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Review

Exercise for knee osteoarthritis pain: Association or causation?

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SUMMARY

Exercise is universally recommended as a primary strategy for the management of knee osteoarthritis (OA) pain. The recommendations are based on results from more than 100 randomized controlled trials (RCTs) that compare exercise to no-attention control groups. However, due to the inherent difficulties with adequate placebo control, participant blinding and the use of patient-reported outcomes, the existing RCT evidence is imperfect. To better understand the evidence used to support a causal relationship between exercise and knee OA pain relief, we examined the existing evidence through the Bradford Hill considerations for causation. The Bradford Hill considerations, first proposed in 1965 by Sir Austin Bradford Hill, provide a framework for assessment of possible causal relationships. There are 9 considerations by which the evidence is reviewed: Strength of association, Consistency, Specificity, Temporality, Biological Gradient (Dose-Response), Plausibility, Coherence, Experiment, and Analogy. Viewing the evidence from these 9 viewpoints did neither bring forward indisputable evidence for nor against the causal relationship between exercise and improved knee OA pain. Rather, we conclude that the current evidence is not sufficient to support claims about (lack of) causality. With our review, we hope to advance the continued global conversation about how to improve the evidence-based management of patients with knee OA.

Introduction

Exercise is universally recommended as a primary strategy for the management of knee osteoarthritis (OA) pain.[1,2] These recommendations are largely based on more than 100 randomized controlled trials (RCTs) in various healthcare settings across the globe reporting that exercise is superior to no-attention control groups for self-reported pain.[3] However, it has been very challenging to conduct OA exercise trials that would fulfill the main requirements for identification of efficacy of the intended main therapeutic element(s) of the intervention. The main reasons include the complexity of the intervention being assessed without a clearly defined active treatment component, the self-reported nature of the outcome assessment, in connection with challenges in implementing and maintaining blinding. The importance of these challenges has been highlighted by recent studies with active attention and open-label placebo as comparators[4,5] that sparked a debate about the efficacy of exercise on knee OA pain.[6,7] Further, lack of participant blinding in RCTs leads to substantial overestimation of effects for patient-reported outcomes.[8] Both lack of blinding and use of patient-reported outcomes are inevitable premises when investigating the effect of exercise on knee OA pain. In this light, we believe that there is a need for a critical review of the evidence supporting a causal relationship between exercise and knee OA pain relief.

The starting point is that "perfect" RCTs usually provide sufficient evidence for causation. Unfortunately, such “perfect” RCT would be extremely challenging to implement in the field of exercise as treatment for knee OA pain, and it has not yet been achieved. Therefore, application of other means to help answering the causal question should be considered.

A classical framework for causal inference is the Bradford Hill considerations of causation that were proposed in 1965 by Sir Austin Bradford Hill.[9] The considerations were prompted by situations of environmental exposures where experimental evidence is impossible or unethical to produce. Hill is one of the scientists most credited with uncovering the causal link between smoking and lung cancer (notably without experimental evidence). Importantly, the Bradford Hill viewpoints are not formal criteria, but rather a set of considerations that could structure discussions about causation. Bearing in mind the imperfectness of the experimental evidence supporting a causal link between exercise and knee OA pain improvement, we find the Bradford

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Hill framework a useful tool for an analysis of a potential causal link between exercise and knee OA pain relief.

Accordingly, the purpose of this paper is to review the current evidence supporting a causal link between exercise and pain relief in knee OA, using the Bradford Hill's considerations of causation.

Hill's considerations

Hill's considerations include aspects of observational evidence of an association that should be considered before deciding that causation is the most likely interpretation: *Strength of association, Consistency, Specificity, Temporality, Biological Gradient (Dose-Response), Plausibility, Coherence, Experiment,* and *Analogy* (Table I). As the available evidence on exercise and knee OA pain that we consider consists of RCTs, we have omitted two considerations as they are satisfied by default in RCTs: *Temporality* (exposure must precede outcome temporally) and *Experimental* (the existence of RCTs). While the *Temporality* consideration supports the existence of a causal relationship between exercise therapy and improved knee OA pain, the *Experimental* consideration only provide limited support due to the imperfectness of the experimental evidence.

Strength of association

Hill's first consideration, '*Strength of association*', emphasizes that strong associations can mitigate doubts about a proclaimed exposure-outcome relationship. However, Hill also emphasized that "*We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so*."

In 1999, one of the first systematic reviews on exercise (mainly against no treatment) for knee OA pain relief included 7 studies with pain as an outcome.[10] Meta-analysis was not performed, but the individual study effect sizes (ES) ranged from 0.07 (no effect) to 0.58 (moderate) in favor of exercise. In 2001, the first Cochrane review reported a pooled ES of 0.39 (95% confidence interval [CI] 0.30 to 0.47) from 17 studies.[11] In the 2008 update (32 studies), the ES was 0.40 (95% CI 0.30–0.50).[12] In 2014, a meta-analysis of 47 studies found an ES of 0.50 (95% CI 0.39–0.62),[13] confirmed by the 2015 Cochrane review (ES 0.49, 95% CI 0.39–0.59) from 44 studies.[3] This was stated to be equivalent to a reduction of 12 points a 0–100 pain scale, surpassing minimal important between-group differences (MID) for pain scales (MID range 8.4–20.0).[14,15] In an individual participant data meta-analysis,[16] including 31 studies, the estimated overall effect of exercise was 6.4 points (95% CI 4.3–8.5) on a 0–100 scale, which is below the above-mentioned minimal MIDs. A recent (2024) very comprehensive meta-analysis covering 202 comparisons[17] showed an overall ES of 0.19 (95% CI 0.07–0.31). It is important to note that the reported ESs include contributions from placebo effect and contextual factors, as wells as bias from lack of blinding in combination with self-reported outcome (pain).

Altogether, the average strength of association between exercise and pain relief is weak, as judged by the small to moderate pooled ESs produced in meta analyses of RCTs over the last 25 years.

Consistency

Hill's consideration '*Consistency*' relates to replicability, i.e., if an association is consistently found across independent studies *performed by different persons, in different places, circumstances and times*. Replication of the association in various studies makes causation more likely.

It is evident from the many meta analyses[3,11–13,18] that the association between exercise and knee OA pain has been investigated in independent studies using a wide variety of exercise types, pain assessment tools and study durations and the ES reported in meta analyses are average effects from all these different regimes. However, there are very few instances where the same exercise intervention (with defined structure, dosing, and timing) has been studied in more than one RCT. This precludes assessment of consistency with respect to the same exercise regime being implemented in different settings. Furthermore, in the available evidence the details of the exercise interventions are often not described with sufficient detail to allow for replication.[18]

A closer look on the evidence reveals that in a large proportion of the individual studies that underlie the meta analyses, the uncertainty of the estimate (95%CI) includes a potential benefit in favor of the control group (defined as ES≥0.20): In the earliest Cochrane review,[11] 4 out of 17 studies (≈25%) the 95% CIs of the effect estimates included ESs favoring the control group. In the updated Cochrane review from 2015[3] this number increased to 15 out of 44 studies (≈34%), in the 2014 meta-analysis by Juhl et al.,[13] 24 of 47 studies (≈51%), and in the 2024 review[17] 167 out of 202 comparisons (≈83%) included potential benefit for the control group in the effect estimate uncertainty measures. These studies must be considered as inconclusive and do not support that the association between exercise and knee OA pain reduction has been consistently observed. In other words, although the pooled average estimates of treatment effect are similar across meta analyses, the individual study estimates are highly variable, which is substantiated by the heterogeneity statistics in the meta analyses (I^2)

Bradford Hill's considerations	Explanation
Strength of association	Effect size. Strong association makes causality more likely. However, a weak association does not mean that there is not a causal effect.
Consistency	Reproducibility. Replication of the association in more than one study makes causation more likely.
Specificity	Causation becomes more likely if the association between exposure and outcome is specific without other reasonable explanations.
Temporality	The effect must occur after the cause to imply causation.
Biological Gradient	Dose-response. If a greater exposure leads to greater response in the outcome, it can support causation. Reversibility of the association can support causation.
Plausibility	If the association can be explained by existing models (i.e., theories about mechanism(s) of action) it increases likelihood of causation.
Coherence	Coherence association relates to the interpretation of the data in relation to what is already known about the outcome and exposure, the association should not conflict with current knowledge about the disease and the exposure.
Experiment	If the association has been demonstrated in an experiment, it can support causation.
Analogy	Indirect evidence. If the same association has been observed for other related outcomes it may support causation.

Table I

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A summary of the Bradford Hill viewpoints.

that range from 29% to 97%.[3,11–13,17,18] Further, one of the meta analyses[13] included a 95% predictive interval of the ES ranging from −0.19 to 1.20, suggesting a wide range of potential outcomes in future studies (from negative effect (ES −0.19) to a large effect (ES 1.20).

While there are several studies done under different circumstances, the least variable conditions of the studies are lack of blinding and placebo control, which are important factors in the interpretation of the evidence. When exercise (in different types and settings) is compared to other types of controls (attention controls, low-dose exercise, sham, open-label placebo), it typically does not provide any pain relief above that in the control group.[4,5,19,20]

In summary, the association between a specific exercise regime and knee OA pain relief has typically not been replicated. However, the control conditions in the RCTs are consistent while significant variability exists in individual study estimates.

Specificity

Hill's third consideration "*Specificity*" refers to the specific association between exposure and outcome and can be assessed by answering the question "Are there no other reasonable explanations than involvement of the factor in question?". Causation becomes more likely if the outcome occurs with no other reasonable explanation than the exposure.

There are other reasonable explanations for the observed association between exercise and knee OA pain relief than exposure to exercise. With the predominant use of no attention control groups, the self-reported nature of the outcome assessment, and the inherent problems with implementing and maintaining blinding, placebo response and contextual factors are likely unequally distributed between treatment and control groups. This results in biased effect estimates that include both the placebo response and response related to contextual factors. A generic estimate of the placebo effect on self-reported pain has been suggested to be 6.5 (95% CI 3.6–9.6) on a 0–100 scale,[21] which in a crude indirect application represents between 50% and 100% of the above estimates from studies with no attention comparators groups.[3,16]

Additionally, the term 'exercise' is not specific as it encompasses various types of exercise (e.g., strength training, aerobic exercise, and so-called neuromuscular exercise) with different intensities, frequencies, and durations. Importantly, the different exercise types may have distinct physiological effects (e.g., enzymatic, neural, structural, and more). The responses are also quite specific to the exercise modality: greater muscle strength and muscle hypertrophy with strengthening exercise; improved cardiopulmonary fitness and muscle capillarization with aerobic exercise. It would not be unreasonable to conjecture that some of these specific responses could be stronger associated with pain relief than others. However, it has not been possible to discriminate between the different types of exercise in terms of their effect on knee OA pain.[3,13] It thus seems that the known specific responses to different exercise types are unrelated to the pain relief associated with exercise.

In summary, exercise is not the only reasonable explanation for the observed improvements in knee OA pain, and different specific exercise types seemingly yield similar average effect sizes altogether suggesting an unspecific association.

Biological gradient (Dose-Response)

This consideration involves assessment of biological gradients or a dose-response relationship. If the size of knee OA pain relief increases incrementally as the dose of the exercise increases, it provides support for a causal relationship. Reversibility of the association, e.g., the pain is worsened if exercise is stopped augments the likelihood of causation.

Most of the studies have not been designed specifically for assessment of dose-response relationships in exercise for knee OA. Such studies are challenging as there is no consensus on what dose (of which modality) of exercise that is necessary for inducing therapeutic effect. A 2015 Cochrane review found no advantage of high-intensity over low-intensity exercise for knee OA pain improvement.[22] The START and VIDEX trials compared high and low-intensity strength training.[4,23] Similarly, the multicentre SWENOR study compared high and low-dose medical exercise therapy.[20] None of these studies found differences between exercise intensities in the response on knee OA pain. In a systematic review of exercise for knee OA[24] there were no essential differences in the pain responses between studies that applied exercise programs that adhered to the American College of Sports Medicines definition of strength training and studies that did not, while there difference was clear for the muscle strength gain.

Given that knee OA is a chronic condition, and that exercise presumably has no curative effects on knee OA, reversibility of pain should be expected once exercise is stopped or paused. In the 2015 Cochrane review,[3] the benefit of exercise on knee OA pain declined two to six months after exercise (ES 0.24, 95% CI 0.14–0.35) and was lost after 6 months post exercise (ES 0.08, 95% CI −0.15 to 0.30), suggesting reversibility of the initial pain response to an exercise intervention.

In summary, while some attempts have been made, so far, no study has demonstrated a dose-response relationship between exercise and knee OA pain relief. However, the association seem to be reversible, in that the initial pain relief associated with an exercise intervention does seem to taper when exercise is stopped.

Plausibility

Plausibility can be considered by assessing whether the association can be explained in the presence of existing biological or social models (i.e., theories about mechanism(s) of action).

Some theories have been proposed. For example, stronger muscles have been proposed to provide unloading of the knee joint that in turn should lead to less pain. However, when compared to no treatment, strength training did increase muscle strength and improve pain but did not lead to unloading of the knee joint during walking.[25] Similarly, neuromuscular exercise is promoted as a means to correct unfavorable gait mechanics, but gait seems to be unaffected after 12 weeks of neuromuscular exercise compared to no treatment despite benefits on pain.[26] Aerobic exercise has been reported to reduce systemic inflammation in non-knee OA populations[27] which provides a plausible mode of action of aerobic exercise for knee OA pain. However, a systematic review of studies of aerobic exercise in knee OA populations concluded that the applied aerobic exercise interventions in general did not decrease the systemic inflammation (but improved pain)—likely caused by suboptimal exercise dosage.[28] In a diet and exercise intervention, changes in inflammatory markers were suggested to be 'medium' size mediators of knee OA pain relief independently of changes in BMI,[29] but the combined intervention precludes firm assertions about exercise. Further, a recent individual participant data meta-analysis investigated if changes in muscle strength, proprioception, and range of motion mediated the effects of exercise on knee OA pain.[30] The authors concluded that mechanisms of action of exercise for knee OA remains a black box as 98% of the effectiveness of exercise remained unexplained.

It is important to note that pain is not only coupled to biological or pathophysiological processes. Pain is an experience that are affected by a range of factors including cognitive, social, and psychological factors.[31] It is plausible that these factors are a source of pain relief associated with exercise and the mechanisms may be outside

Bradford Hill's considerations	Exercise for knee OA pain
Strength of association	The association is weak, as judged by the consistently small to moderate effects sizes and includes the effects of placebo.
Consistency	The association has typically not been replicated in several studies evaluating the same exercise program. Up to ≈ 50% of individual studies are inconclusive. There exist multiple studies with a variety of exercise regimes.
Specificity	Exercise is not the only reasonable explanation for the observed improvements in knee OA pain associated with exercise. Other reasonable explanations include placebo effect, and contextual factors, for example related to lack of blinding in combination with self-reported outcome measures.
Temporality	All existing RCTs fulfill this consideration, as the exercise intervention precedes the pain outcome.
Biological Gradient	Dose-response relationship does not seem to exist, but the effect seems to be reversible.
Plausibility	It is possible to neither confirm nor refute the existence of biological, psychological, cognitive, or social mechanisms of action, but at present the mechanism(s) of action remains unidentified.
Coherence	The relationship between exercise and knee OA pain relief is neither consistent nor conflicting with the current body of knowledge about knee OA pain, as the current knowledge of fundamental disease mechanisms, including OA pain, have few clinically useful implications for the design and delivery of exercise interventions.
Experiment	Experimental evidence exists in the form of RCTs, but these are "imperfect", and only support of causation partly.
Analogy	The evidence is equally imperfect for similar conditions. Causation by analogy is not valid.

Table II Osteoarthritis and Cartilage

A summary of the Bradford Hill considerations as related to the possible causal relationship between exercise and knee OA pain relief.

the biomedical paradigm.[32–34] This could imply that the pain relief is not necessarily related to the exercise itself but to the social and cultural aspects including the context and contemporary socio-cognitive biases, such as the ritual, culture, social acceptability, expectations, attention from caring and enthusiastic clinicians, and much more. This would also align with current knowledge about the importance of context and meaning.[35]

It is also very important to note that our knowledge of the human biology, exercise physiology, knee OA pathology, sociology, and psychology (and their interactions) is constantly evolving. As Bradford Hill stated, '*It will be helpful if the causation we suspect is biologically plausible, though this is a feature we cannot demand. What is biologically plausible depends on the biological knowledge of the day*.'[9]

In summary, it is neither possible to confirm nor refute the existence of biological, psychological, cognitive or social mechanisms of action, but at present the mechanism(s) of action remains unidentified.

Coherence

Considering coherence of an association relates to the interpretation of the data in relation to what is already known about the disease and exposure. In the present context this means that the association between exercise and knee OA pain relief should not conflict with what we know about the development of knee OA pain or exercise.

Although the knowledge about knee OA illness and disease mechanisms have increased significantly over the last decades, many fundamental aspects of knee OA and knee OA pain mechanisms remain undiscovered. In that sense, an association between exercise and knee OA pain relief is neither consistent nor conflicting with current knowledge of knee OA.

In attempts to increase the specificity and effectiveness of knee OA treatment, subgroups of knee OA patients that may potentially respond differently to treatments have been suggested. These include different pain types such as centralized vs peripheral pain, or intermittent vs constant pain, inflammatory knee OA, post-traumatic knee OA, and more.[16,36] However, very few exercise trials on specific clinical phenotypes exist. A recent trial suggests no effect of subgroup-specific exercise over usual non-stratified exercise.[37] Further, attempts to identify factors or patient characteristics associated with a more favorable pain response to exercise have been largely negative with the exception of a high level of pain and poor physical function at the start of the intervention[16] and baseline use of analgesics.[38,39]

In summary, the relationship between exercise and knee OA pain relief is neither consistent nor conflicting with the current body of knowledge about knee OA pain, as the current knowledge of fundamental disease mechanisms, including OA pain, have few clinically useful implications for the design and delivery of exercise interventions.

Analogy

The analogy consideration suggests that if a similar association exists in similar conditions, it may support causation. However, analogies should rely on solid and scientifically established true causal relationships to be valid.

Exercise is recommended as a pain-relieving treatment option for several similar conditions of which hip OA is the most imminent (in fact, the Cochrane reviews also pertains to hip OA). Other conditions with similarly poorly understood pathogeneses are also on the list, such as patellofemoral pain syndrome, low back and neck pain, and a range of shoulder and elbow pathologies, not to mention soft tissue conditions (e.g., tendinopathies and myopathies). While exercise also is seemingly effective in reducing pain in these conditions, the evidence is as imperfect as for knee OA; the studies are also characterized by lack of blinding in combination with self-reported outcome measures, and no adequate placebo/sham control groups.

While these analogies seemingly could support causation in knee OA, none of the associations have been proven causal.

Summary

In summary, when applying Hill's nine considerations to the current body of evidence related to exercise for knee OA pain, only a few supports a causal relationship between exercise and improvements in knee OA pain (Table II).

Concluding remarks

The starting point of this evidence review was that the experimental evidence (RCTs) when it comes to exercise therapy for knee

OA pain is imperfect. Although there are many studies, they do not constitute a robust platform from which one can call out causation. Our look on the evidence through the considerations of Bradford Hill has neither brought forward indisputable evidence for nor against the causal relationship between exercise and improved knee OA pain. Rather, we conclude that the current evidence is not sufficient to support claims about causality. Importantly, this does not infer the opposite. What our application of the Bradford Hill considerations on the current evidence hopefully can do, is to help accept the uncertainty of the evidence and to stimulate the exercise therapy community in OA to identify ways forward in the continued pursuit of better care and optimized resource usage in a patient population with many unmet needs that continues to grow.

It is important to emphasize that the Bradford Hill considerations should be viewed as guidelines and not a set of criteria that must be satisfied for a causal relationship to exist. By consequence, it is not possible to articulate specific limitations for all viewpoints to be overcome in order to appraise more confidently the presence or absence of a causal relationship. However, there are possible ways to get closer to an answer to the causal question. For example, the specificity of different exercise interventions could be explored in studies designed specifically for this (comparative effectiveness). Also, the existence of a biological gradient could be further explored in studies specifically designed for the capture of a potential dose-response relationship. Basic and translational science efforts in detecting possible modes of actions of (various types of) exercise in the modulation of pain and nociception would be highly valuable contributions in the way forward. Finally, the expansion of knowledge about fundamental disease and pain mechanisms in (knee) OA would aid the identification of more well-defined patient populations for which various exercise types may be targeted or dissuaded. In the clinical science, the major challenges with blinding and the use of patient-reported outcomes for pain will probably linger and continue to hinder isolation of the true effects of exercise from that of placebo and context.

The current scientific literature about exercise as treatment of knee OA pain has informed clinical guidelines and recommendations across the world. These all point in the same direction with unconditional recommendations of exercise as first line treatment of knee OA. Although the existing evidence suggests that exercise is not harmful for knee OA, and has beneficial effects on the overall health, the evidence about effectiveness on knee OA pain is very imperfect. The universal guideline consensus fails to acknowledge this, which also amplifies the belief in a causal relationship. This carries the risk of resources and attention being taken from further scientific endeavors into finding truly effective treatments (potentially including some exercise types or regimes) and instead given to widespread implementation of exercise programs and concepts with biased small-to-moderate ESs under the impression that causality has been established with no lingering uncertainties. Without acceptance of uncertainties, there are few incentives for further scientific exploration and gain of new knowledge, which in turn may prove detrimental for patient management.

Still, it is important to emphasize that exercise, physical activity, and non-sedentary lifestyle is strongly associated with a reduced risk of premature mortality and major non-communicable diseases.[40] Therefore, all people, including those with knee OA, should be encouraged to lead physically active lives. While we do encourage people with knee OA to exercise for the overall health benefit and prevention of comorbidities, we conclude that the existing evidence is not sufficient to infer or rule-out causality between exercise and improvements in knee OA pain. We encourage the scientific exercise community in OA to continue the advancement of knowledge to improve the evidence-based management of patients with knee OA.

Bradford Hill summarizes this point nicely in his speech to the Royal Society of Medicine in 1965:

> *"All scientific work is incomplete. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time".*

Contributions

M Henriksen, J Runhaar and M Englund conceived the idea behind the work that was refined following inclusion of A Turkiewicz in the discussion. M Henriksen drafted the first versions of the manuscript. All authors read and critically revised the manuscript, and all authors approved the final manuscript and submission of the article.

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Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form and declare: no financial interests with any organization that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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