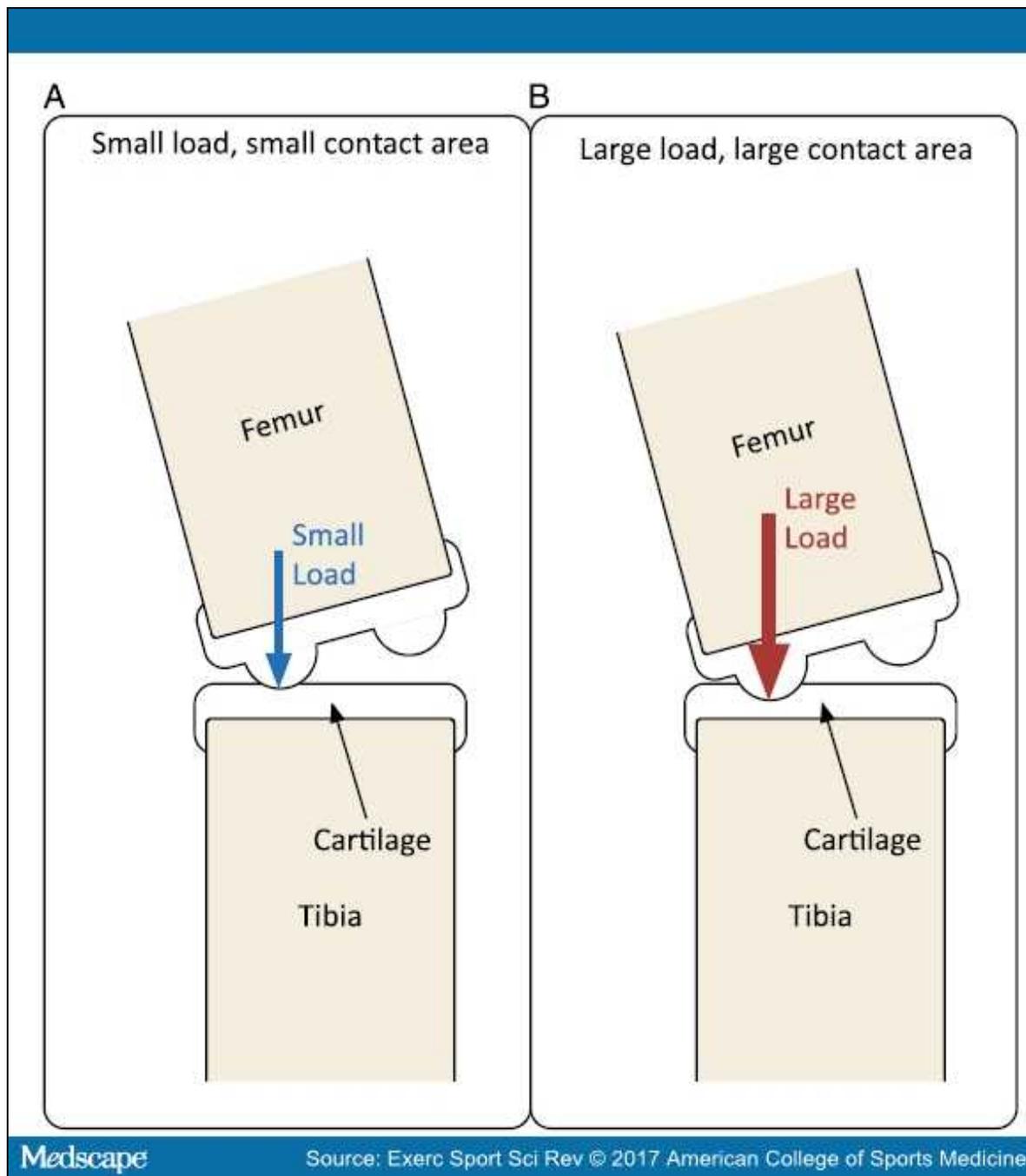

Figure 4.

Cartoon of tibiofemoral contact mechanics with relatively low (A) and relatively high (B) compressive tibiofemoral load. Contact area of the articular surfaces increases with the greater load, reducing the effect of a greater load on cartilage stress (load/area).

Potential Mechanism II: Running Conditions Cartilage

Relatively high peak loads in running have typically been considered a risk for OA and other less serious injuries.[23,34] Seedhom[43] proposed an alternative hypothesis that cartilage health *in vivo* is regulated by the greatest stress the cartilage frequently sustains during activities of daily living. A related mechanism for tolerance of joints loads in running is that living cartilage in a healthy state becomes conditioned to withstand the frequent stresses of running, given sufficient stimulus, rest, and nutrition. This pathway is summarized in Figure 2.

The role of cartilage conditioning in joint health is difficult to test directly for the same practical limitations that make it difficult to perform long-term clinical trials on running, aging, and OA. However, the notion of cartilage conditioning has some compelling indirect support:

- The ankle experiences greater localized joint stresses than the knee, and ankle OA is much less common than knee OA. [43]

- Healthy knee cartilage tends to be thicker in weight-bearing regions of the joint.[2]

- Knee cartilage glycosaminoglycan content, which affects lubrication and shock absorption, was greater in recreationally active individuals than in sedentary individuals, and greater in high-volume runners than in recreationally active individuals.[45]

- Running training reduced the response of serum cartilage oligomeric protein, a biomarker for collagen network stability and the incidence and progression of OA, to a bout of walking.[10]

- Long-term joint immobilization in individuals with leg bone fractures reduced imaging-based indices of knee cartilage quality.[21,39]

The latter three points are particularly relevant when considering the disparity in knee OA prevalence between runners (a highly active group) and obese adults (typically less active). Obese adults place greater loads on their joints during activities like walking compared with lower weight adults, but the sensitivity of their joints to these loads may be compromised by a lack of cartilage conditioning owing to infrequent loading. Relatedly, many obese adults accrue a large amount of their annual weight gain over a brief period of high calorie intake and low physical activity.[41] Cartilage may decondition during this period and will face greater loads when physical activity is resumed.

A simple phenomenological model of cumulative damage suggests cartilage conditioning can play a major role in fatigue life of the superficial collagen fibers, a tissue that has recently been suggested to have little if any capacity for biological growth and repair beyond early adulthood.[18] Data on the fatigue life of these fibers in human articular cartilage are well fit by the following equation:[48]

$$N = a_T \exp(-\sigma/b) \qquad [\text{Eq. 2}]$$

$$a_T = a_0 \exp(-a_1 T) \qquad [\text{Eq. 3}]$$

where N is the number of loading cycles that can be sustained before fracture, σ is the peak stress per cycle in MPa, T is the age of the cartilage in years, and a_0, a_1, and b are constants. The simplest model of cumulative damage for a structure sustaining multiple stress cases (*e.g.,* walking and running) is the Miner's Rule:

$$C = \sum_{i=1}^{p} \frac{n_i}{N_i} \qquad [\text{Eq. 4}]$$

where n_i is the number of loading cycles for stress case i with peak stress σ_i, N_i is the number of loading cycles of that stress that can be sustained before failure, and C is the fraction of fatigue life consumed by p different stress cases. Combining equations 2–4:

$$C = \sum_{i=1}^{p} \frac{n_i}{a_T \exp(-\sigma_i/b)} \qquad [\text{Eq.5}]$$

In this model, the onset of OA is defined as $C > 1$, indicating fracture of the superficial collagen fibers.

Equations 2 and 3 are empirical in nature and do not represent any particular mechanisms of cartilage damage, nor do their parameters represent specific properties of cartilage. However, Weightman *et al.*[48] found that the parameter b in equations 2 and 3 was necessary to fit the data well, was independent of age, and varied widely between human articular cartilage specimens from different cadavers (CV = 43%). Increasing b increases the number of loading cycles that can be sustained before failure. This parameter could be viewed as modeling the lifetime loading history of the cartilage to the extent that it was able to positively adapt. The parameter b is thus the most suitable candidate for modeling cartilage conditioning:

$$b = b_0 + b_1 \sigma_{max} \qquad [\text{Eq.6}]$$

Where σ_{max} is the greatest stress the cartilage frequently sustains. In the present demonstration of the model, the constants b_0 = 0.0951 and b_1 = 0.0979 were set so that b ranged by ± two standard deviations around the mean from Weightman *et al.*,[48] with the lowest value representing a sedentary lifestyle (σ_{max} = 0.5 MPa) and the highest value representing frequent loading of the cartilage with half the ultimate stress (σ_{max} = 12.7 MPa). The values of the other parameters, taken from Weightman *et al.*,[48] were a_0 = 2.4771•10^{15} and a_1 = 0.2093. Average gait data from inverse dynamics and static optimization (Miller *et al.*, 2014) were input to a finite element model of the knee[14] to produce estimated values of σ_{max} = 1.5 MPa for walking and 3.1 MPa for running.

Figure 5 shows the fatigue life predictions of the model for different levels of cartilage conditioning, demonstrating the ability of conditioned cartilage to sustain progressively greater stresses. The model predicts that runners are essentially immune to superficial collagen fiber failure from joint stresses in running (billions of loading cycles required for $C > 1$), that walkers may have a small risk if they perform a high volume of running with mechanics that place relatively high stresses on the knee, and that sedentary individuals have a high risk. The model also predicts the benefits of frequent walking and moderate running on protection from superficial collagen fiber failure with aging (Fig. 6) as well as the potential detriment of extreme volumes of running seen in the literature.[29] Note that the model made these predictions at ages relevant to the human lifespan and the common age range of OA diagnoses even without adjusting its parameters for this purpose.
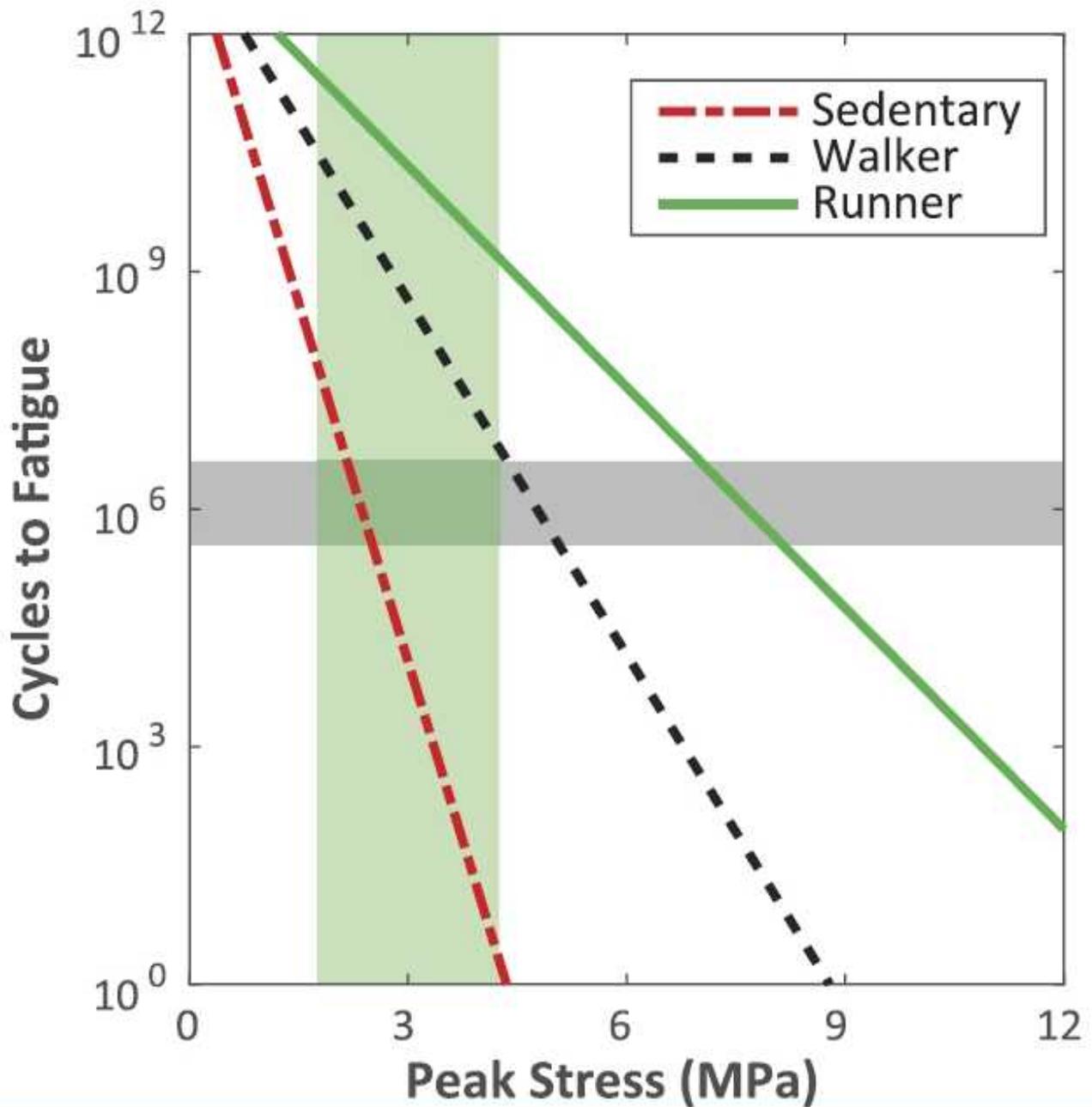
Figure 5.

Fatigue life of human knee cartilage from the cumulative damage model for the sedentary case (dash-dotted line), for cartilage conditioned to walking (dashed line), and for cartilage conditioned to running (solid line). The horizontal shaded area is the approximate range of loading cycles for a year of running 10–100 miles·wk−1. The vertical shaded area is the approximate range of peak stress per cycle in running.
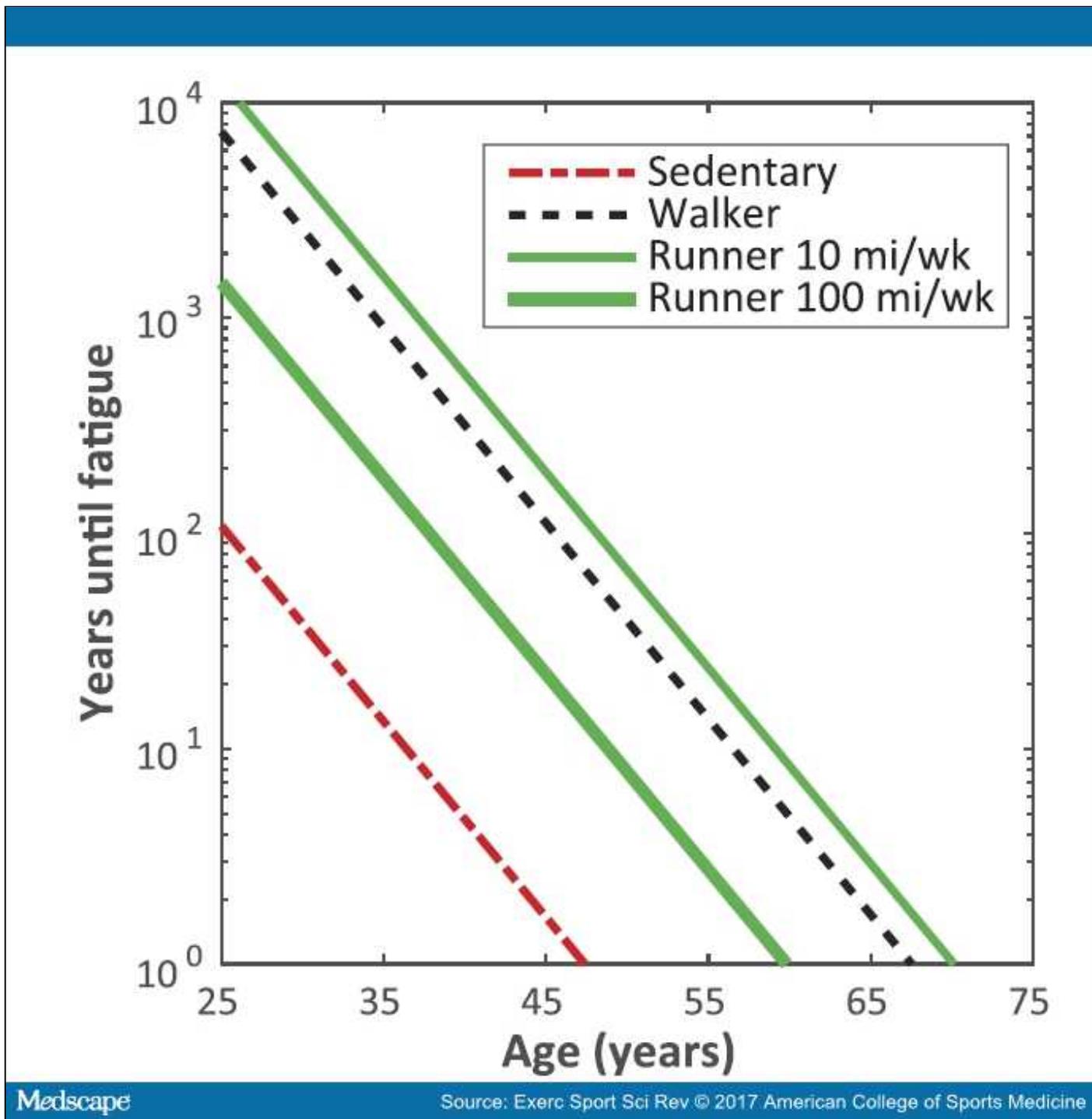
Figure 6.

Years until cartilage fatigue predicted by the cumulative damage model for an individual who begins walking 10,000 steps per day (plus any indicated running mileage) at the age indicated on the horizontal axis while possessing different levels of cartilage conditioning: sedentary (dash-dotted line), conditioned from walking (dashed line), conditioned from 10 miles·wk^{-1} of running (thinner solid line), and conditioned from 100 miles·wk^{-1} of running (thicker solid line).

Exceptions and Limitations

Some important exceptions to the two proposed mechanisms of cumulative load and cartilage conditioning should be noted before discussing their implications. The proposed hypothesis and its mechanisms relate to joint loads and the risk for OA in runners specifically as a population, and do not necessarily imply that running can be well tolerated by other populations with greater OA risk. Although studies on new runners suggest that the initiation of running training does not negatively affect joint health,[20,47] these studies are limited in duration, and their findings do not necessarily generalize to at-risk populations such as

obese adults, amputees, or traumatic injuries. For example, a recent study found that biomarkers for collagen turnover and systemic inflammation responded differently to a bout of running in subjects with and without history of traumatic knee injury and were related to physical activity level and quality of life.[9]

Relatedly, this article has focused largely on mechanical loading and specifically on compressive loading. Concerning mechanical loading, the interaction between mechanical and inflammatory factors in the OA disease process has not been emphasized, although the related topic of cartilage sensitivity to mechanical loading in particular populations (*e.g.,* sedentary obese vs active runners) has been noted. The interaction between mechanics and inflammation is likely particularly important in obesity-related OA[17] or in other special populations where the normal homeostasis of the joint as an organ may be disrupted. These implications should be considered in any application of the proposed mechanisms where the population in question may not have a normal/healthy *runner-like* response to mechanical loading. For example, it was recently shown that *lower* peak knee joint loads during walking were associated with greater risk of developing radiographic knee OA at a 5-yr follow-up in individuals who underwent anterior cruciate ligament (ACL) reconstruction.[49] Concerning compressive loading, the stresses considered here are defined as simple stresses in classical mechanics, referring to their uniaxial nature. Simple stresses are relevant because most of the data on fatigue life in cartilage are expressed in relation to simple stresses (*e.g.,*[3,48]), but stress in continuum mechanics is a tensor with up to nine components needed to fully define the state of mechanical stress within a material. Shear loads on the surface of cartilage are generally small because of its low coefficient of friction, but the state of stress within cartilage will in general be a tensor even when the external load is purely axial. This situation is further complicated by the depth-dependent orientation of collagen fibers and, relatedly, by the fact that cartilage material properties are in general anisotropic. A truly mechanistic understanding of cartilage failure in OA will require greater knowledge of how superficial loads affect the state of stress throughout cartilage, *e.g.,* at the bone-cartilage interface.

Concerning the proposed cumulative damage model (Eqs. 2–5), the Miner's Rule (Eq. 4) is the simplest model of cumulative damage, and it seemed to make reasonable predictions for this particular application (Fig. 6). However, this simple model does not account for important phenomena like the probabilistic nature of fatigue or the dependency of fatigue on the sequence of stress case applications, nor does its phenomenological nature include specific mechanisms of anabolism/catabolism at the cellular level. More detailed models will be needed to account for these aspects of structural fatigue. A long-term application of such models is the forecasting of individual risk for musculoskeletal impairments and the personalized prescription of exercise as preventive medicine (*e.g.,* what types and volumes/intensities of exercise should an individual perform for optimal joint health). The level of model complexity needed for this purpose is currently unknown.

Lastly, as noted in the Introduction, the proposed hypothesis and mechanisms relate to OA in a specific joint (the knee) in a specific population (distance runners). Knee OA is notable for the wide range of populations that seem to have a high risk of developing the disease including obese adults, older adults, individuals with traumatic joint injuries, individuals with contralateral limb loss, women, and African Americans. Suggestions for how the proposed mechanisms may relate to knee OA in populations other than runners have been made, but general extensions to arbitrary joints in arbitrary populations are speculative at this time and should be made cautiously. A single theory that elegantly explains OA in an arbitrary joint of an arbitrary population may not be possible. One possibility is that knee OA between these populations is in fact several different diseases with different causal mechanisms, but similar symptoms.

Conclusions

This article proposed two mechanisms for explaining why the high peak knee joint loads in running do not seem to increase the risk of developing knee OA in runners. The first proposed mechanism (low cumulative load in running) perhaps raises more questions than it answers because it is unknown which load-related variables in locomotion are most important for accurately forecasting the consequences of loading on joint health (*e.g.,* ground reaction force, joint moment, contact force, cartilage stress) and which features of those variables (*e.g.,* peak, impulse, average, loading rate) are most important. Assessments of cumulative load have recently been popular (*e.g.,*[13,34,35]), but this popularity should not be interpreted as evidence that cumulative load is superior to peak load or any other particular metric for assessing injury and OA risk in runners. A more cautious take-home message from these studies is that researchers should think carefully about which variables and which features of those variables are most relevant for addressing a load-related research question (*e.g.,* how would this feature be expected to affect cartilage fatigue?). Whether peak stress is more relevant than traditional variables from gait mechanics for assessing cartilage fatigue, the majority of *in vitro* cartilage studies express fatigue life in terms of peak stress or strain rather than peak load. There is little evidence on how the fatigue life of cartilage relates to peak load specifically, so any conclusions on fatigue drawn purely from peak load run a risk of being speculative unless the load can be related to cartilage stress with confidence. More work is needed to determine how traditional gait mechanics variables from traditional rigid-body musculoskeletal modeling approaches (*e.g.,* inverse dynamics, static optimization, forward dynamics, electromyogram (EMG)-driven modeling) relate to cartilage mechanics (*e.g.,*[5]), and to what extent *in vitro* fatigue life data can be generalized to cartilage fatigue *in vivo*.

The second proposed mechanism (running conditions cartilage) suggests a reorientation, if not an inversion, of the wear-and-tear hypothesis for knee OA. Specifically, this mechanism suggests that OA results not from excessive load magnitudes but rather from unusual loads. An *unusual* load here is one that produces stresses the joint is not conditioned to sustaining that now

must suddenly be sustained on a frequent basis. An example case is an individual who undergoes unilateral lower limb amputation in adulthood who now may favor their intact limb when walking with a prosthesis or may use new gaits such as one-legged hopping,[26] potentially after a long period of unloading and deconditioning owing to injury, surgery, and recovery.

Concerning the experience of new/unusual joint loads, the replacement rate of collagen, which provides cartilage with much of its strength, seems to be virtually halted in human tibial cartilage on reaching skeletal maturity.[18] This result does not imply that cartilage is inert from young adulthood onward (the replacement rate of glycosaminoglycans, which provide joint lubrication and shock absorption, remained high), but it suggests an important public health message: lack of cartilage loading early in life can limit the achievable level of cartilage quality later in life. A useful related extension of the present cumulative damage model would be the inclusion of additional stress cases for occupation or leisure. Sports participation in general does not necessarily increase knee OA risk, but a history of participation in some sports such as soccer does seem to increase this risk.[12,27] Some testable hypotheses for this phenomenon within the framework of cartilage conditioning could be that the less repetitive nature of loading in soccer does not condition cartilage as effectively as the more repetitive loads in running, or that shear loading, which may be greater in soccer versus running because of the greater frequency of abrupt lateral movement and braking/accelerating, overwhelms the fatigue life of cartilage to a greater extent than compressive loading.

Summary

In summary, this article has suggested two potential biomechanical mechanisms for the hypothesis that joint loads in running often do not initiate knee OA: 1) cumulative load and peak joint stress in running are not particularly high, and 2) joint loads in running condition cartilage to withstand these stresses without joint deterioration. These two mechanisms are not necessarily in competition, although a primary role for one (*e.g.,* joint stresses in running are low) would seem to diminish the importance of the other (*e.g.,* joint stresses in running condition cartilage). Both potentially can be rendered ineffective by extreme volumes of running (Fig. 2).

Testing either mechanism in a well-controlled fashion is a daunting prospect given the long time course over which knee OA initiates and progresses, the difficulty in defining the onset of the disease, and the large number of potential confounding factors involved. An ideal study would likely need to include large groups of relatively inexperienced runners, followed over at least 10 years as they perform various ecologically relevant training programs, with possible control groups of sedentary individuals, walkers, or individuals using other modes of exercise with similar physiological load but less mechanical load (*e.g.,* swimming, cycling). Before undertaking such a task, this review has suggested some more accessible related topics that could inform how best to design such a study: determining how various features of knee joint loading from gait mechanics relate to cartilage stress from tissue mechanics, and determining to what extent populations with a high risk for developing knee OA place unusual loads (but not necessarily high-magnitude loads) on the knee.

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