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Osteoarthritis and Cartilage

A lifespan approach to osteoarthritis prevention☆

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SUMMARY

Prevention is an attractive solution for the staggering and increasingly unmanageable burden of osteoarthritis. Despite this, the field of osteoarthritis prevention is relatively immature. To date, most of what is known about preventing osteoarthritis and risk factors for osteoarthritis is relative to the *disease* (underlying biology and pathophysiology) of osteoarthritis, with few studies considering risk factors for osteoarthritis *illness*, the force driving the personal, financial and societal burden. In this narrative review we will discuss what is known about osteoarthritis prevention, propose actionable prevention strategies related to obesity and joint injury which have emerged as important modifiable risk factors, identify where evidence is lacking, and give insight into what might be possible in terms of prevention by focussing on a lifespan approach to the *illness* of osteoarthritis, as opposed to a structural disease of the elderly. By targeting a non-specialist audience including scientists, clinicians, students, industry employees and others that are interested in osteoarthritis but who do not necessarily focus on osteoarthritis, the goal is to generate discourse and motivate inquiry which propel the field of osteoarthritis prevention into the mainstream.

Introduction

Osteoarthritis (OA) is the most common joint condition. It affects more than 300 million people worldwide, suffering from pain and physical disability[1]. The total cost of OA in Western countries has been estimated to account for up to 2.5% of the gross domestic product, with hip and knee joint replacements responsible for the majority of direct medical costs[2]. In principle, all synovial joints can be affected by OA, but knee OA is clinically most prevalent.[3,4]

The *disease of OA* (Fig. 1) is characterized by pathological changes in joint tissues resulting in structural alterations of the articular cartilage and subchondral bone. Changes also occur in the menisci, ligaments, joint capsule, synovium, and periarticular muscles. Consequently, cartilage health, often measured by cartilage thickness, is a common therapeutic target of disease modifying interventions. Given that virtually no cartilage or meniscal collagen matrix replacement happens beyond skeletal maturity[5,6] there are inherent challenges to finding a cure, which may explain why to date no disease modifying drugs have been found effective in clinical trials[7]. Similarly, cartilage thickness loss is only associated with small increases in knee pain, suggesting that chondroprotection with the aim of decreasing pain may be extremely challenging and perhaps unachievable.[8]

The illness of OA (Fig. 1) is characterized by pain, functional impairments, muscle weakness, joint stiffness and reduced health-related quality of life[9]. The distinction between OA *disease* and *illness* is essential as it is OA *illness* that drives people to seek healthcare, take sick leave and retire early, and OA-related pain (*illness*), not structural changes (OA *disease*) that is associated with reduced time-to-mortality[10]. Therefore, it is the *illness*, as opposed to the *disease*, that needs to be avoided to reduce the enormous individual and societal burden of OA.

Given there is no cure for OA *disease*, and we only can offer persons who have OA *illness* modestly effective symptomatic treatments[11], the concept of prevention is attractive. The field of OA prevention is relatively young. To date, most of what is known

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Fig. 1 OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Common outcomes of osteoarthritis disease and osteoarthritis illness (two distinct but related concepts).

about preventing OA and risk factors for OA is relative to the *disease* of OA, with few studies considering risk factors for the *illness* of OA (Table I). Further, as our understanding of disease mechanisms grow it is important to acknowledge that OA may emerge as heterogenous disease that culminates in a common illness. Despite these important knowledge gaps, obesity and joint injury have emerged as strong and highly prevalent modifiable risk factors for OA *disease* and aspects of OA *illness* (Table I).

This narrative review will broadly summarize what is known about OA prevention, identify where evidence is lacking, propose actionable prevention strategies related to obesity and joint injury, and give insight into what might be possible by adopting a lifespan approach to preventing OA *illness* as opposed to preventing structural disease in the elderly. By targeting a non-specialist audience that is interested in osteoarthritis but who do not necessarily focus on osteoarthritis the goal is to propel the field of OA prevention into the mainstream.

What is osteoarthritis prevention

Osteoarthritis prevention can encompass a wide range of activities that aim to reduce risk factors (threats to joint health). These activities can either focus on preventing risk factors (*disease* or *illness*), or preventing progression to *disease* or *illness* once a risk factor(s) exists. Given that some risk factors are present early in life, these efforts can bridge the entire lifespan (Fig. 2).

Risk factors can be prevented by reducing exposure, or increasing resistance to associated hazards. These efforts can target an entire population (e.g., public health campaigns for healthy weight) or, in situations in which the prevention strategy is more complex or requires skilled administration, focus on groups with high natural exposure to a hazard (e.g., young persons at high risk of joint injury from sport participation).

Slowing down or halting the progression to OA after a risk factor exists involves early detection and diagnosis of OA *disease* or *illness*,

	Knee OA		Hip OA		Hand OA*	
	Disease	Illness	Disease	Illness	Disease	Illness
Modifiable risk factors						
Local muscle weakness	+[12]	+[12]	?	?	++[13]	?
Traumatic joint injury	+++[14–16]	?	?	?	?	?
Overweight/obesity	++[15,16]	+++[17]	+[18,19]	+[18,19]	+[13,20]	?
Altered joint shape and malalignment	+[21,22]	?	+++[23]	++[24]	?	?
High-impact sports	+++[25]	?	++[26]	++[26]	?	?
High occupational loading	++[27]	?	++[27,28]	++[27,28]	++[13,29]	?
Non-modifiable risk factors						
Structural changes**	++[30]	+[30]	?	?	?	?
Female sex	+[16]	?	?	?	++[29]	?
Older age	++[15,16]	?	?	?	++[13,29]	?
Genetic predisposition#	+[31]	++[32]	+[31]	++[32]	++[13,31]	?

+ Weak risk factor (OR 1 to 2); ++ Moderate risk factor (OR 2 to 3); +++ Strong risk factor (OR >3) based on available systematic reviews, meta-analyses or high-quality cohort study for incident OA; ? No meta-analysis or high-quality cohort study for incidence OA available; *Including thumb OA; #In combination; **Currently there is no evidence that structure can be modified.[7]

Table I OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Overview of highly prevalent risk factors for incidence of osteoarthritis disease and illness

Fig. 2 OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Opportunities for preventing osteoarthritis across the lifespan.

screening for additional risk factors, reducing risk factor recurrence (e.g., re-injury), and efforts that optimize or restore knee health and function. These strategies typically target 'exposed' individuals or groups.

The most important risk factors for osteoarthritis

There are a wide variety of internal (e.g., adiposity, sex, genetic predisposition) and external factors (e.g., occupational loading, joint injury) that increase one's risk for OA *disease* and *illness*. Some risk factors are systemic in nature (e.g., female sex/gender, adiposity), increasing the risk of OA *disease* and *illness* across multiple joints, while others are joint specific (e.g., joint shape, injury).

Before deciding what risk factor to target with a prevention strategy, four important features of the risk factor must be considered: 1) if and when it is most modifiable, 2) its prevalence, 3) the strength of its association with features of OA *disease* and/or *illness*, and 4) how easy it is to detect. A non-modifiable risk factor like sex or genetic predisposition is not amenable to intervention but can help identify high-risk populations in which other modifiable factors can be targeted. The prevalence of a non-modifiable risk factor is also important as it directly relates to the size of the high-risk target population. Despite being modifiable, some risk factors are more easily or appropriately influenced at certain life

stages. For example, as the majority of knee joint injuries occur in adolescence and early adulthood efforts to reduce injuries must be introduced during this period. Similarly, as childhood obesity is a determinant of adult obesity, activities to prevent childhood obesity may be more effective than efforts aimed at reversing obesity in adulthood. The strength of a risk factor's association with features of OA *disease* or *illness*, and its prevalence greatly influence the potential impact of a preventive strategy. Targeting a strong risk factor with a very low prevalence will prevent fewer OA cases than targeting a strong risk factor that is highly prevalent. However, at an individual level, risk factors with varying levels of strength may be relevant treatment targets. Finally, targeting risk factors that can be easily detected in diverse settings without sophisticated technologies or skilled personnel will result in a strategy more amenable to scale-up and widespread implementation.

Important targets for OA prevention based on prevalence and strength of the association with incident cases of OA *disease* and *illness* are summarized in Table I.

Although it seems obvious that interventions could either prevent the occurrence or positively affect modifiable risk factors, prevention of OA *disease* or *illness* has rarely been studied. The available evidence related to the risk factors summarized in Table I is discussed below with particular focus on knee OA, overweight/obesity and joint trauma given that the bulk of evidence lies in these areas.

Overweight/obesity and weight control/loss for osteoarthritis prevention

The current obesity epidemic is largely driven by the (over) consumption of processed, energy-dense food[33]. The purchase and consumption of food is an interplay between price, palatability and habits, influenced by culture and ethnicity. Given these strong interactions, it is unlikely that a single intervention will entirely prevent the development of overweight/obesity[34].

Currently, there is no direct evidence that preventing overweight/obesity will reduce the development of OA *disease* or *illness*. Yet knowing that being overweight/obese puts an individual at increased risk for knee OA *disease* (and other chronic diseases), as well as increases reporting of pain (i.e., OA *illness*) in the presence of structural changes[35,36], there is an urgency to accelerate efforts to prevent the incidence of overweight/obesity. Since obese children and adolescents are five times more likely to be obese in adulthood than those who were not obese[37], targeting overweight/obesity early in life is advocated. However, as 70% of obese adults were not obese in childhood or adolescence[37], targeting childhood obesity alone will not prevent all adult obesity.

Given the multidisciplinary nature of primary care it is an important setting for overweight/obesity prevention. However, a 2014 systematic review of treatments applicable to primary care that evaluated sustained (>12 months) weight gain prevention of normal body weight individuals identified only a single 1980s study[38]. Despite this knowledge gap, it is likely that a primary care intervention to prevent overweight/obesity would be a combined lifestyle approach that targets physical activity and diet, through behavioural change techniques (i.e., motivational interviewing and cognitive behavioral therapy)[39]. It may also be important to consider population-based approaches, which have shown to be more powerful for curbing other unhealthy habits (i.e., smoking and alcohol use) than individual approaches. Currently, population-based approaches to prevent overweight/obesity are advocated, but implementation across countries is limited.[39]

Another approach to prevent OA is weight loss in those free of OA *disease* or *illness,* but with surplus body weight. In 1996, Felson and colleagues estimated that a reduction in body weight (from obese to overweight or overweight to normal-weight) would reduce symptomatic knee OA development by 21% in men and 33% in women[40]. Still it took almost 20 years before the first preventive randomized controlled trial targeting weight loss in overweight/obese individuals free of knee OA was published[41]. Although this trial demonstrated no significant difference on knee OA incidence (defined as a symptomatic radiographic OA, the combination of OA *disease* and *illness*), between a lifestyle intervention and a no-attention control group, it provided important information about the potential of weight loss in overweight/obese individuals as a preventive measure for knee OA. First, although it was difficult to positively affect the lifestyle of middle-aged women through physical exercise classes and dietician consultation (small average changes in body weight and low intervention adherence), those with higher adherence demonstrated a lower incidence of knee OA *disease*/*illness* after 30 months than the control group (adjusted OR 0.34, 95% CI 0.11–1.06)[41]. Second, those reaching the target of a 5 kg or 5% reduction in body weight, showed significantly lower incidence rates of knee OA *disease* after 30 months, and knee OA *disease* and *illness* after 6.5 years[42,43]. These results show proof of concept and should stimulate researchers to better understand how to increase adherence to similar interventions to prevent knee OA. Moreover, these results can be used by clinicians to educate and motivate overweight/obese individuals about the benefits of weight loss (see Fig. 3).

There is little evidence available about the potential of weight loss among overweight/obese individuals to prevent hip or hand OA *disease*[15,19,20]. Replicating studies investigating the relationship between weight changes and the development of hip and/or hand OA *disease* (or *illness*), as done for knee OA[40,42,43], could shed a light on the potential of this intervention. However, given the weak associations between overweight/obesity and the development of hip or hand OA *disease* (see Table I), the relevance of weight loss for hip or hand OA prevention may be questioned.

Although there is only a single weight loss trial on the prevention of OA, there are numerous studies that evaluate the effect of weight loss in overweight/obese individuals to prevent cardiovascular disease[44], diabetes[45], and cancer[46]. Most of these trials aimed to improve health status or to prevent a decline in health. Given the bidirectional association between OA and the presence of comorbidities[47,48], evaluating the possible effect on OA development in future trials is highly recommended.

Joint trauma and trauma management for osteoarthritis prevention

The prevention of post-traumatic OA (PTOA) involves preventing joint injuries or delaying or halting the progression to OA in persons with a previous joint injury. PTOA is particularly relevant to the knee joint as knee injuries are highly prevalent[49], particularly between the ages of 15–35 years[50] and associated with a 6-fold (HR 5.7; 95%CI 5.0,6.6) greater risk of structural knee OA by 11 years[51]. This risk varies by injury type with anterior cruciate ligament (ACL) tears (HR 8.2; 95%CI 5.9,11.4), meniscal tears (HR 7.6; 95%CI 5.5,10.5), and intra-articular fractures (HR 7.0; 95%CI 4.2,11.7), presenting a greater risk than collateral ligament tears (HR 4.9; 95% CI 3.3,7.3)[51]. Knee trauma is also associated with a 7-fold (OR 6.96, 95%CI 4.73,10.31) increased odds of arthroplasty.[52]

Preventing joint injury

There is high-level evidence of the effectiveness of injury prevention strategies. Exercise programs that incorporate neuromuscular control and strengthening exercises have been shown to consistently reduce the risk of knee and ankle injuries in youth[53] and adults[54–56] at high risk due to sport participation. Despite the effectiveness of injury prevention programs across multiple

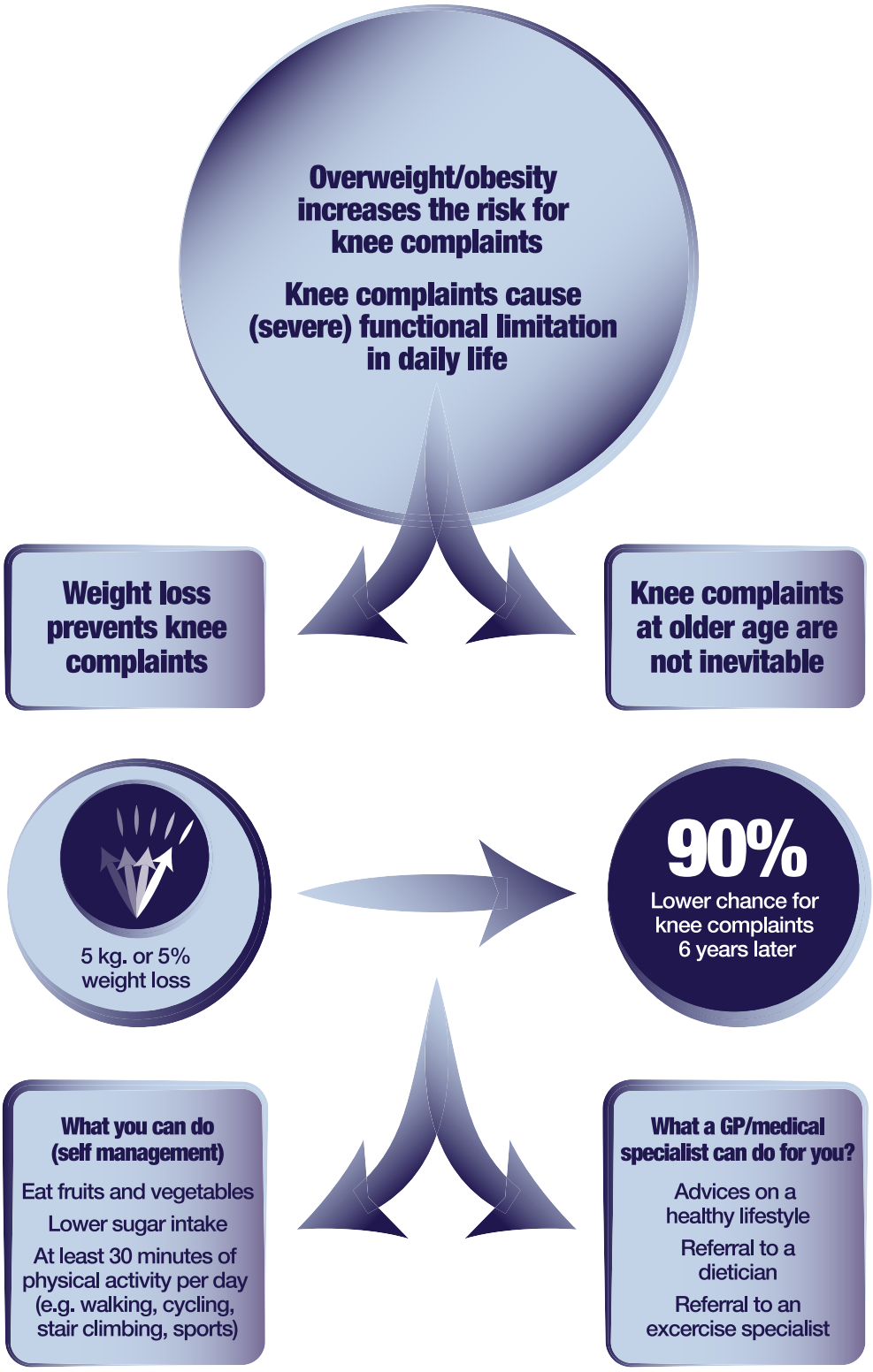

Fig. 3 OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Reducing the risk of osteoarthritis in overweight and obese persons.

sports[53–56], distribution of multi-faceted educational materials[57], widespread support across many national and international professional organizations, and recognition of these programs in national OA strategies[58,59], wide spread sustained implementation has been challenging[60]. Preliminary evaluation of strategies to improve the uptake of these programs including coach/teacher workshops[61], and co-developing strategies to promote, teach, adopt, and adhere to injury prevention programs with sport teams and sporting organizations[62,63] are promising. Ongoing efforts that incorporate implementation science and behaviour change theory are likely needed before population level benefits of injury prevention programs on the OA burden are realized.[64]

Despite typically being a population based (i.e., sport club or organization level) strategy, there may also be a rationale for targetted delivery of injury prevention programs. For example, it may be prudent to identify and target individual young athletes with relatives who have suffered a major knee injury given the strong (70%) genetic contribution and familial clustering for ACL injuries (regardless of sex).[65]

Preventing progression to knee OA after injury

The pathogenesis of post-traumatic knee OA *disease* and *illness* is multifactorial and involves several interconnected mechanisms (i.e., alterations in cartilage metabolism impacting articular tissue integrity[66], inflammation[55,67], altered joint loading[68,69], epigenetic changes, and genetic predisposition[70]). Theoretically, it may be possible to prevent or slow down the onset of PTOA *disease* and *illness* by strategically targetting modifiable aspects of these mechanisms across the trajectory from trauma management, to supported recovery, and ongoing self-management (Fig. 4). For example preventing re-injury and engaging in activites that promote joint health may preserve articular tissue integrity. Similarily, preventing re-injury, optimizing articular inflammation and minimizing total body adiposity may slow down inflammatory processes. Finally, addressing movement adaptations, muscle function[12,71] and weight gain[72] may promote normal joint loading.

Currently, there is limited evidence to support the above theoretical arguments given challenges associated with conducting clinical trials across the extended period between joint injury and OA *disease* or *illness* onset, the heterogeneous nature of knee injuries, lack of consensus about how to define early OA *disease* and *illness*, and the diverse treatment options available[73,74]. Below we summarize the evidence for strategies (interventions) that improve both interim targets (i.e., clinical and functional outcomes) related to knee trauma, as well as features of OA *disease* and *illness* with the aim of prompting lines of future inquiry.

Exercise and education

The role of exercise in preventing PTOA is an emerging area of research. A 2016 systematic review identified 18 primarily small moderate quality quasi-experimental (no randomization) clinical studies that provided conflicting evidence about exercise for preventing knee OA *disease* after ACL injury[75]. Despite these findings, efforts to understand the role of exercise-based activities (exercise therapy, general exercise and physical activity) in preventing the features of OA *illness* should not be abandoned as these activities are important for reducing the risk of subsequent injury[76], promoting articular tissue health[77–79], and reducing adiposity[80], altered movement patterns, and muscle weakness[9]. Additionally, guidelines for managing knee injuries[81] and knee OA[11] recommend exercise due to an overwhelming body of evidence demonstrating improvements in clinical outcomes[82], many of which are also features of OA *illness* (i.e., knee-related pain, symptoms, function and quality of life).[83–85]

Based on a recent scoping review[86] and reports from persons at risk for PTOA[87] it is important that exercise-based strategies for preventing OA take into consideration the influence of psychological (e.g., fear of motion, re-injury anxiety, confidence), social (e.g.,

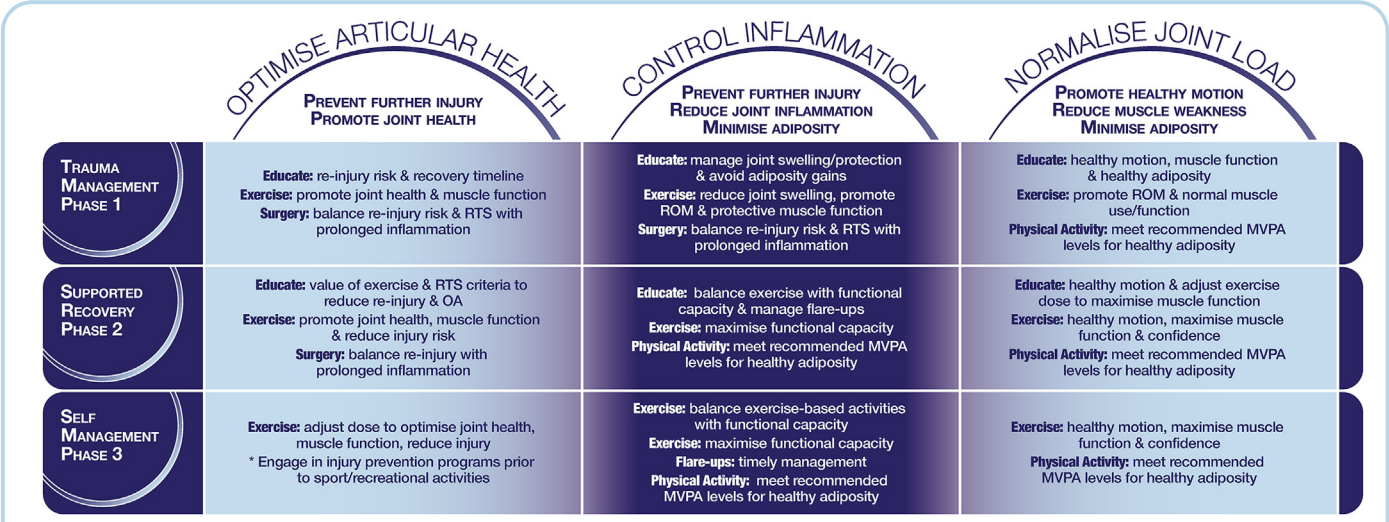

Fig. 4 OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Treatment targets and corresponding strategies for preventing post-traumatic osteoarthritis. Trauma management = Immediately following injury, re-injury and/or surgery, Supported recovery = Period between trauma management and discharge from formal healthcare, Self-management = Following discharge from formal healthcare. MVPA (Moderate to Vigorous Physical Activity: Age <18 years = 420 min of moderate intensity activity per week; ≥18 years = 150 min of moderate intensity activity per week (activity that causes perspiration). ROM = Range of Motion, RTS = Return to Sport.

support, autonomy), and contextual (e.g., access to exercise facilities, availability, culture) factors. It is also important to acknowledge that exercise behaviours are directly influenced by ones attitudes (i.e., a mindset or tendency to act), priorities, and perceptions (i.e., an individual's interpretation of an experience) of exercise[88–90]. Education can play an important role in shaping these views, and informational support about exercise is commonly sought after a knee injury.[86]

Early after trauma, information about re-injury[91] and OA risk[51], realistic recovery and return-to-activity timelines[92], managing joint inflammation, as well as the importance of exercise-therapy, healthy movement patterns, and avoiding weight/adipose tissue gain may support preventative efforts. As function improves, topics that emphasize managing exercise therapy dose to optimize muscle function, pacing exercise-based activities based on functional capacity, managing flare-ups and the value of return-to-sport criteria for mitigating future injury risk may be important[93-96]. Given that many who experience a joint injury in their second and third decade will have to navigate joint-related obstacles, increased OA risk, and potentially OA *illness* across their lifespan, it is vital to equip them with knowledge and practical understanding to do this[74]. It is essential that these resources are put in place and tested when they are recovering from their injury to promote self-efficacy for self-management. This may include understanding when to engage with medical and allied health professionals.

Surgery

A common argument for surgical procedures like ACL reconstructions (ACLR) that aim to restore the stability of the knee, is that they also prevent OA and should be performed early after injury. This belief is contradicted by the evidence with a recent meta-analyses demonstrating that ACLR is associated with more structural OA *disease* at 10 years compared to non-surgical treatments[97]. Early surgery may also prolong the traumatic inflammatory response and contribute to cartilage damage and bone remodelling[98]. In the first randomized controlled trial (KANON) that compared early ACLR plus exercise therapy to exercise therapy only with the possibility for delayed surgery, no between group difference in patient-reported outcomes or OA *disease* were detected at two or five year follow-up[99,100]. In addition, treatment with exercise therapy alone was prognostic for *less* knee symptoms compared with early ACLR plus exercise therapy at 5 years. These findings suggest that delaying ACLR may positively change prognostic factors for OA *illness*. Interestingly subsequent non-ACL surgery due to concomitant injuries was associated with more self-reported features of OA *illness* in both those treated with early ACLR and exercise therapy, and those treated with exercise therapy alone.[101]

Another common argument for early ACLR is to prevent future meniscal and cartilage injury, and subsequent OA. A second recently published randomized controlled trial comparing early ACLR to exercise therapy and delayed ALCR found more meniscal surgery in the early ACLR group, both at the time of, and after the ACLR[102]. Together with the finding of equivalent numbers of meniscal injuries and surgeries between treatment groups in the KANON study[100], this suggests that early ACLR does not save the meniscus or reduce future OA risk.

Lastly, there are few randomized trials comparing treatment approaches for isolated meniscal tears in young adults, or the extent meniscal surgery influences the development of OA. To the best of our knowledge there are no published trials comparing the effect of repair vs partial resection of the meniscus. However, two trials comparing arthroscopic partial meniscal resection to exercise therapy in young adults with a meniscal tear have completed recruitment but are not yet reported.[103,104]

Based on the existing evidence it is likely that any strategy to reduce the risk of PTOA *illness* will be multifaceted. Rehabilitation consisting of exercise therapy (and patient education) should be the first line of treatment regardless of subsequent surgical or non-surgical management[32]. In the case of an ACL tear, surgical reconstruction may be considered if the patient experiences persistent instability episodes, or is unable to return to their desired physical activities despite adherence to exercise therapy, or prefers surgery[33,34]. Pre-habilitation should precede any surgical reconstruction, which should subsequently be followed by an extensive period of supervised exercise therapy.[32]

Other strategies for preventing PTOA

It is important to delineate exercises-therapy which targets specific therapeutic goals from physical activities that contribute to overall general health. Recommended levels of general physical activity have been shown to be important for musculoskeletal health[77,105], controlling adiposity[80] and may be important for cartilage health.[106]

The role of medications, intra-articular injections, medications, assistive devices (e.g., braces, and crutches that reduce loss of balance and re-injury or normalize joint loading pattern), diet and other interventions in mitigating the risk of PTOA is unknown. Important lines of inquiry include determining what agents, braces and aspects of diet may promote joint health and the mechanisms underlying any protective effect.

Targetting other risk factors for osteoarthritis

Beyond obesity and joint injury, there are differing levels of evidence supporting the targeting of other modifiable and non-modifiable risk factors for prevention of OA *disease* and *illness* outlined in Table I.

Muscle weakness

Currently, there is no evidence that exercise programs targeting muscle weakness can prevent OA *disease* or *illness*. A recent systematic review found that knee extensor muscle weakness is associated with a small increased risk of knee OA *disease* and *illness* based on five prospective studies[12]. Although muscle weakness is a clear target after knee injury to improve function, it also maybe a target to reduce OA risk in injured and uninjured populations. *Physical inactivity,* closely linked to muscle weakness, has been put forward as a potential risk factor for knee and hip OA *disease* and *illness*[107]. Currently there is a lack of evidence in this area, likely due to challenges in objectively measuring physical activity in population-based studies.

Joint shape

Hip deformities such as cam deformity or acetabular dysplasia are moderate to strong risk factors for hip OA *disease*[108]. Cam deformity and mild dysplasia increase the risk of hip OA *disease* in the middle-aged, but not the older population[109]. Cam deformity is also thought to contribute to femoroacetabluar impingement syndrome (FAIS), which is a painful hip disorder that may be caused by a premature contact between the femur and acetabulum during hip movement. In patients with FAIS, arthroscopic hip surgery (reshaping the hip and repair of cartilage and labral damage) has been compared to physiotherapy-led care in three randomized controlled trials[110–112]. Meta-analyses show small, likely clinically insignificant differences favouring surgery at 6-months, but no difference at 2-years[113–117]. Further, a recent randomised controlled trial comparing hip arthroscopy to sham surgery found no difference for pain at 1-year[118]. It is unclear whether surgery or non-surgical treatment will prevent OA in the longer-term.

Severe hip dysplasia is strongly associated with onset of hip OA *illness* at young age[119]. The most common form of hip dysplasia is

developmental hip dysplasia in infants. Given that early treatment with abduction orthoses can support normal hip development, many health care systems have screening programs. However, when a normal morphology is not achieved, or the dysplasia is undetected, it can contribute to hip OA *disease* and *illness* in early adulthood. There also are several indications that some hip dysplasia may not appear until childhood.[120,121]

Joint malalignment

Varus and valgus malalignment have been shown to be small to moderate risk factors for knee OA *disease*[122,123]. While varus malalignment is associated to the more common medial compartment OA, valgus malalignment is associated with incident lateral compartment cartilage damage[124]. Malalignment may cause these effects, in part, by increasing the risk of meniscal damage.[124,125]

Occupational or sport overload

Occupations with high physical load are risk factors for hip and knee OA. In the hip, farming or construction industry occupations are associated with OA *disease*/*illness*[126], while for the knee it is occupations that involve frequent kneeling and heavy lifting[127]. Several elite high-impact (i.e., running, soccer, handball, ice hockey, wrestling, weight lifting) sports demonstrate a dose–response association (moderate to strong) with increased risk of hip[128] or knee OA *disease*/*illness*[25]. In a recent meta-analyses including 25 studies of over 125,000 runners, investigators found an U-shaped dose–response relationship as both 'too much' (i.e., elite running; 13.3% 95% CI: 11.6%, 15.2) and 'too little' (i.e., not running; 10.2% 95% CI: 9.9%, 10.6%) running was associated with more hip and knee OA *disease* than recreational running (3.5% 95% CI: 3.4%, 3.6%).[129]

The relationship between sport participation and knee OA seems mainly driven by injury[25], while the relationship between high-impact sports and hip OA appears to be partially driven by the development of bony cam deformity due to high impact loading during the late pubertal growth spurt[128,130]. Efforts to modify loads applied during sports or performance art where the hip is excessively loaded during external rotation (e.g., martial arts, ice hockey, ballet) during this growth period may represent an important prevention strategy.

Sex/gender

Women are at a higher risk for knee OA *disease* and *illness* then men, with a steep increase in incidence after the age of 50[3,131,132]. The increased risk of OA *disease* and *illness* in women is likely due to biological (sex) and sociocultural (gender) differences. Although most studies have focused on biological mechanisms such as menopausal transition or biomechanical differences to explain this risk, it is possible, that gendered approaches to sport development/training, injury prevention and medical interventions[133], occupation, sport and physical activity preferences, socioeconomic status, and differences in societal roles may also contribute and need to be considered.

Genetics

It has been estimated that the overall genetic contribution to OA *disease* is between 40% and 80%[134]. This contribution is stronger for hip than the knee. Large effects are seen for some rare mutations (monogenetic disorders) and result in early-onset OA[134]. The contribution of many common DNA variants to OA development is more frequent and results, together with other risk-factors, in late-onset OA[134]. The risk due to of each of these common variants alone is generally very small. Recently, polygenetic risk scores based on DNA variants have been developed for both hip and knee OA *disease*[135]. Possibly in the future, such scores could be used to define individual risk of OA *disease*, and accordingly adjust other risk factors in order to prevent development.

Interaction of osteoarthritis risk factors

Although there is limited knowledge about the prevelence or level of interaction of co-existing risk factors, it is likely that these scenarios compound the risk for OA (Fig. 5). Examples of interactions that have been reported include knee joint trauma, female sex/gender and adiposity[136], knee joint trauma, female sex/gender and muscle weakness[137], female sex/gender and adiposity[18], knee joint trauma and hand osteoarthritis[138,139], as well as overload due to sport and FAIS[140]. Early identification of co-existing risk factors should be incorporated into ongoing preventative efforts.

Discussion

The steeply increasing prevalence of hip and knee OA *disease* are often attributed to increases in life expectancy and body weight. When tested using large skeletal samples spanning prehistoric (hunter-gathers and early farmers) through the early industrial to post-industrial eras, this hypothesis does not hold true[107]. Encouragingly, this suggests that environmental changes associated with the post-industrial era are at play and implies that OA *disease* is more preventable than is commonly assumed. The repudiation of this common belief points to the need for a paradigm shift in how we identify risk factors to one that focuses on risk factors that have emerged in the post-industrial era. One example is physical inactivity, which has become an epidemic in the post-industrial era and is associated with thinner cartilage with lower proteoglycan content, and weaker muscles less capable of evenly distributing joint loads.

A similar paradigm shift is needed for how we approach OA prevention. Due to the complexity and multifactorial nature of OA, there are numerous opportunities to prevent OA *disease* and *illness* spanning infancy through childhood, adolescence, and early to late adulthood. Throughout this review we have presented examples of at-risk groups ranging from infants with developmental hip dysplasia that, if identified early, can be resolved with abduction orthoses; young persons who belong to familial clusters of ACL injury or OA where individual counselling and targeted injury prevention programs may be appropriate; youth and young adults who experience a joint related trauma who would benefit from optimising articular tissue health, controlling inflammation and normalising joint loads; to persons of all ages struggling with overweight and inactivity where lifestyle interventions would be appropriate. Given the diversity of ages, contributing factors, and presentations of these at-risk groups, there is the need for multiple complementary approaches to OA *disease* and *illness* prevention throughout the entire lifespan.

The field of OA prevention is young and many knowledge gaps and barriers have to be overcome. Apart from defining high-risk groups and preventive interventions, we must define what outcome measures to use to investigate the effectiveness of preventive actions. When the intention is to prevent a risk factor, the absence of the development of the risk factor will most probably convince. When the intention is to modify the risk factor and prevent OA *disease*/*illness*, or to prevent the development of OA *disease*/*illness* in the case of a non-modifiable risk factor, we will require dedicated outcome measures. Although there have been some efforts to propose definitions for early OA[83,141,142] consensus for these definitions and surrogate markers of OA *disease* and *illness* are also needed.

Fig. 5 OSTEOARTHRITIS PREVENTION Osteoarthritis and Cartilage

Example of risk factor interaction for osteoarthritis disease or illness development.

The burden of OA is driven by *illness* (i.e., pain, disability) as opposed to the structural features of the *disease*. With that said, a significant proportion of research related to understanding underlying mechanisms, risk factors and treatment of OA, particularly in the early stages of OA, is focused on an outcome of OA *disease* (e.g., imaging outcomes). This is a significant disconnect, particularly when considering the poor regenerative capacity of cartilage[5], and requires those in the field to pause and reflect on whether their goal is to prevent the *disease* or *illness* of OA. This reflection will influence the choice of outcome and result in the identification of knowledge gaps and avenues for future research (Text Box 1), as well as shine light on barriers (Text Box 2) that will need to be overcome prior to propelling the OA prevention field forward.

Despite the identified barriers and knowledge gaps, concrete actions to prevent the *illness* of OA based on the current evidence and theoretical arguments can be taken (Text Box 3). Ideally these actions should be proactive and target opportunities across the lifespan.

Text Box 1
Knowledge Gaps and Priorities for Future Research.

- Validated definitions for early structural OA disease or OA illness
- Surrogate outcomes for early structural OA disease and early OA illness
- Risk factors for early structural OA disease and early OA illness
- Risk factors for established OA illness
- Interaction of risk factors
- Feasible methods to screen for risk factors to identify high-risk groups
- Methods for affecting exercise and physical activity behaviour change
- Economic and societal benefits of OA prevention
- Role of social determinants of health in OA prevention

Text Box 2
Barriers to Moving the Field of OA Prevention Forward.

- Lack of validated measures to identify persons with early OA
- Lack of validate measures to evaluate the development of OA within a feasible timeframe
- Prevention typically occurs outside the health care system
- Lack of feasibility of screening for some risk factors (i.e., those that require sophisticated equipment and or skilled assessors)
- Challenge to motivating behaviour change in persons at increased risk but without symptoms or of a young age
- Proving cost savings as they are often not tangible

Text Box 3
Actions for Preventing OA.

- Promote healthy levels of adiposity across the lifespan, starting in childhood
- Promote healthy loading of articular cartilage and musculature across the lifespan, starting in childhood
- Implement injury prevention programs for at-risk populations (i.e., child, adolescent and adult sport and recreational activities)
- Manage the development of additional risk factors after joint trauma

Conclusion

The field of OA prevention is relatively young and has focused on modifying outcomes of OA *disease*. Those engaged in preventing OA, either in research or clinical settings should explicitly consider OA as a *disease* and an *illness*. Given the limited regenerative capacity of cartilage, it is likely that prevention of OA *disease* may be more achievable than reversal of *disease*. As *illness* is the primary driver of the OA burden, *illness*, and features of OA *illness*, should be viewed as equally important prevention targets as features of OA *disease*. Consideration of the various opportunities and modes of interventions that exist across the lifespan is also critical for preventing OA. These should include screening and early diagnosis, education/counselling, exercise-based activities, and lifestyle modification in addition to traditional medical practices (e.g., pharmaceuticals, injection therapies, surgery). Although overweight/obesity and joint trauma may currently be seen as most amenable to prevention, efforts to identify risk factors established or amplified in the post-industrial era and interventions to address should also be prioritized.

Author contributions

All four authors had an equal role in conceiving and contributing to this narrative review. JLW and JR co-led combining sections written by all authors to create a first draft. All authors provided feedback on the draft document and approve the final submission.

Conflict of interest

Dr. Whittaker is supported by a Michael Smith Foundation or Health Research Scholar Award and Arthritis STARS Career Development Award. She also holds grants from the BC SUPPORT Unit, and Canadian MSK Rehab Network, outside the submitted work. Dr. Runhaar has nothing to disclose. Dr. Bierma-Zeinstra reports grants from Dutch Arthritis Association, the Netherlands Organization for Health research and development, FOREUM, and EU as well as personal fees from Pfizer and Osteoarthritis & Cartilage, outside of the submitted work. Dr. Roos is the deputy editor of Osteoarthritis and Cartilage, developer of Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures, and founder of the Good Life with Osteoarthritis in Denmark (GLA:D), a not-for profit initiative to implement clinical guidelines in primary care.

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