Competing With Knee OA – Challenges And Opportunities

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IRONMAN
WORLD CHAMPIONSHIP
MEDICAL SYMPOSIUM

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Miami

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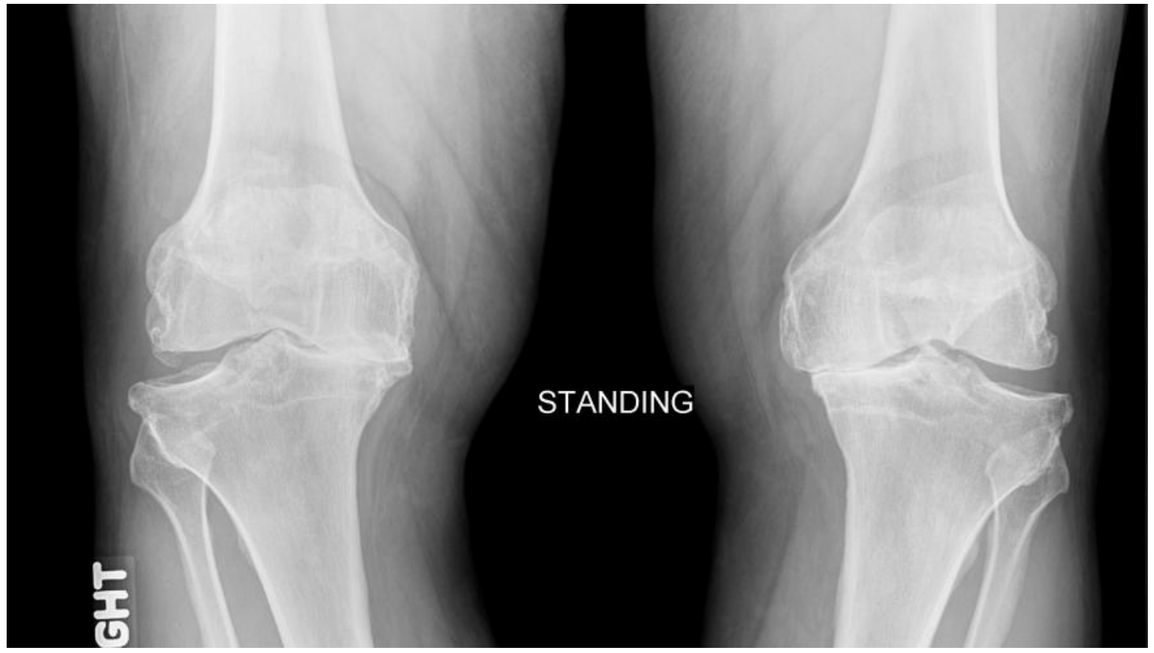
Doctor – Should I Stop Running?



Is there more to this story that we are missing?

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Outline

- **Pathogenesis of OA**
- **Treatment Guidelines**
- **Running and OA – Basic Science**
- **Running and OA – Clinical Studies**

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Pathogenesis of OA – Changing Paradigm

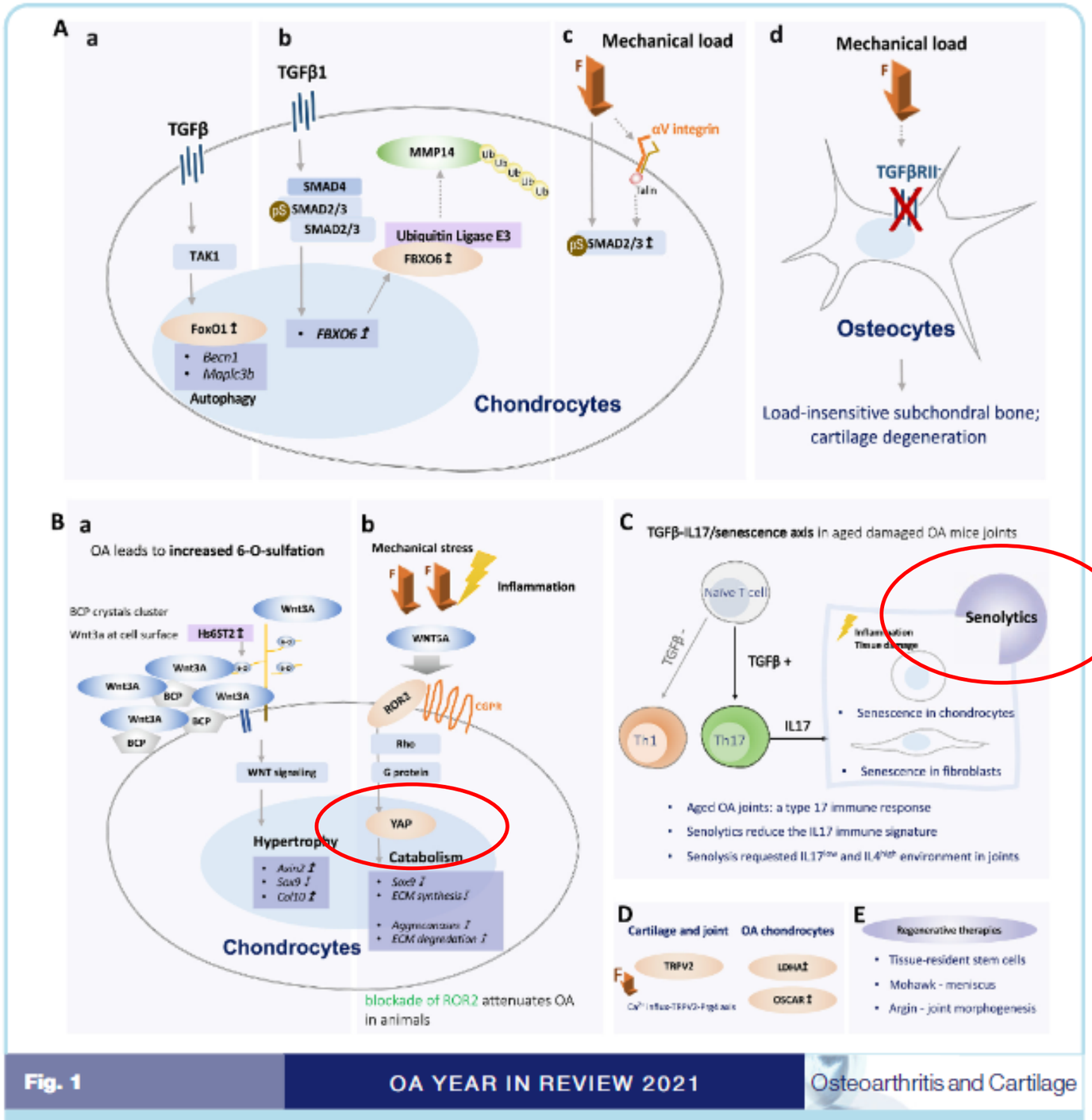

Fig. 1 OA YEAR IN REVIEW 2021 Osteoarthritis and Cartilage

Summary of molecules and signaling findings in joint and cartilage homeostasis within this 2020–2021 review.
A. TGFβ signaling in cartilage homeostasis and mechanobiology, ***a.*** TGFβ-FoxO1 ***via*** TAK1 signaling[1]; ***b.*** TGFβ-SMAD2/3-FBXO6-MMP14 ubiquitination[2]; ***c.*** Chondrocytes sense mechanical stress and TGFβ ***via*** αV integrin- and talin-centered cytoskeletal reorganization[3]; ***d.*** Subchondral bone osteocytes sense mechanical signals ***via*** TGFβRII[4]. **B. WNT signaling in cartilage and joint health**, ***a.*** BCP-Wnt3a-chondrocyte hypertrophy[5]; ***b.*** Wnt5a-ROR2-YAP[6]. **C. TGFβ-IL17/senescence axis in aged, damaged OA joints: the dynamic of senolytics**[17], **D. TRPV2** in cartilage and joint[34]; **LDHA**[35] and **OSCAR**[36] in OA chondrocytes. **E.** Regenerative therapies[22–24]. **BCP** basic calcium phosphate; **ROR2** receptor tyrosine kinase-like orphan receptor 2; **LDHA** lactate dehydrogenase A; **OSCAR** osteoclast-associated receptor; **TRPV2** transient receptor potential vanilloid 2.

Jiang Y *Osteoarthritis & Cartilage* 2022

How will these molecular targets lead to successful new treatment approaches?

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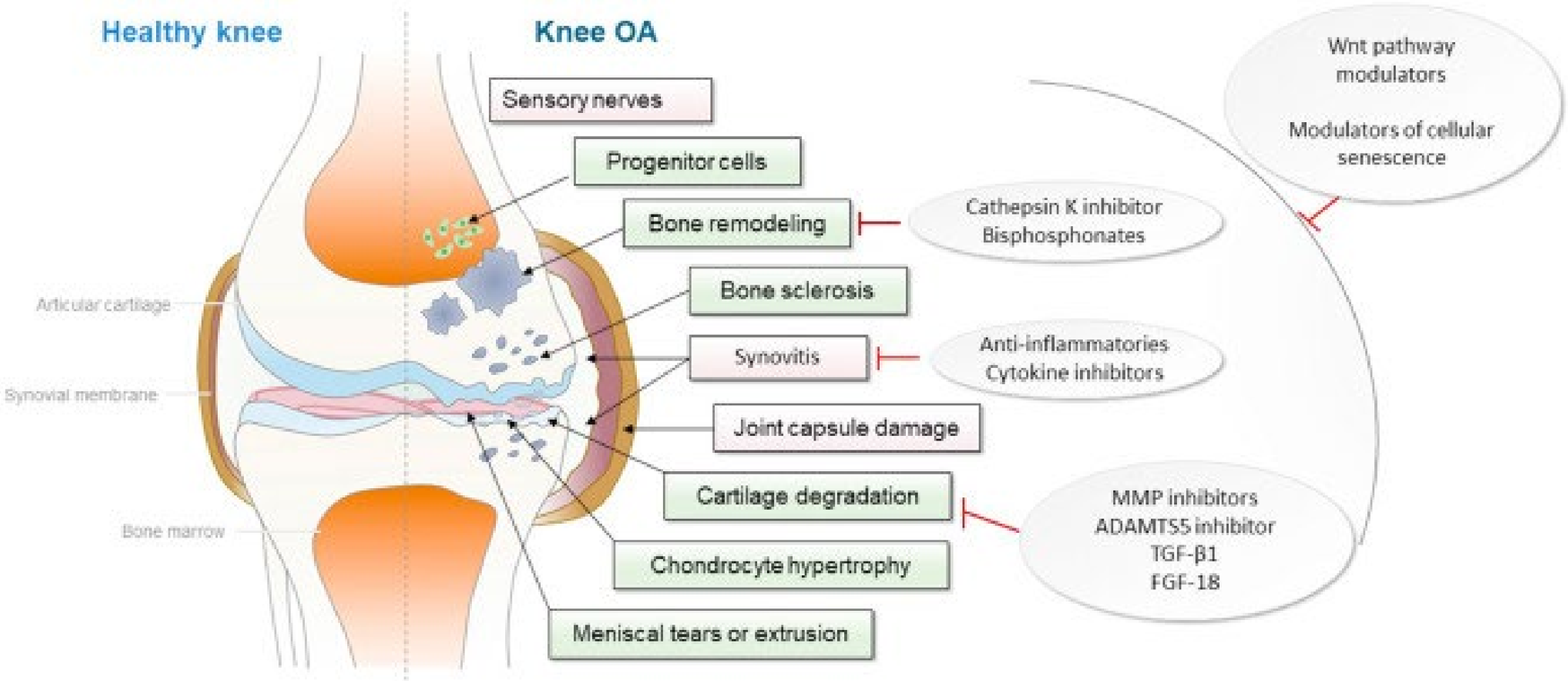
OA Molecular Phenotyping – Lost In Translation?



"The biggest challenge for OA drug discovery and development are the translation of preclinical discoveries to the clinical setting."

Mobasheri & Loeser *Nat Rev Rheumatol* 2024

Problems cannot be solved with the same level of awareness that created them.

Albert Einstein

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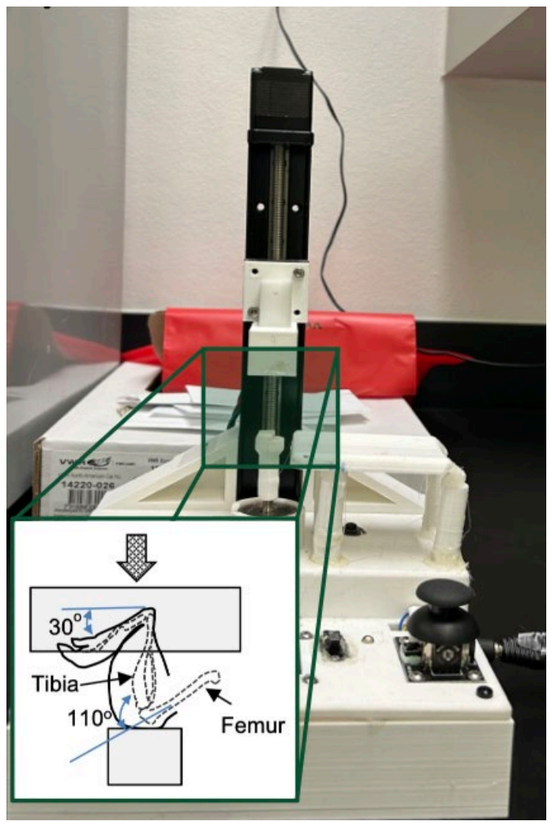
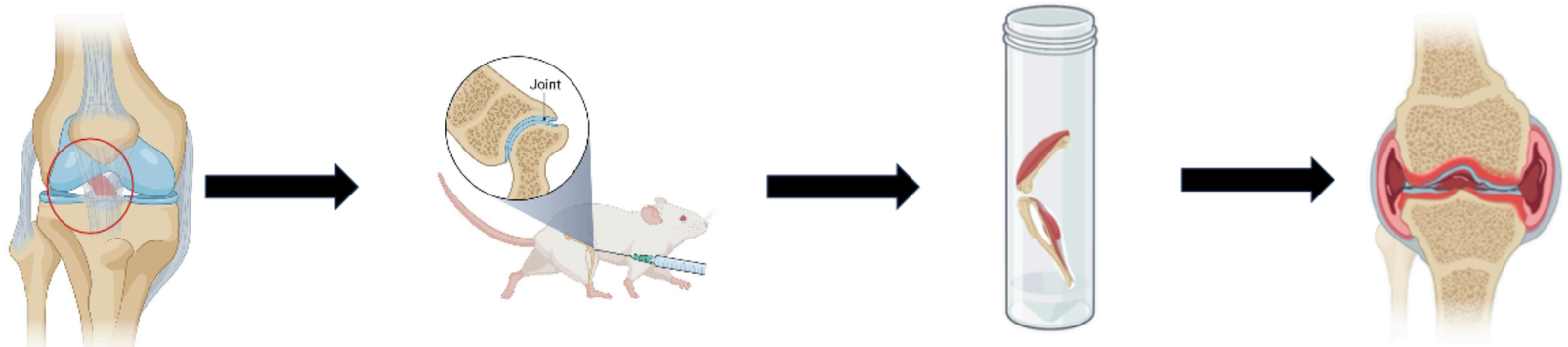
PTOA – A Distinct Phenotype?

- *In vivo* model monitoring OA incidence and progression following ACL injury

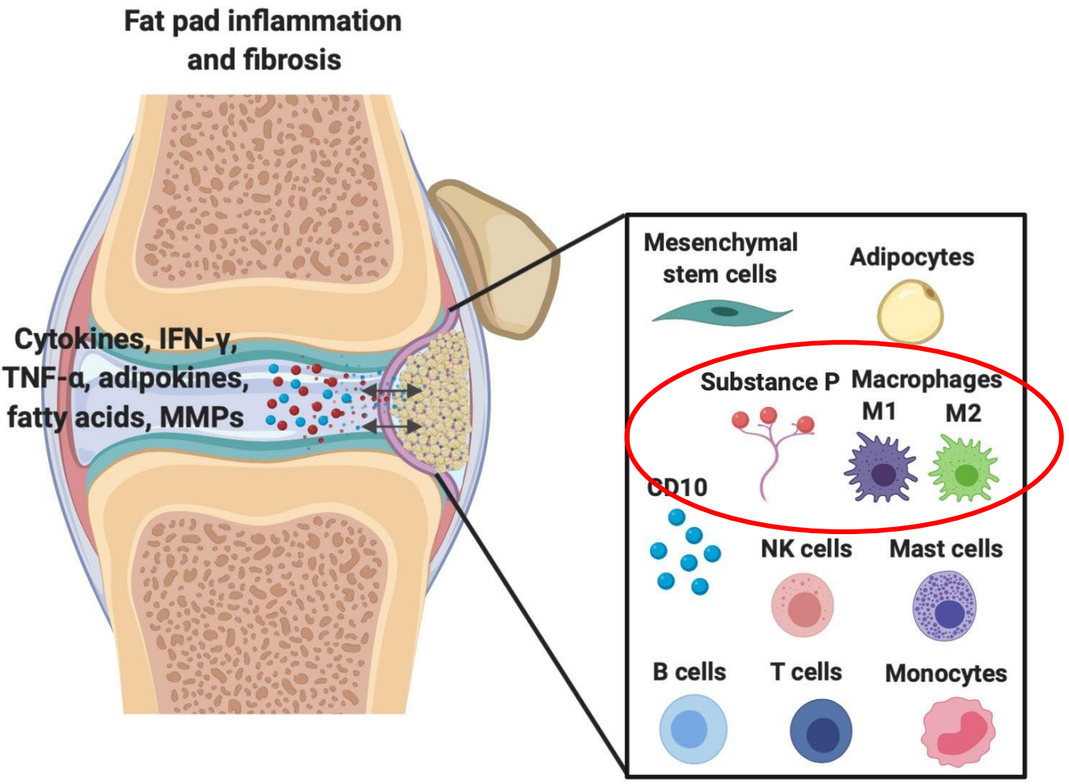


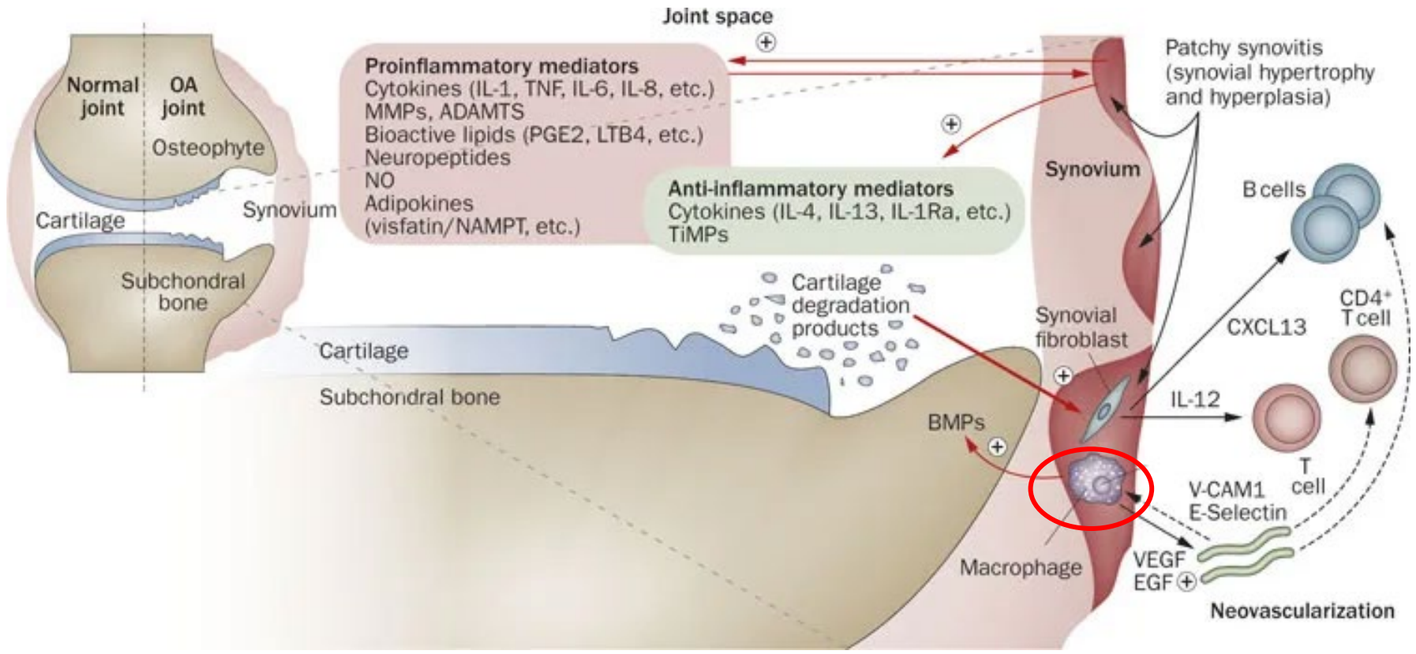


ACL Injury → Intra-articular Inhibitor Injection → Tissue Fixation → Osteoarthritis?

Osteoarthritis & Cartilage – In Review

Extensive molecular cross-talk and important cellular components between the IFP and the synovium within the joint capsule which are responsible for inflammation/fibrosis





Greif et al., 2020 *Front. Bioeng. Biotechnol*

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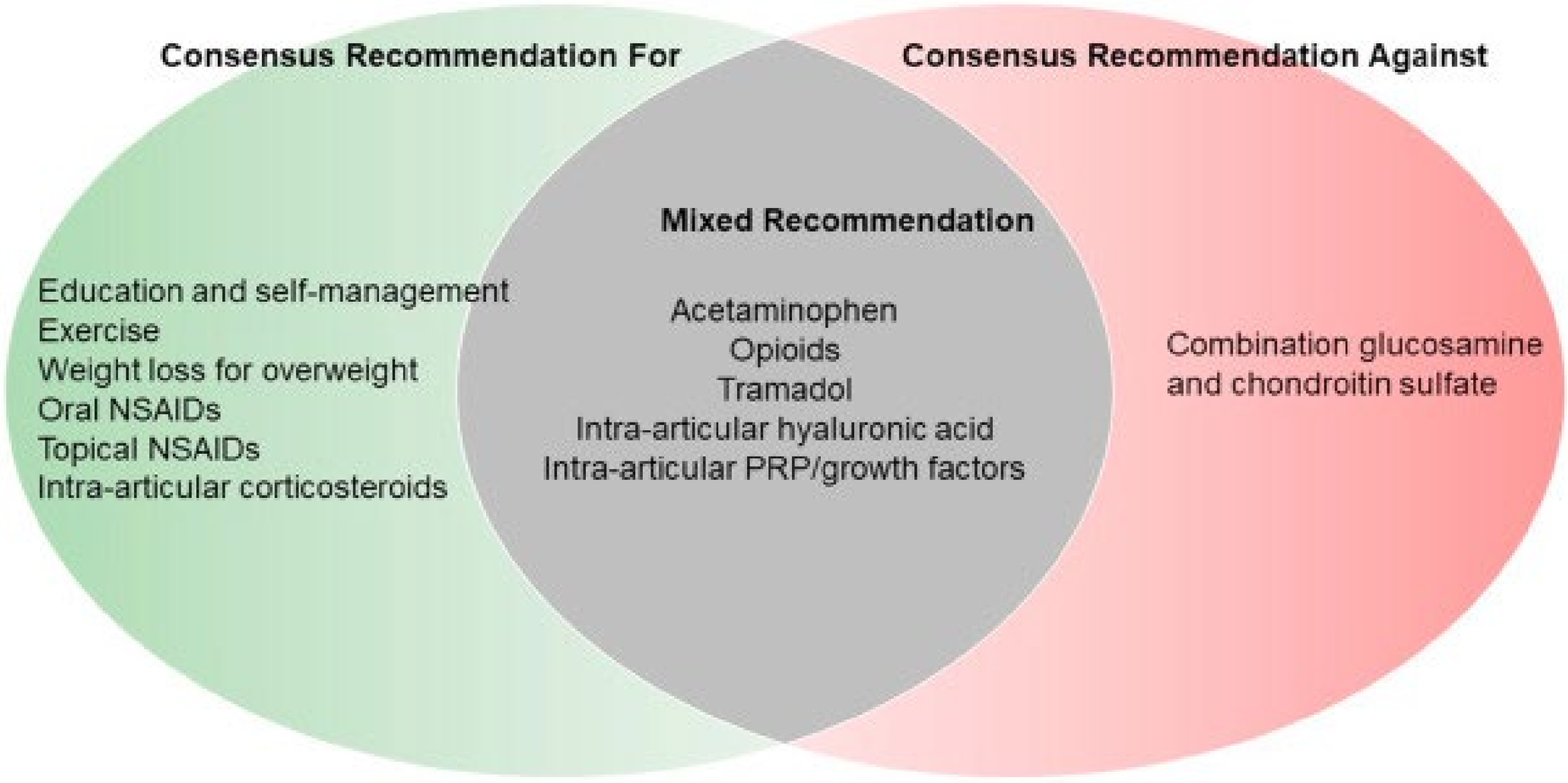
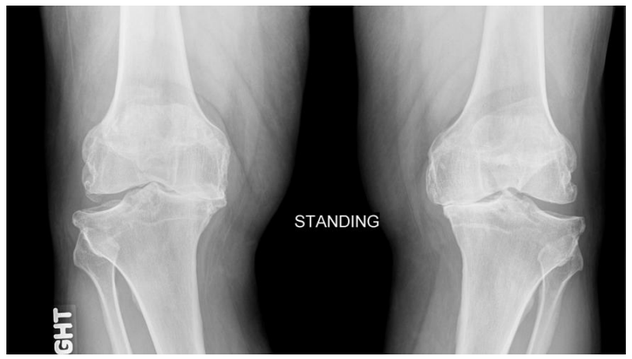
Treatment Guidelines for OA



What About Running?



Kennedy S, Tambiah JRS, Lane NE. *Best Practice & Research Clin Rheum* 2023

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Mesenchymal Stem Cell Therapies – The Future Of Orthobiologics and OA?

THE GOAL OF LIFE

is to die young

As late as possible!

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Naja M et al. Comparative effectiveness of nonsurgical interventions in the treatment of patients with knee OA

Medicine 2021

- 15 – 30% of patients express dissatisfaction with total joint arthroplasty (Parvizi, Nunley, Berend et al. *Clin Orthop Relat* Res 2014)
- Systematic review and network meta-analysis (Bayesian approach)
- RCTs evaluating nonsurgical treatment strategies – majority - mild to knee OA (KL 1-2)
- Primary outcome – change from baseline in WOMAC total score at 12 months
- Secondary outcomes – WOMAC at 3 and 6 months, VAS at 12 months
- 13 trials – 7 strategies (PRP, corticosteroids, MSCs, hyaluronic acid, ozone, NSAIDs with or without physiotherapy)
- Quality – Cochrane Collaboration tool for risk of bias
- GRADE methodology – quality of evidence

Naja M et al. Comparative effectiveness of nonsurgical interventions in the treatment of patients with knee OA

Medicine 2021

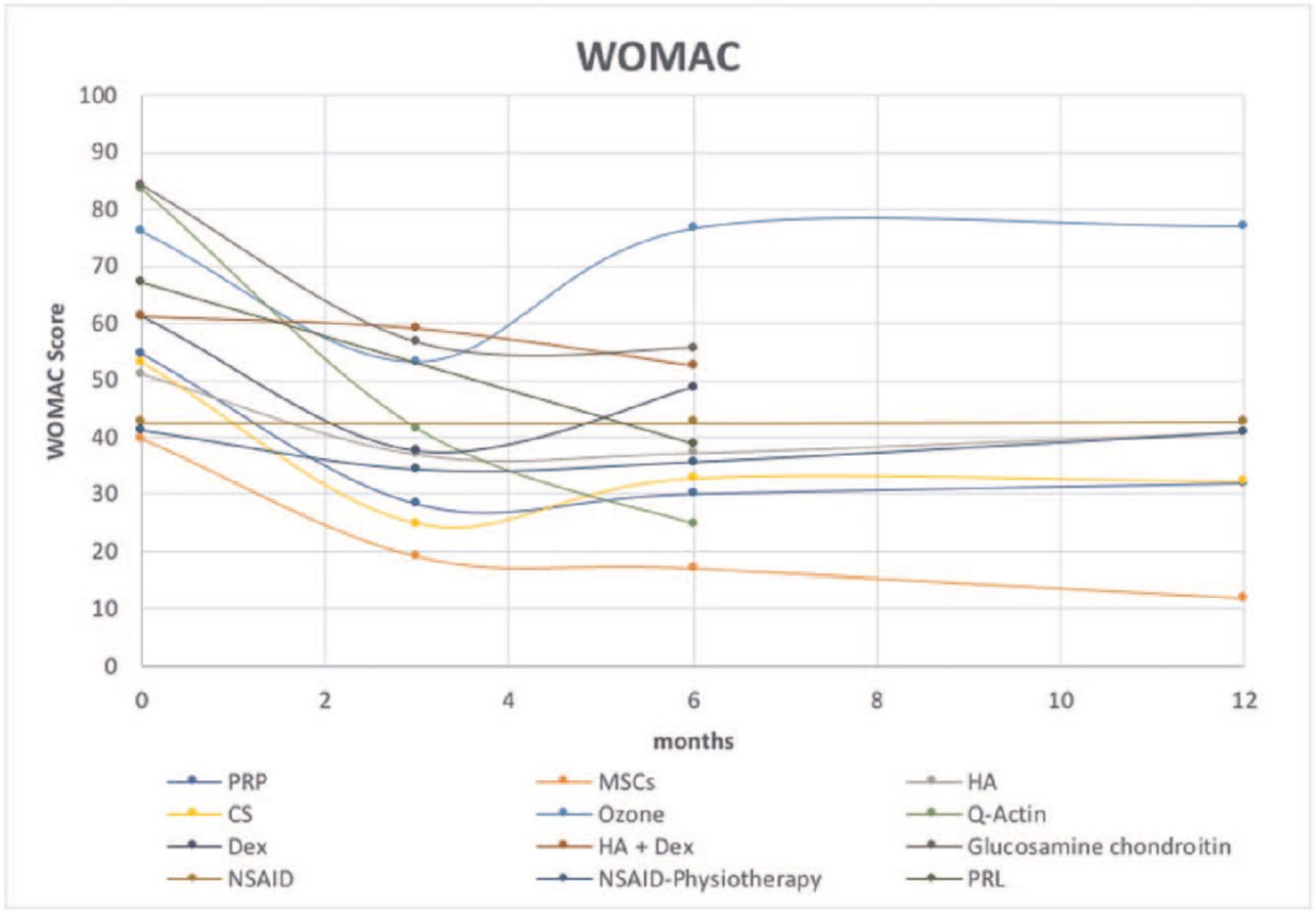

Figure 2. Curves showed the total scores variation of knee OA strategies from baseline to the last follow-up visit according to Western Ontario and McMaster university (WOMAC). OA = osteoarthritis.

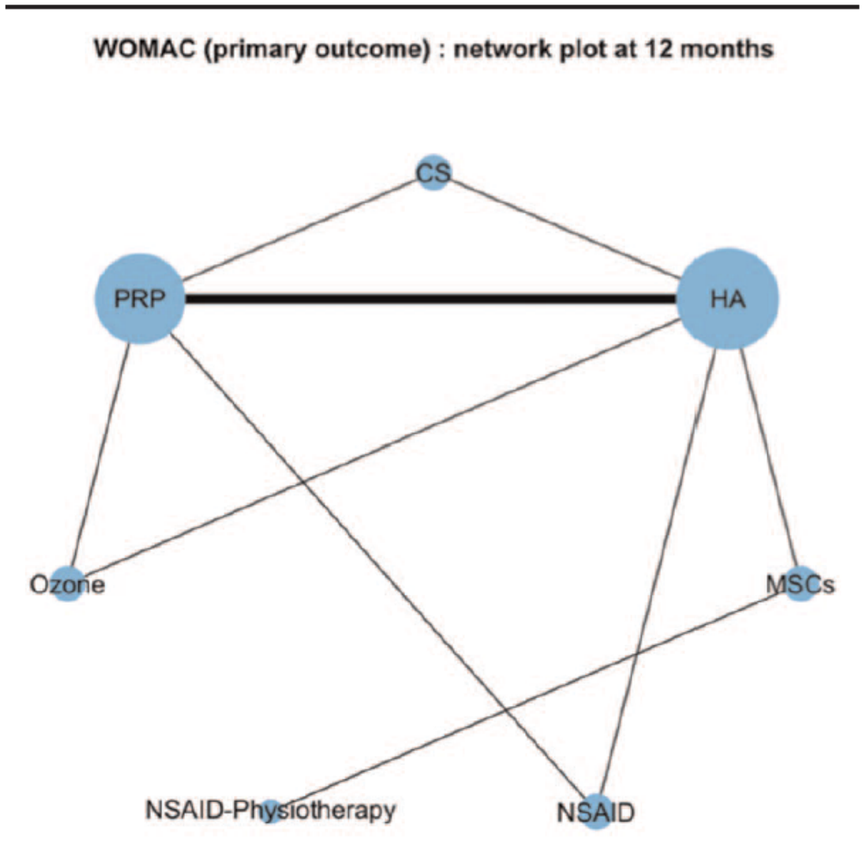

Figure 3. Network plot for the primary outcome. The area of every circle is proportional to the number of randomly assigned patients and indicates the sample size. The width of the lines is proportional to the number of trials that directly compared the 2 strategies.

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Naja M et al. Comparative effectiveness of nonsurgical interventions in the treatment of patients with knee OA

Medicine 2021

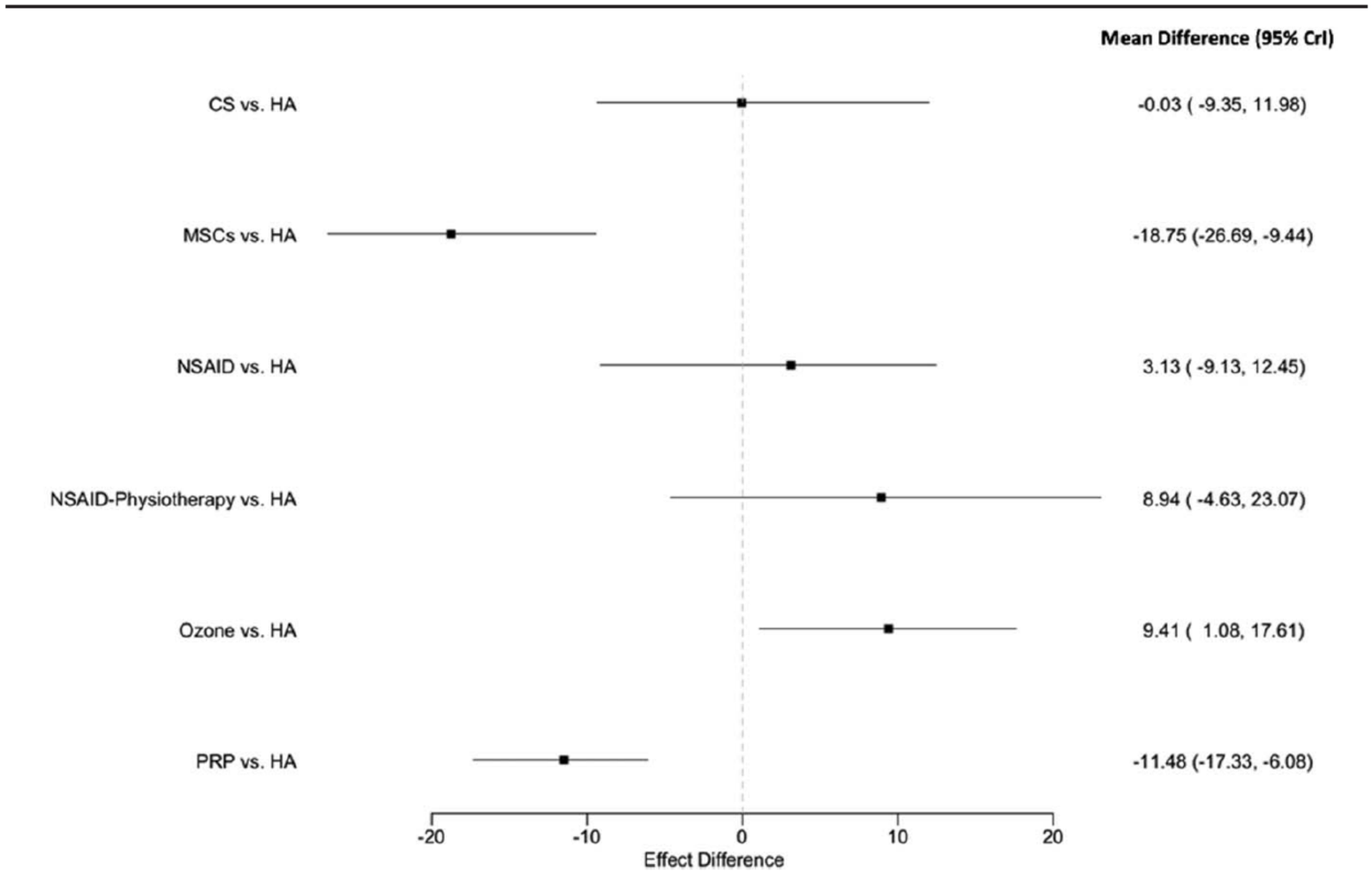

Figure 4. Forest plot for the strategies' effects compared with the reference treatment for primary outcome (WOMAC score at 12 months). Estimates are expressed on a 0 to 100 scale. Point estimates refer to the posterior mean. The bars indicate 95% credibility intervals (CrIs). WOMAC = Western Ontario and McMaster university.

- Reference treatment = hyaluronic acid
- Both MSCs and PRP produced differences with a decrease in WOMAC with MSCs showing highest probability of treatment effect
- Other 4 strategies – no differences

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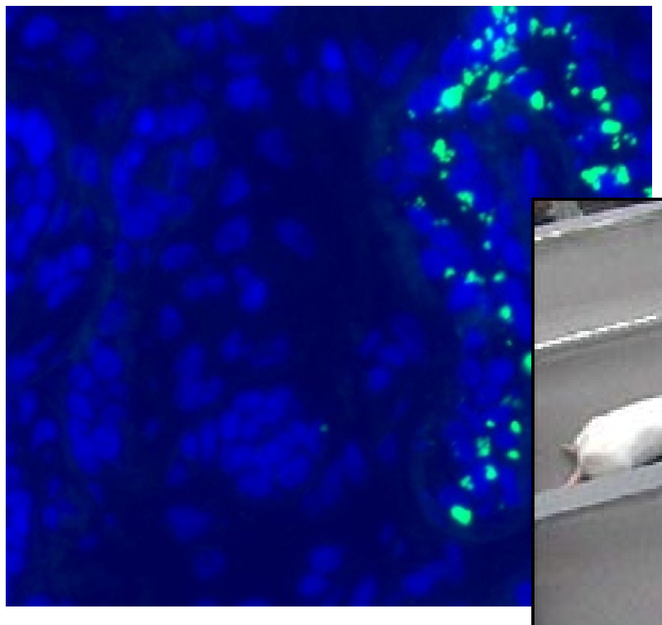
Bench To Parkside Or Parkside To Bench?

How can we match clinical phenotypes with disease (molecular) endotypes to improve care?

Society



Cell

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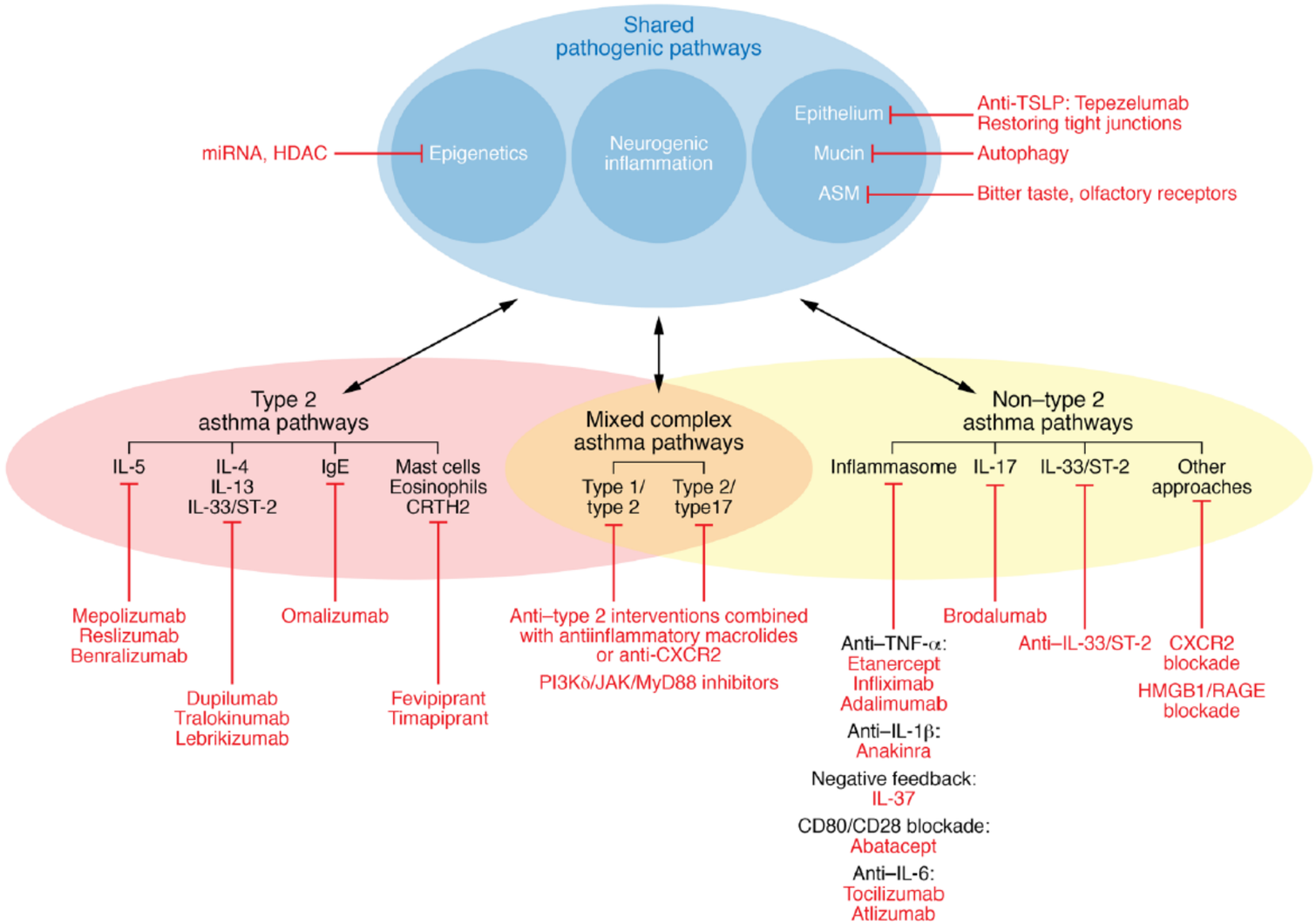
Matching Molecular Endotypes And Clinical Phenotypes – Allergic Diseases



Agache and Akdis *J Clin Invest* 2019

"One of the most exciting developments in OA research has been the emergence of clinical phenotypes and molecular endotypes which will pave the way toward an understanding of the therapeutic subtypes (theratypes) of OA, as has been proposed for other inflammatory diseases, such as allergy and asthma."

Mobasheri & Loeser 2024

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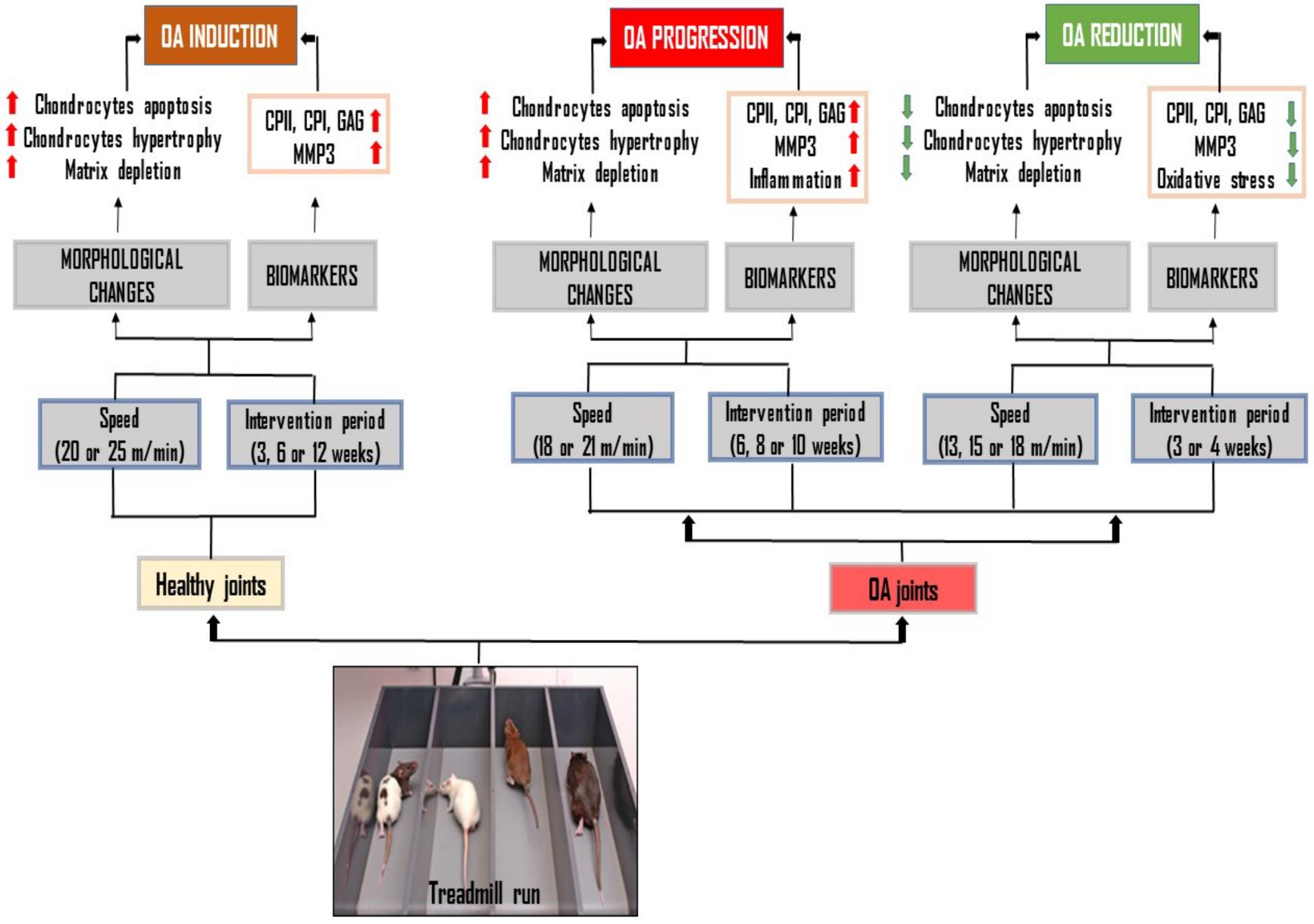
Basic Science – What Do We Know

- Immobilization induces OA in dogs and rabbits (Videman 1995, Palmoski 1981)
- Articular cartilage is avascular and receives nutrients through synovial fluid
- Moderate running (1h @ 4km/h) increases femoral articular cartilage (Kiviranta 1988)
- But 3-4 h @ 6 km/h decreases femoral articular cartilage (Kiviranta 1992)
- Maybe some movement is necessary to prevent OA, but repetitive impact (at certain ‘dose’ – magnitude, duration, frequency) also causes OA?

Animal Model Studies - Summary



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Changes in Cartilage Biomarker Levels During an Ultramarathon

- Roos and Dahlberg 2005 – increase glycosaminoglycan content in the weight-bearing posterior medial femoral condyle after moderate exercise
- Schutz et al 2014 – multistage marathon – initial increase in T2 signal followed by slight decrease throughout remainder of race and no change in ankle cartilage thickness
- Mundermann et al 2017 Am J Sports Med - 36 runners (49.0 +/- 10.7 years), blood samples before and during similar event (Italy -> Norway)
- Serum COMP, MMP-1, MMP-3, MMP-9, C2C, and CPII levels by ELISA
- Linear mixed models used to detect significant changes over time with covariates including body weight, running speed, and daily running time

Changes in Cartilage Biomarker Levels During an Ultramarathon

- COMP, MMP-3, MMP-9 levels all increased within 11 days and remained elevated
- No change in MMP-1, C2C, CPII
- Linear correlation between MMP-3 and COMP levels for all participants (r^2 = .969) – is MMP-3 involved in degradation of COMP?
- Is high dose running bad for you?
- Studies suggest initial increase in T2 in both ankle and knee followed by decrease to steady state over time when short term rest intervals are included
- Hinterwimmer et al 2014 – 6 month training program, 3-D MRI before training, pre- and post-marathon – Minimal cartilage volume/thickness decreases noted

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Clinical Science – Before 2000

	Activity Causes OA	No Difference
Cohort	Lane 1999 (women) **Spector 1996*** **Kujula 1994*** Lindberg 1993* **Marti 1989*** Felson 1988 (men only) Klunder 1980* **Cheng 2000**	**Kettunen 2001, Kujula 1995** **Lane 1990, 1993, 1998** **Konradson 1990*** **Sohn 1985*** **Puranen 1975***
Case-Control	Lau 2000 Vingard 1993 (T&F) Vingard, 1998	**Vingard 1993**
Cross-Sectional		**Panush 1986** **Lane 1986** **Solonen 1966***

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Long Distance Running and Knee Osteoarthritis

A Prospective Study Chakravarty et al 2008 *Am J Prev Med*

- Prospective study of 45 long-distance runners and 53 controls, mean age 58 (range 50-72) studied 1984-2002
- Serial knee radiographs scored for Total Knee Score (TKS) by modified KL grading
- Multivariate regression analyses for relationship between runner versus control and radiographic outcomes – age, gender, BMI, education, initial radiograph, and disability scores as covariates
- Initial analysis – 6.7% of runners and O% controls with OA
- End of study – runners did not have more prevalent OA (20 vs. 32%, p = 0.25) nor more cases of severe OA (2.2 vs. 9.4%, p = 0.21) than did controls
- Higher BMI, initial radiographic damage, greater time from initial radiograph – worse radiographic OA at final assessment
- No association with gender, education, previous knee injury, mean exercise time
- No report of clinical symptoms, only tibiofemoral OA reported, ? Selection bias (healthy runners)

Does running protect against knee OA? Or promote it? Assessing the current evidence – Leech and Batt AJSM 2015

- 10 key papers examining effect of recreational running and risk for knee OA
- 7 studies – no relationship (first study 1993 review of Framingham data)
- Lo G et al. Arthritis & Rheum - 2014 – “Habitual running any time in life is not detrimental and may be protective of symptomatic knee osteoarthritis”
- Driban et al. J Athl Train 2015 – Is participation in certain sports associated with knee osteoarthritis? A systematic review.
- Self selection bias in these studies – largely examined older participants who remain able to run in later life
- ‘The shape of the curve representing increased (or decreased) risk of knee osteoarthritis as a consequence of running is unknown, and specifically how much running (if any) is too much?’

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Running and Knee Osteoarthritis: A Systematic Review and Meta-analysis

Kate A. Timmins,* PhD, Richard D. Leech,* MSc, Mark E. Batt,*$_{y}$ MB BChir, DM, FFSEM, and Kimberley L. Edwards,*$_{z\S}$ PhD
University of Nottingham, Nottingham, UK

AJSM 2016

Purpose: To determine the association between running and the development of knee OA.
Study Design: Systematic review and meta-analysis.
Methods: Four electronic databases were searched, along with citations in eligible articles and reviews and the contents of recent journal issues. Two reviewers independently screened the titles and abstracts using prespecified eligibility criteria. Full-text articles were also independently assessed for eligibility. Eligible studies were those in which running or running-related sports (eg, triathlon or orienteering) were assessed as a risk factor for the onset or progression of knee OA in adults. Relevant outcomes included (1) diagnosis of knee OA, (2) radiographic markers of knee OA, (3) knee joint surgery for OA, (4) knee pain, and (5) knee-associated disability. Risk of bias was judged by use of the Newcastle-Ottawa scale. A random-effects meta-analysis was performed with case-control studies investigating arthroplasty.
Results: After de-duplication, the search returned 1322 records. Of these, 153 full-text articles were assessed; 25 were eligible, describing 15 studies: 11 cohort (6 retrospective) and 4 case-control studies. Findings of studies with a diagnostic OA outcome were mixed. Some radiographic differences were observed in runners, but only at baseline within some subgroups. Meta-analysis suggested a protective effect of running against surgery due to OA: pooled odds ratio 0.46 (95% CI, 0.30-0.71).

Conclusion: It was not possible to determine the role of running in knee OA. Moderate- to low-quality evidence suggests no association with OA diagnosis, a positive association with OA diagnosis, and a negative association with knee OA surgery. Conflicting results may reflect methodological heterogeneity. More evidence from well-designed, prospective studies is needed.

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Does running protect against knee OA? Or promote it? The OAI Version Of The Story

- Lo et al *Arthritis Care & Research* 2017
- Retrospective cross-sectional study of OAI participants (2004-2014) with knee radiographs, symptom assessment, lifetime physical activity surveys
- 2637 participants – 55.8% female, 64.3 +/- 8.9 yrs age, BMI 28.5 +/- 4.9 kg/m^2
- 29.5% ran (at some time in their lives)
- Unadjusted OR for prior/current runners compared with those who never ran
- Pain (0.83 and 0.71), Radiographic OA (0.83 and 0.78), Symptomatic OA (0.81 and 0.64)
- Adjusted models were similar

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Does running protect against knee OA? Or promote it? The OAI Version Of The Story

- Lifetime physical activity questionnaire – validated and used to establish links between lifetime physical activity and bone mineral density, risk for diabetes, and risk for ovarian cancer
- 75% reported running at least 250 times in their lives, 50% at least 800 bouts, 25% at least 2,000 bouts
- Observational study – people chose whether or not to run
- Cross-sectional study – influence of running in those with preexisting knee OA **cannot** be ascertained
- “There is no increased risk of symptomatic knee OA among self-selected runners compared with nonrunners. In those without OA, running does not appear to be detrimental to the knees.”

Running Does Not Increase Symptoms or Structural Progression in People with Knee Osteoarthritis: Data from the Osteoarthritis Initiative

Grace H. Lo, MD, MSc[1,2], Sarra M. Musa, MD[1], Jeffrey B. Driban, PhD[3], Andrea M. Kriska, PhD[4], Timothy E. McAlindon, MD, MPH[3], Richard B. Souza, PT, PhD[5], Nancy J. Petersen, PhD[1], Kristi L. Storti, PhD, MPH[6], Charles B. Eaton, MD, MS[7], Marc C. Hochberg, MD, MPH[8] Rebecca D. Jackson, MD[9], C. Kent Kwoh, MD[10], Michael C. Nevitt, PhD[11], and Maria E. Suarez-Almazor, MD, PhD[12]

Published in final edited form as:
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Abstract

Introduction—Higher levels of moderate to vigorous physical activity improve all-cause mortality and cardiovascular events. However, the effect of running, a moderate to vigorous activity, in those with knee osteoarthritis (OA), a common arthritis that occurs with aging, a high risk group for mortality and cardiovascular events, is unclear. Therefore, we aimed to evaluate the association of self-selected running on OA symptom and structure progression in people with knee OA.

Methods—This nested cohort study within the Osteoarthritis Initiative (OAI) (2004–2014) included those over 50 years old with OA in at least one knee. Runners were defined using a self-administered questionnaire at the 96-month visit. At baseline and 48-months, symptoms were assessed and radiographs were scored for Kellgren-Lawrence (KL) grade (2–4) and medial Joint Space Narrowing (JSN) score (0–3). We evaluated the association of self-selected running with outcomes: KL worsening, medial JSN worsening, new knee pain, and improved knee pain over 48 months, adjusting for baseline age, sex, body mass index (BMI), KL score, contralateral KL score, contralateral knee pain, and injury. If data were not available at the 48 month visit, then they were imputed from the 36 month visit.

Results—1,203 participants had a mean age of 63.2 (7.9) years, BMI of 29.5 (4.6) kg/m^2, 45.3% male, and 11.5% runners. Data from 8% of participants required imputation. Adjusted odds ratios for KL grade worsening and new frequent knee pain were 0.9 (0.6 – 1.3) and 0.9 (0.6 – 1.6) respectively. Adjusted odds ratio for frequent knee pain resolution was 1.7 (1.0 – 2.8).

Conclusions—Among individuals over 50 years old with knee OA, self-selected running is associated with improved knee pain and not with worsening knee pain or radiographically defined structural progression. Therefore, self-selected running, which is likely influenced by knee symptoms and may result in lower intensity and shorter duration sessions of exercise, need not be discouraged in people with knee OA.

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Osteoarthritis in Athletes Versus Nonathletes: A Systematic Review

Filippo Migliorini, MD, PhD, MBA, Emanuela Marsilio, MD,† Ernesto Torsiello, MD,† Andrea Pintore, MD,† Francesco Oliva, MD, PhD,† and Nicola Maffulli, MD, MS, PhD, FRCP, FRCS(Orth)†‡§*

Sports Med Arthrosc Rev • Volume 30, Number 2, June 2022

Introduction: Joint overload and sport-related injuries may accelerate the development of osteoarthritis (OA). A systematic review of the literature was performed to establish the risk of athletes to develop premature OA compared with nonathletes.

Materials and Methods: This systematic review was conducted according to the PRISMA guidelines. PubMed, Google scholar, Embase, and Web of Science databases were accessed in June 2021. All the published clinical studies investigating OA onset in athletes versus nonathletes were considered. Studies reporting data on secondary and/or post-traumatic OA were excluded.

Results: Data from 32 articles (20,288 patients) were retrieved. The mean age was 67.8 ± 10.0 years and the mean body mass index was 25.0 ± 2.5 kg/m^2. 74% (6859 patients) of the athletes suffered from premature OA. Of them, 21% were active in soccer, 11% in handball, 11% in ice-hockey, 3% in football, and 0.3% in rugby. 26% of the athletes reported no significant differences in OA progression compared with healthy controls. Of these athletes, 47% were runners, 5% dancers, and 1% triathletes.

Conclusion: Certain sports, such as soccer, handball, ice-hockey, and rugby are more likely to be associated with premature knee and hip OA. Conversely, runners and ballet dancers do not evidence significant increase in OA. Moderate and recreational exposure to aerobic sports does not accelerate the development of OA.

- Retrospective design, lack of blinding, OA not graded
- Considerable heterogeneity in sex, age, activity

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Does Running Increase the Risk of Hip and Knee Arthritis? A Survey of 3804 Marathon Runners

Matthew J. Hartwell, MD,*† Joseph E. Tanenbaum, MD, PhD,† George Chiampas, DO,†
Michael A. Terry, MD,† and Vehniah K. Tjong, MD†

Sports Health 2024

Background: Long-distance running is a popular form of cardiovascular exercise with many well-described health benefits, from improving heart health to the management of obesity, diabetes, and mental illness. The impact of long-distance running on joint health in recreational runners, however, remains inconclusive.

Hypothesis: The prevalence of osteoarthritis in runners is not associated with an athlete's running-related history, including the number of marathons completed, cumulative years of running, average weekly mileage, and average running pace.

Study Design: Prospective cohort study.

Level of Evidence: Level 3.

Methods: A survey was distributed to all participants registered for the 2019 or 2021 Chicago marathon (n = 37,917). Surveys collected runner demographics and assessed for hip/knee pain, osteoarthritis, family history, surgical history, and running-related history. Running history included the number of marathons run, number of years running, average running pace, and average weekly mileage. The overall prevalence of osteoarthritis was identified, and a multivariable logistic regression model was used to identify variables associated with the presence of hip and/or knee osteoarthritis.

Results: Surveys were completed by 3804 participants (response rate of 10.0%). The mean age was 43.9 years (range, 18-83 years) and participants had completed on average 9.5 marathons (median, 5 marathons; range, 1-664 marathons). The prevalence of hip and/or knee arthritis was 7.3%. A history of hip/knee injuries or surgery, advancing age, family history, and body mass index (BMI) were risk factors for arthritis. Cumulative number of years running, number of marathons completed, weekly mileage, and mean running pace were not significant predictors for arthritis. The majority (94.2%) of runners planned to run another marathon, despite 24.2% of all participants being told by a physician to do otherwise.

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Sports Health 2024

Table 3. Multivariable logistic regression analysis of risk factors for hip and/or knee pain and arthritis

Risk Factor	Pain[a]		Arthritis[b]	
	OR	*P* value	OR	*P* value
History of hip/knee surgery	1.50 (1.20-1.87)	<0.01*	5.85 (4.33-7.92)	<0.01*
Age, per year	0.99 (0.98-0.99)	<0.1*	1.08 (1.06-1.10)	<0.01*
History of hip/knee injury that prevented running	3.30 (2.85-3.83)	<0.01*	5.04 (3.45-7.34)	<0.01*
Family history of hip/knee arthritis	1.16 (0.98-1.37)	0.12	3.47 (2.52-4.79)	<0.01*
BMI, per kg/m^2	1.02 (0.99-1.05)	0.05	1.10 (1.05-1.15)	<0.01*
Pace for training runs, per minute/mile	1.04 (0.98-1.10)	0.19	0.88 (0.79-0.99)	0.03
Female sex, compared with men	1.43 (1.20-1.70)	<0.01*	1.41 (0.99-2.01)	0.08
Participation in other sports	1.04 (0.90-1.21)	0.59	0.87 (0.64-1.17)	0.35
Weekly mileage, per mile	0.99 (0.98-0.99)	<0.01*	0.99 (0.98-1.01)	0.36
No. of marathons, per marathon	0.99 (0.98-0.99)	<0.01*	1.00 (0.99-1.01)	0.56
Duration of running, per year	1.00 (0.99-1.01)	0.64	1.00 (0.98-1.01)	0.66
Cross training	0.88 (0.74-1.04)	0.14	0.98 (0.69-1.40)	0.91

BMI, body mass index; OR, odds ratio.
[a]History of hip and/or knee pain within the past year that prevented running.
[b]History of hip and/or knee arthritis.
*Significant after Bonferroni correction ($P < 0.01$).

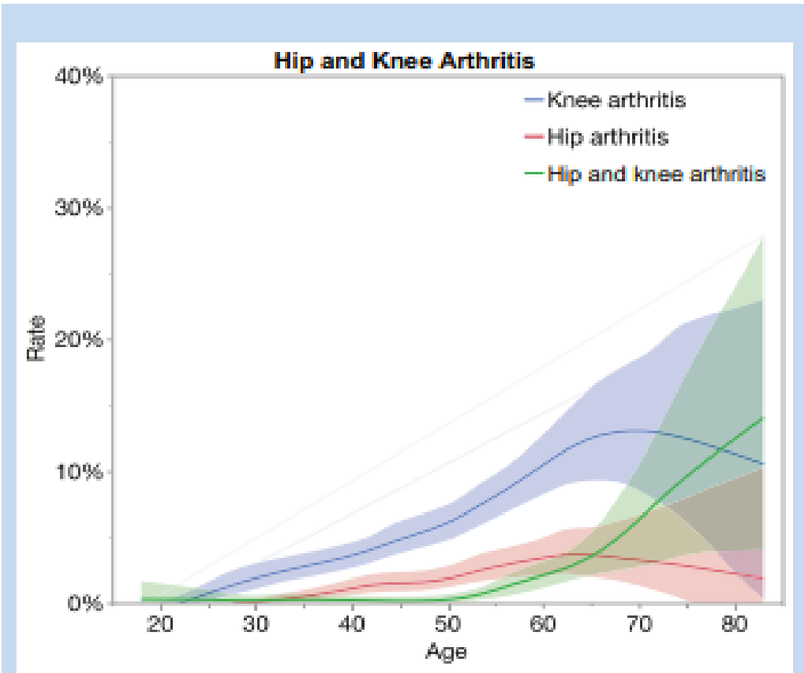

Figure 2. Overall prevalence of hip and/or knee arthritis by age.

Conclusion: From this largest surveyed group of marathon runners, the most significant risk factors for developing hip or knee arthritis were age, BMI, previous injury or surgery, and family history. There was no identified association between cumulative running history and the risk for arthritis.

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Does Running Increase the Risk of Hip and Knee Arthritis? A Survey of 3804 Marathon Runners

Matthew J. Hartwell, MD,*† Joseph E. Tanenbaum, MD, PhD,† George Chiampas, DO,†
Michael A. Terry, MD,† and Vehniah K. Tjong, MD†

Sports Health 2024

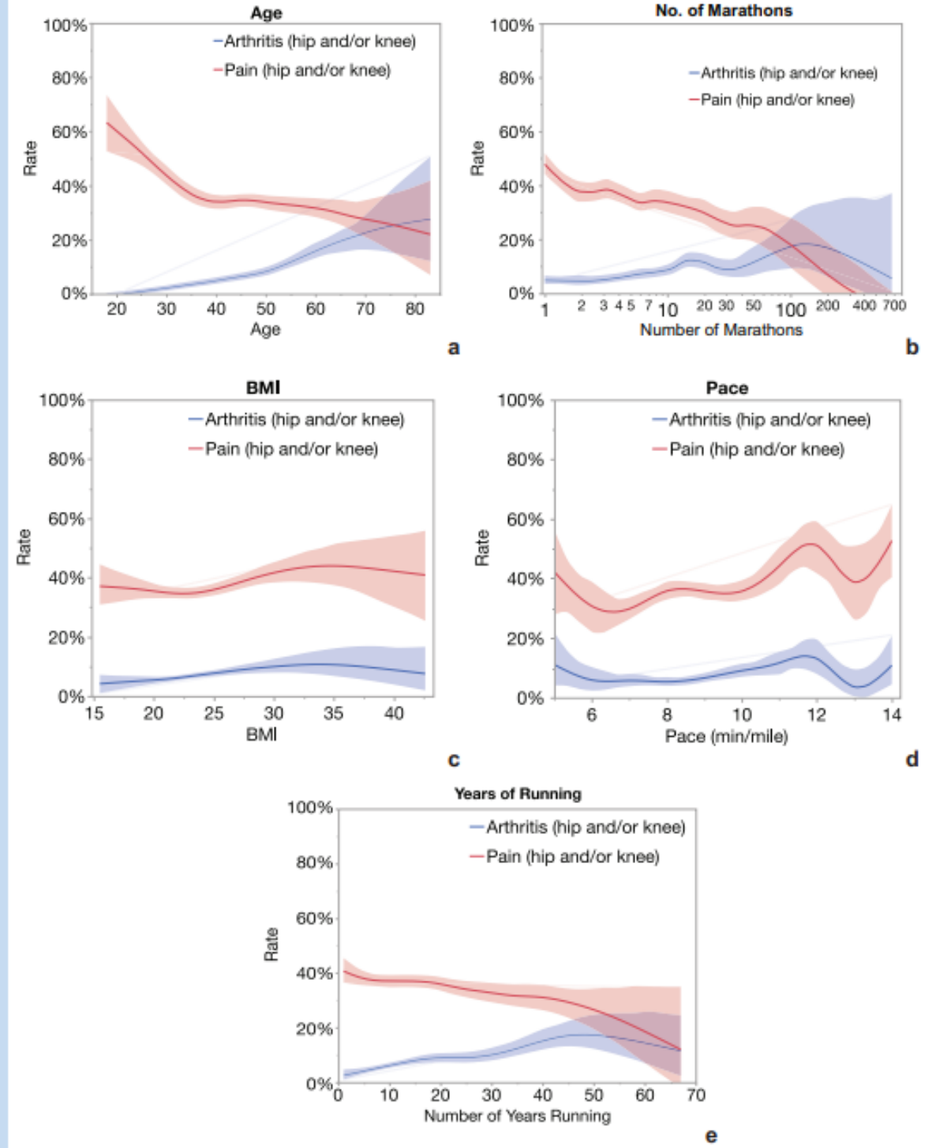

Figure 3. Prevalence of hip and/or knee arthritis and pain by (a) age, (b) number of marathons completed, (c) BMI, (d) average pace during training runs, and (e) number of years running. BMI, body mass index.

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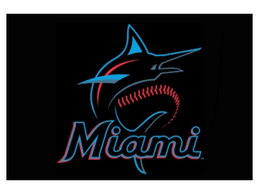
The association between running volume and knee osteoarthritis prevalence: A systematic review and meta-analysis

M. Burfield [b], M. Sayers [a], R. Buhmann [a, *]

[a] School of Health and Behaviour Sciences, University of the Sunshine Coast, Maroochydore, Australia
[b] School of Health and Behavioural Sciences, Australian Catholic University, Brisbane, Australia

Physical Therapy in Sport 2023

- Historically – KOA attributed to excessive mechanical loading (Radin et al, 1972)
- OA – multifactorial disease affecting entire knee joint – cartilage, subchondral bone, synovium, meniscus
- Running itself (at proper dose – magnitude, duration, frequency) beneficial for cartilage health
- In vitro studies – highly cyclic loading at low magnitude increases biomarkers of cartilage health (Griffin & Guilak, 2005)
- Cyclic loading – facilitates transfer of nutrition from synovial fluid to cartilage and meniscus
- Some level of regular running is beneficial for cartilage health



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The association between running volume and knee osteoarthritis prevalence: A systematic review and meta-analysis

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- Question – Do these beneficial changes in markers of cartilage health result in low knee OA prevalence in long-term runners?
- Conflicting evidence – higher knee OA prevalence in competitive runners, but not recreational runners, when running for longer than 15 years (Alentorn-Geli et al, 2017)
- Knee OA prevalence lower in runners compared with controls (Alentorn-Geli et al, 2017)
- Runners – 50% reduced odds of undergoing future knee surgery secondary to OA
- Is it possible that a dose-response curve explains contradictory results?

The association between running volume and knee osteoarthritis prevalence: A systematic review and meta-analysis

M. Burfield [b], M. Sayers [a], R. Buhmann [a, *]

[a] School of Health and Behaviour Sciences, University of the Sunshine Coast, Maroochydore, Australia
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Physical Therapy in Sport 2023

ABSTRACT

There is conflicting evidence regarding whether regular running is associated with knee osteoarthritis prevalence. Previous evidence reports lower knee osteoarthritis prevalence in recreational runners compared with professionals (with a higher training volume) and controls (who have a lower training volume). The aim of this systematic review and meta-analysis was to determine if weekly running volume is associated with knee osteoarthritis prevalence. Four databases (PubMed, Web of Science, Scopus and SPORTDiscus) were searched from earliest record to November 2021. Included studies must i) recruit participants who ran regularly and recorded weekly running volume; ii) include a control group (running <8 km per week); iii) record knee osteoarthritis prevalence (either by radiological imaging or self-reported diagnosis from a doctor or physiotherapist). Study bias was assessed using the Newcastle-Ottawa Scale (NOS). Pooled effects were estimated using a random effects model. Odds ratios with 95% prediction and confidence intervals are reported. Nine observational case control studies with a total of 12,273 participants (1272 runners) were included in the meta-analysis. Most of the included studies were rated as having a very high (n = 2) or high (n = 3) risk of bias on the Newcastle Ottawa Scale. There was no difference in knee osteoarthritis prevalence between runners and controls (OR = 0.97, 95% CI = 0.56 to 1.68). Runners undertaking 8–32.1 km (OR = 1.17, 95% CI = 0.77 to 1.80), 32.2–48 km (OR = 1.04, 95% CI = 0.48 to 2.31) or > 48 km per week (OR = 0.62, 95% CI = 0.35 to 1.10) did not exhibit higher knee osteoarthritis prevalence compared with controls. It is unclear whether running volume is associated with increased knee osteoarthritis prevalence, future large-scale, high quality prospective studies are required.

The association between running volume and knee osteoarthritis prevalence: A systematic review and meta-analysis

M. Burfield [b], M. Sayers [a], R. Buhmann [a, *]

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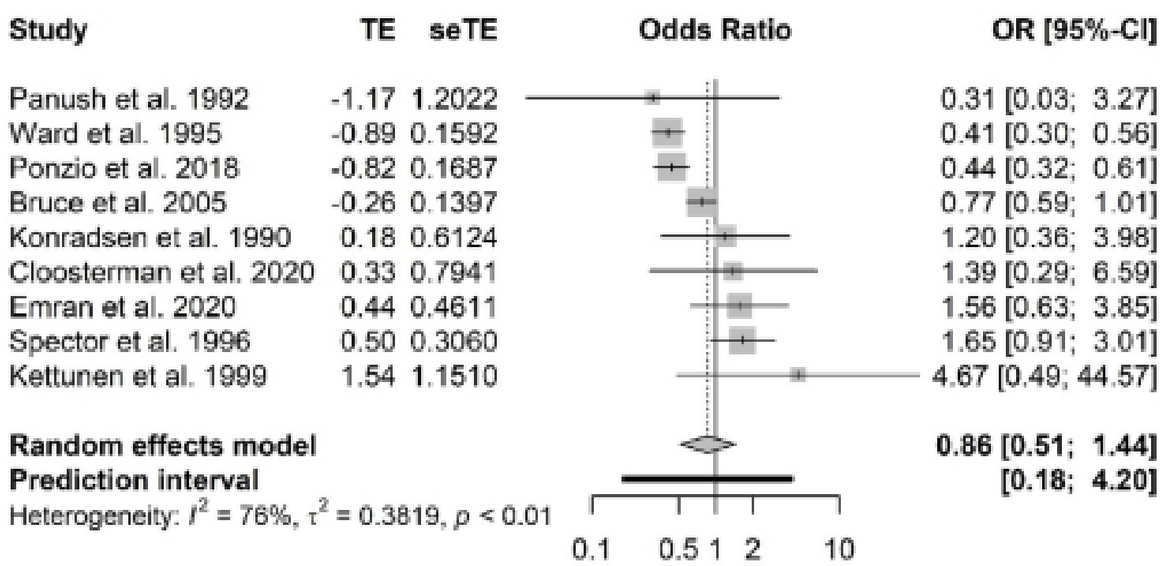

Fig. 2. Forest plot of analysis estimating knee OA prevalence in runners compared with controls. TE = effect size, seTE = standard error of the effect size, OR = odds ratio, CI = confidence interval.

- No difference in knee OA prevalence between runners and controls

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The association between running volume and knee osteoarthritis prevalence: A systematic review and meta-analysis

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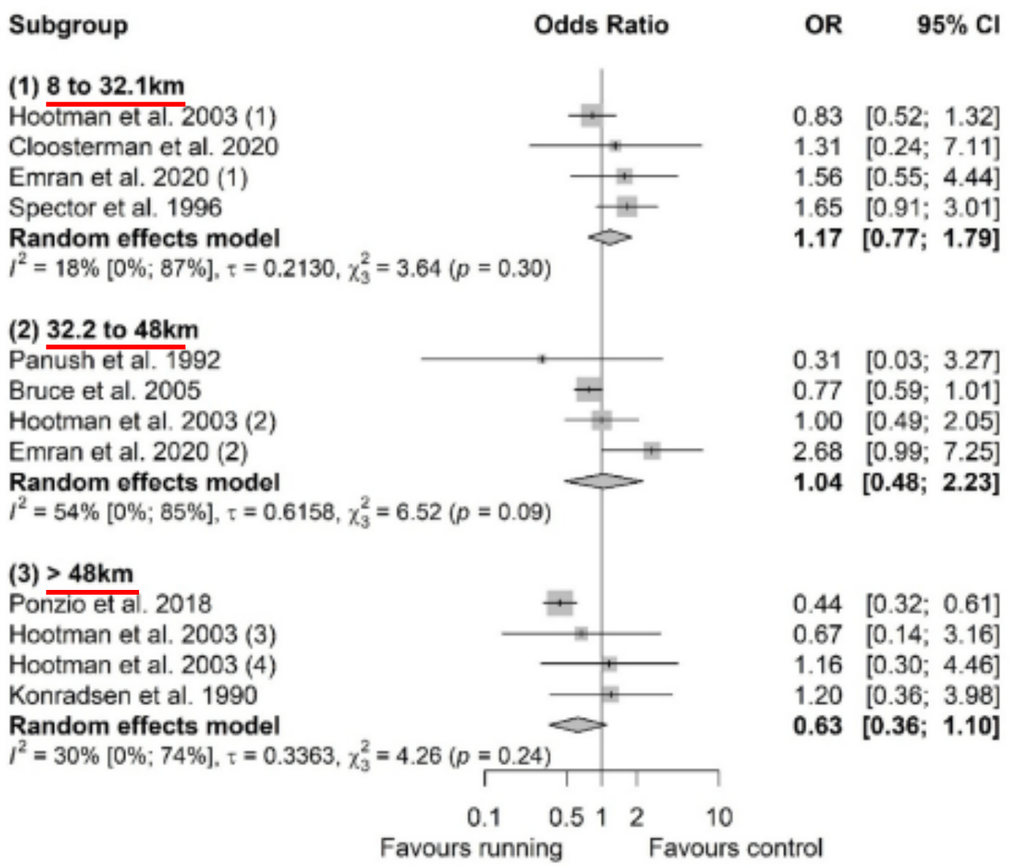

Fig. 3. Forest plot demonstrating the standardized mean difference in disability scores in habitual runners compared with controls. Results of meta-analysis are not displayed here, given the high likelihood of re-sampling of participants within these studies. SD = standard deviation, SMD = standardized mean difference, CI = confidence interval.

"It is unclear whether running volume is associated with increased risk of osteoarthritis."

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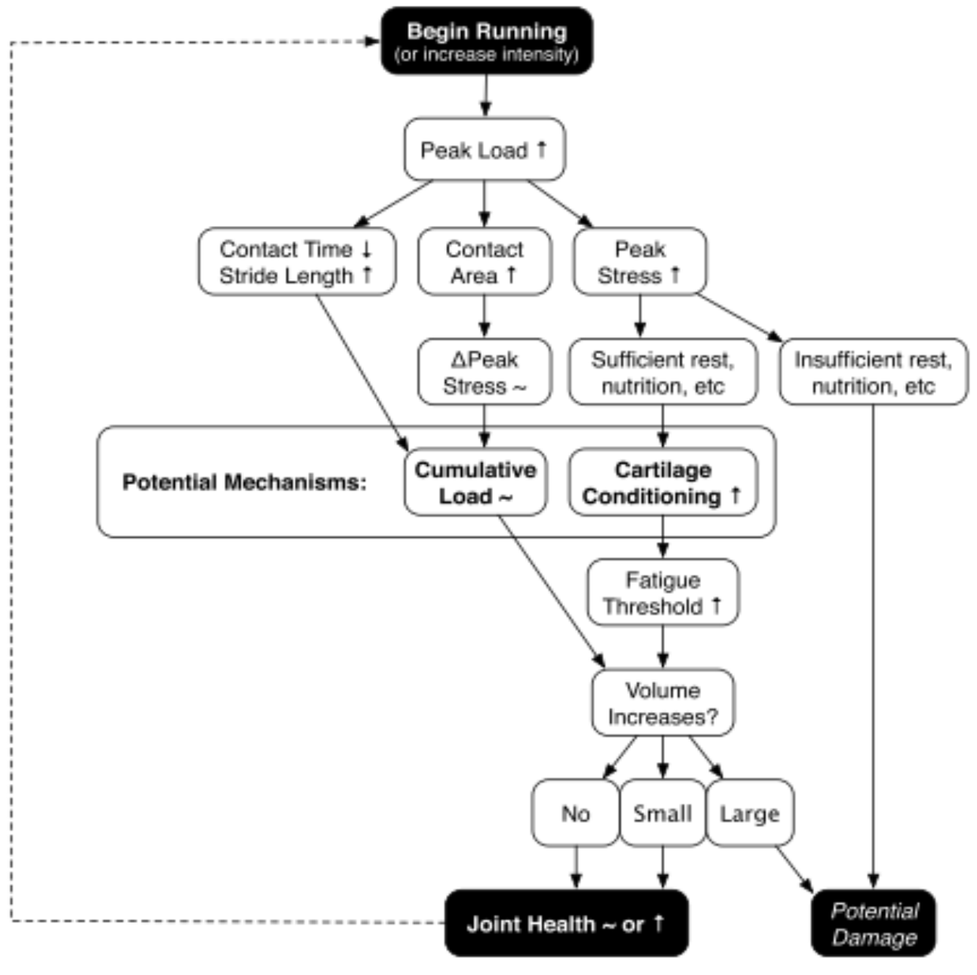
Joint Loading in Runners Does Not Initiate Knee Osteoarthritis

Ross H. Miller
Department of Kinesiology, University of Maryland, College Park, MD
Neuroscience & Cognitive Science Program, University of Maryland, College Park, MD

Exer Sports Sci Review 2017

- OA – complex balance of anabolic and catabolic cellular metabolism mediated by local mechanical, as well as systemic inflammatory factors
- *In vitro* – human articular cartilage fatigue life (number of loading cycles until fracture) decreases exponentially as peak stress per loading cycle increases
- If peak load increases peak cartilage stress, cartilage adapts to withstand this new stress given sufficient rest, nutrition, and absence of comorbidities



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Exer Sports Sci Review 2017

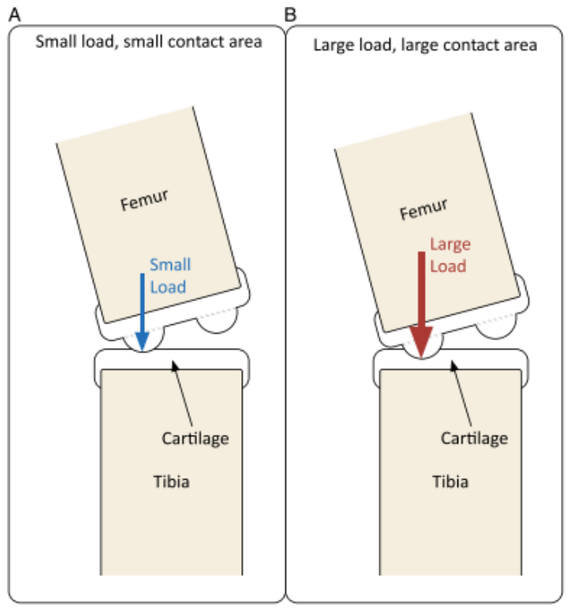

Figure 4. Cartoon of tibiofemoral contact mechanics with relatively low (A) and relatively high (B) compressive tibiofemoral load. Contact area of the articular surfaces increases with the greater load, reducing the effect of a greater load on cartilage stress (load/area).

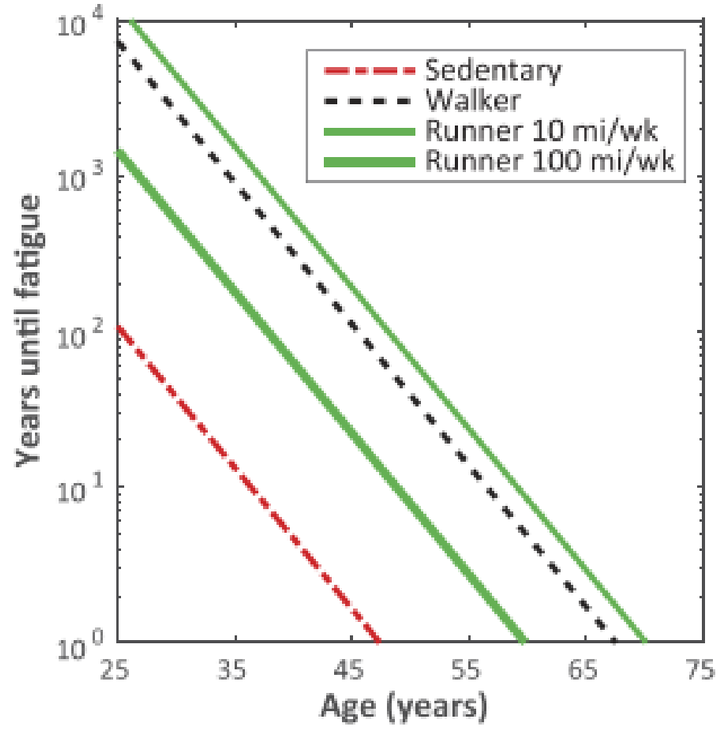

Figure 6. Years until cartilage fatigue predicted by the cumulative damage model for an individual who begins walking 10,000 steps per day (plus any indicated running mileage) at the age indicated on the horizontal axis while possessing different levels of cartilage conditioning: sedentary (dash-dotted 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).

- Peak load per stride in running is quite high but average load accumulated per stride is surprisingly low (total dose of running – magnitude/duration/frequency remains in question)
- Due to viscoelastic nature of cartilage, internal strains induced by high peak loads during running are relatively low
- Living cartilage in a healthy state adapts to withstand higher stresses

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Review

Is running good or bad for your knees? A systematic review and meta-analysis of cartilage morphology and composition changes in the tibiofemoral and patellofemoral joints

S.L. Coburn †, K.M. Crossley †, J.L. Kemp †, S.J. Warden † ‡, T.J. West †, A.M. Bruder †, B.F. Mentiplay †, A.G. Culvenor † *

Osteo & Cartilage 2022

SUMMARY

Background: The general health benefits of running are well-established, yet concern exists regarding the development and progression of osteoarthritis.

Aim: To systematically review the immediate (within 20 min) and delayed (20 min–48 h) effect of running on hip and knee cartilage, as assessed using magnetic resonance imaging (MRI).

Method: Studies using MRI to measure change in hip or knee cartilage within 48 h pre- and post-running were identified. Risk of bias was assessed using a modified Newcastle–Ottawa Scale. Percentage change in cartilage outcomes were estimated using random-effects meta-analysis. Certainty of evidence was evaluated with the Grading of Recommendations Assessment, Development and Evaluation tool.

Results: Twenty-four studies were included, evaluating 446 knees only. One third of studies were low risk of bias. Knee cartilage thickness and volume decreased immediately after running, with declines ranging from 3.3% (95% confidence interval [CI]: 2.6%, 4.1%) for weight-bearing femoral cartilage volume to 4.9% (95% CI: 4.43.6%, 6.2%) for patellar cartilage volume. T1ρ and T2 relaxation times were also reduced immediately after running, with the largest decline being 13.1% (95% CI: −14.4%, −11.7%) in femoral trochlear cartilage. Tibiofemoral cartilage T2 relaxation times recovered to baseline levels within 91 min. Existing cartilage defects were unchanged within 48 h post-run.

Conclusions: There is very low certainty evidence that running immediately decreases the thickness, volume, and relaxation times of patellofemoral and tibiofemoral cartilage. Hip cartilage changes are unknown, but knee changes are small and appear transient suggesting that a single bout of running is not detrimental to knee cartilage.

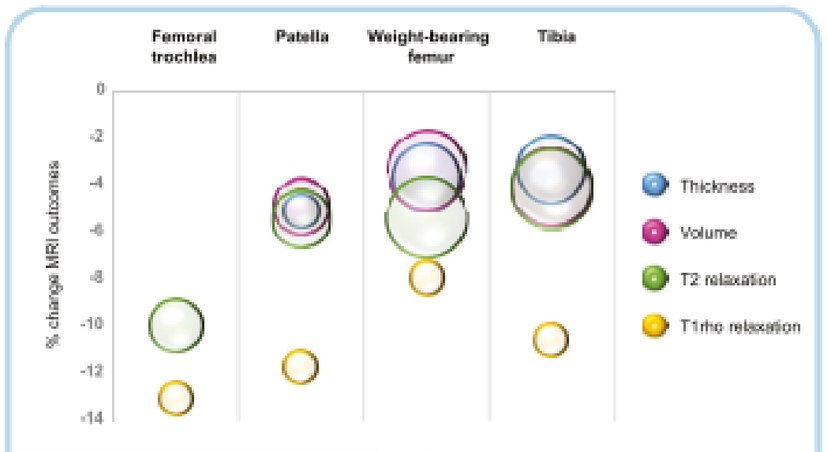

Fig. 5 Osteoarthritis and Cartilage

Summary of changes in MRI knee cartilage measures immediately after running.
Circle size represents number of participants in each analysis.

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Research article

The influence of different sports on cartilage adaptations: A systematic review

Bruno Trovato [a], Luca Petrigna [a], Martina Sortino [a], Federico Roggio [a,b,*], Giuseppe Musumeci [a,c,d]

Helion 2023

ABSTRACT

Molecular composition and structural adaptation are changes in the cartilage tissue after different stimuli. Sports activities with different loads at different angles, speeds, and intensities can modify the molecular composition of the articular cartilage, hence it is crucial to understand the molecular adaptations and structural modifications generated by sports practice and this review aims to synthesize the current evidence on this topic. A systematic search until July 2022 was performed on the database Medline, Pubmed, Scopus, and Web of Science with a collection of 62,198. After the screening process, the included articles were analyzed narratively. Thirty-one studies have been included in the analysis. From the results emerged that running, swimming, ballet and handball were not correlated with detrimental structural or molecular cartilage adaptation; instead, soccer, volleyball, basketball, weightlifting, climbing, and rowing showed signs of cartilage alteration and molecular adaptation that could be early predictive degeneration's signs. From the included studies it came to light that the regions more interested in morphological cartilage changes were the knee in athletes from different disciplines. In conclusion, different sports induce different cartilage modifications both at a molecular and structural level and it is important to know the risks correlated to sports to implement preventive strategies.

Effects of Running on the Development of Knee Osteoarthritis

An Updated Systematic Review at Short-Term Follow-up

Jaydeep Dhillon,* BS, Matthew J. Kraeutler,†# MD, John W. Belk,‡ BA, Anthony J. Scillia,§k MD, Eric C. McCarty,{ MD, Jeremy K. Ansah-Twum,‡ BS, and Patrick C. McCulloch,† MD

Investigation performed at Rocky Vista University College of Osteopathic Medicine, Colorado, USA

AJSM 2023

Background: Some studies have suggested that running increases the risk of knee osteoarthritis (OA), while others believe it serves a protective function.
Purpose: Perform an updated systematic review to determine the effects of running on the development of knee OA.
Study Design: Systematic review; Level of evidence, 4.

Methods: PubMed, Cochrane Library, and Embase databases for studies evaluating the effect of cumulative running on the development of knee OA or chondral damage based on imaging and/or patient-reported outcomes (PROs). The search terms used were “knee AND osteoarthritis AND (run OR running OR runner).” Patients were evaluated based on Xrays, MRIs, and PROs (presence of knee pain, Health Assessment Questionnaire-Disability Index, and KOOS).

Results: Seventeen studies (6 level 2 studies, 9 level 3 studies, and 2 level 4 studies), with 7194 runners and 6947 nonrunners, met inclusion. Mean follow-up time was 55.8 months in the runner group and 99.7 months in the nonrunner group. Mean age was 56.2 years in the runner group and 61.6 years in the nonrunner group.
There was higher prevalence of knee pain in the nonrunner group ($P < .0001$). Although 1 study found a significantly higher prevalence of osteophytes in the tibiofemoral (TF) and patellofemoral (PF) joints within the runner group, multiple studies found no significant differences in the prevalence of radiographic knee OA (based on TF/PF joint-space narrowing or KL grade) or cartilage thickness on MRI between runners and nonrunners ($P > .05$). One study found a significantly higher risk of knee OA progressing to total knee replacement among nonrunners (4.6% vs 2.6%; $P < .014$).
Conclusion: In the short term, running is not associated with worsening PROs or radiological signs of knee OA and may be protective against generalized knee pain.

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Gait analysis of patients with knee osteoarthiritis who can run versus cannot run

Takehiro Ohmi [a,*], Hiroki Katagiri [b,c], Masaki Amemiya [a,b], Koji Ikematsu [d], Midori Miyazaki [d], Hideyuki Koga [b], Kazuyoshi Yagishita [a]

Gait & Posture 2024

A B S T R A C T

Background: Many middle-aged and older adults participate in running to maintain their health and fitness; however, some have to stop running due to osteoarthritis-attributed knee pain. It was unclear whether gait biomechanics and knee physical findings differ between those who can and cannot run.

Research question: What are the gait and knee physical findings of patients with knee osteoarthritis who remain capable of running in comparison to those who are not capable of running?

Methods: This was a cross-sectional study, which recruited 23 patients over the age of 40 who had been diagnosed with knee osteoarthritis. Their knee joint ranges of motion and muscle strength, knee pain, and the maximum gait speed (walk as fast as possible) were measured. Knee alignment was calculated from X-ray images, and the knee joint extension angle and adduction moment during a self-selected gait speed were determined using motion analysis. Participants were divided into two groups—those able to run (n=11) and those unable to run (n=12). The measured and calculated outcomes were compared between groups, and logistic regression analyses of significantly different outcomes were performed.

Results: There were significant group differences in the maximum knee extension angle during stance phase ($p = 0.027$), maximum gait speed during the 10-m walk test ($p = 0.014$), knee pain during gait ($p = 0.039$) and medial proximal tibial angle by X-ray ($p = 0.035$). Logistic regression analyses revealed that the maximum knee extension angle during stance phase (OR: 1.44, 95%CI: 1.06¬1.94, $p = 0.02$) was a significant factor.

Significance: The ability to extend the knee during gait is an important contributing factor in whether participants with knee osteoarthritis are capable of running.

OA location not stated

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Review

Risk factors for running-related injuries: An umbrella systematic review

Clara Knierim Correia [a,*], Jean Marlon Machado [a], Fábio Hech Dominski [a], Marcelo Peduzzi de Castro [b], Heiliane de Brito Fontana [c], Caroline Ruschel [a]

J Sport Health Sci 2024

Abstract

Purpose: This umbrella systematic review (SR) of SRs and meta-analysis seeks to comprehensively synthesize existing literature to identify and consolidate the diverse range of risk factors contributing to running-related injuries (RRIs).

Methods: Systematic searches were conducted on June 28, 2023, across Web of Science, SPORTDiscus, Scopus, PubMed, and Cochrane Library. We included SRs, whether accompanied by meta-analyses or not, that focused on investigating risk factors for RRIs within observational studies. The methodological quality of the SRs was evaluated using the Assessing the Methodological Quality of Systematic Reviews II. To assess the extent of overlap across reviews, the corrected covered area metric was calculated.

Results: From 1509 records retrieved, 13 SRs were included. The degree of overlap between SRs was low (4%), and quality varied from critically low ($n = 8$) to low ($n = 5$). Two hundred seven outcomes assessed in 148 primary studies were identified as being associated with the occurrence of RRIs. The effect sizes of the associations for which risk measures were reported ($n = 131$) were classified as large ($n = 30$, 23%), medium ($n = 38$, 29%), small ($n = 48$, 37%) or no effect ($n = 15$, 11%). Running/training characteristics, health and lifestyle factors, along with morphological and biomechanical aspects, exhibit large effect sizes in increasing the risk for RRIs.

Conclusion: Drawing from the outcomes of the low-quality SRs and associations with large effect sizes, our findings indicate that running/training characteristics and health and lifestyle factors, as well as morphological and biomechanical aspects, are all implicated in elevating the risk of RRIs, emphasizing the multifactorial basis of injury incidence in running. Given the low quality and heterogeneity of SR, individual findings warrant cautious interpretation.

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Review

Risk factors for running-related injuries: An umbrella systematic review

Clara Knierim Correia [a,*], Jean Marlon Machado [a], Fábio Hech Dominski [a], Marcelo Peduzzi de Castro [b], Heiliane de Brito Fontana [c], Caroline Ruschel [a]

J Sport Health Sci 2024

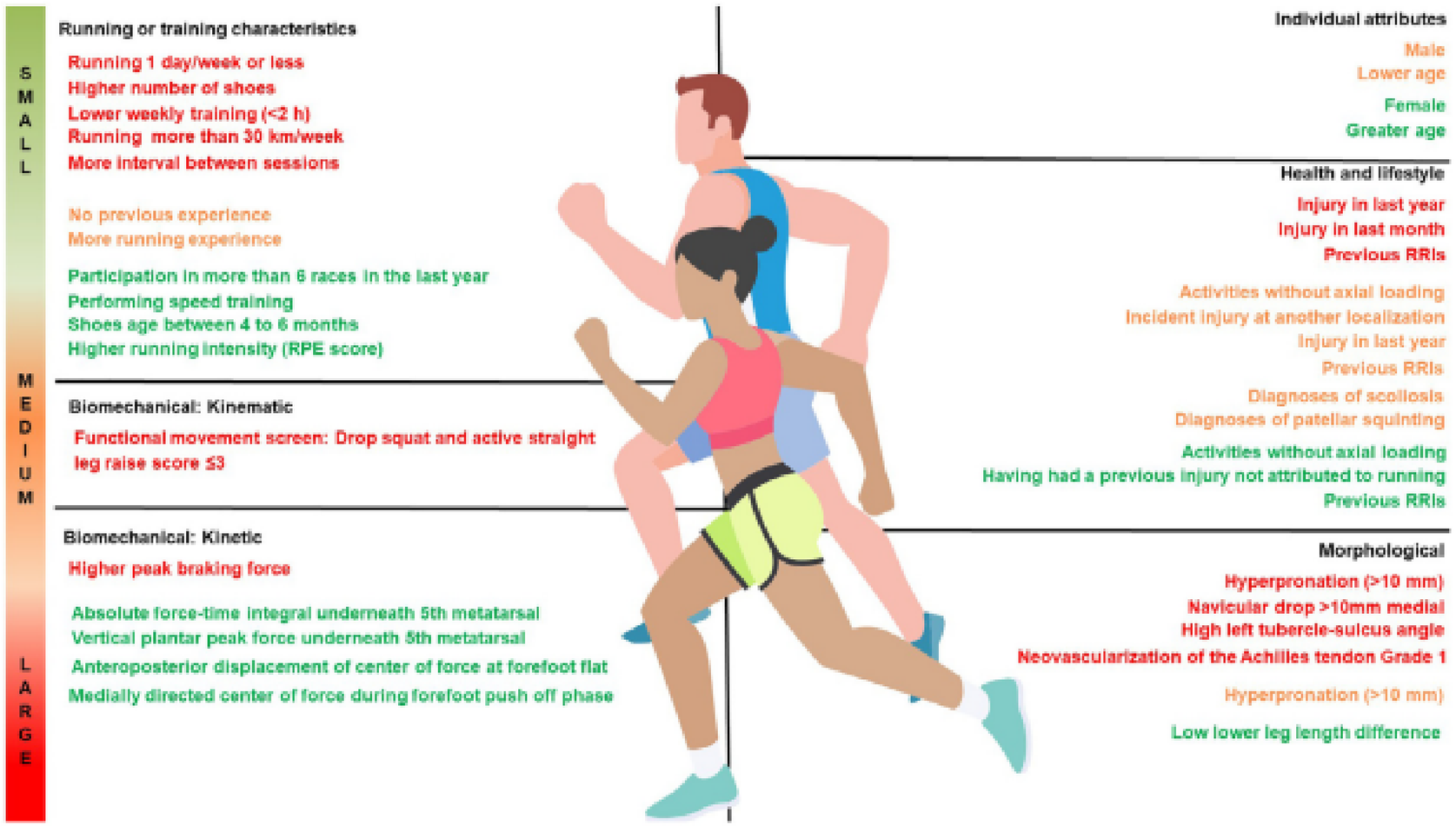

Fig 3. Overview of risk factors for RRIs considering only the systematic reviews with low quality, according to the classification of the effect size of the measures of risk (large, medium, and small effect sizes). Results are shown for studies that showed low quality ($n = 5$). RPE = rating of perceived exercise; RRIs = running-related injuries.

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DANNY VEZNAVER, MSc[5] • THORKELL SNAEBJORNSSON, MD, PhD[1,5,6] • KRISTIAN SAMUELSSON, MD, PhD[1,5,6]
EDUARD ALENTORN-GELI, MD, PhD[3]

Does Playing Football (Soccer) Really Increase the Risk of Knee Osteoarthritis? A Systematic Review and Meta-analysis

J Orthop Sports Phys Ther
2024

OBJECTIVE: To evaluate the relationship between football (soccer) participation and tibiofemoral knee osteoarthritis (OA), considering the influence of competitive level and previous knee injuries.

DESIGN: Etiology systematic review with meta-analysis.

LITERATURE SEARCH: PubMed, Embase, AMED, and Cochrane were searched for relevant publications.

STUDY SELECTION CRITERIA: Studies of football players that included a control group consisting of mainly sedentary nonfootball players, and the relationship of knee OA, were considered. The studies had to report radiographically verified knee OA and specify football activity.

DATA SYNTHESIS: Eleven studies, involving 1805 football players and 4022 control individuals were included. Subgroups consisting of data regarding level of play and previous injuries were also synthesized.

RESULTS: The overall prevalence of knee OA among football players was increased among professional and recreational players, compared with controls. When knee injuries were excluded, there was no difference in knee OA between football players and controls (OR = 1.25; 95% CI: 0.61, 2.54). Football players with a previous knee injury had a greater risk of knee OA when compared with football players with no history of previous knee injury (OR = 4.16; 95% CI: 1.97, 8.77).

CONCLUSION: Football players were at increased risk of knee OA. However, after excluding participants with a history of previous knee injury, there were no differences in knee OA between football players and controls. Previous knee injury was important for developing knee OA. Playing football, in the absence of major knee injuries, did not increase the risk of knee OA. *J Orthop Sports Phys Ther 2024;54(5):328-339. Epub 26 February 2024. doi:10.2519/jospt.2024.12029*

KEYWORDS: *knee, knee injuries, knee osteoarthritis, risk factors, soccer*

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Do the General Public and Health Care Professionals Think That Running Is Bad for the Knees? A Cross-sectional International Multilanguage Online Survey

Jean-Francois Esculier,* PT, PhD, Manuela Besomi, PT, PhD, Danilo de Oliveira Silva, PT, PhD, Samuele Passigli, BSc, PT, Michael Skovdal Rathleff, PT, PhD, Marienke Van Middelkoop, PhD, Christian Barton, PT, PhD, Michael J. Callaghan, PT, PhD, Matthew S. Harkey, PhD, ATC, Alison M. Hoens, BSc, PT, Natasha M. Krowchuk, BSc, and Anthony Teoli, MScPT

Investigation performed at University of British Columbia, Vancouver, Canada

Orthop J Sports Med 2022

Background: Running is a popular sport with widely recognized health benefits. Given the high rates of knee injury in runners and the growing prevalence of knee osteoarthritis (KOA), it may be useful to assess perceptions about running and knee joint health.

Purpose: The objectives of this study were to (1) explore and compare the perceptions of the general public (PUB) and health care professionals (HCPs) on the topic of running and knee health and (2) explore recommendations about running and knee health provided by HCPs.

Study Design: Cross-sectional study.

Methods: We conducted an online survey between June 18 and October 1, 2020. The questionnaire included questions on running and knee health, and HCPs were asked about their typical recommendations and level of confidence in providing recommendations on the topic. Perceptions (proportions) were compared between the PUB and HCPs using the chi-square test.

Results: In total, 4521 responses (PUB, n = 2514; HCPs, n = 2007) were analyzed. A greater proportion of HCPs perceived regular running as healthy for knees (86% vs 68%; $P < .001$). More of the PUB than HCPs ($P < .001$) believed that running frequently (29% vs 13%), long distances (54% vs 45%), and on hard surfaces (60% vs 36%) increased the risk of developing KOA. Running for those with KOA was perceived by the PUB as posing an increased risk of getting more knee pain (48%) and needing joint replacement surgery (38%), more so than by HCPs (26% and 17%, respectively). The majority of HCPs reported being relatively confident in providing evidence-based recommendations about running and knee health and mostly recommended that runners with KOA modify training parameters instead of quit.

Conclusion: More HCPs perceived running as healthy for knees when compared with the PUB. Most HCPs felt confident in providing evidence-based recommendations about running and knee health.

Keywords: osteoarthritis; physical activity; questionnaire; joint

Summary

- Heterogenous nature of OA makes it difficult to study ideal, personalized treatments
- Joint loading – appears to be a ‘U-shaped’ response
- Basic science and translation to humans – acute vs chronic joint loading
- Clinical studies
  - Higher association with sports such as soccer
  - Number of studies and analyses suggest running NOT harmful to the weight-bearing joints
  - Key may be ‘dose’ of joint loading

- Identifying patient phenotypes and matching to molecular endotypes offers promise for more personalized therapies

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