

Strategies for the prevention of knee osteoarthritis

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Abstract | Osteoarthritis (OA) has been thought of as a disease of cartilage that can be effectively treated surgically at severe stages with joint arthroplasty. Today, OA is considered a whole-organ disease that is amenable to prevention and treatment at early stages. OA develops slowly over 10–15 years, interfering with activities of daily living and the ability to work. Many patients tolerate pain, and many health-care providers accept pain and disability as inevitable corollaries of OA and ageing. Too often, health-care providers passively await final ‘joint death’, necessitating knee and hip replacements. Instead, OA should be viewed as a chronic condition, where prevention and early comprehensive-care models are the accepted norm, as is the case with other chronic diseases. Joint injury, obesity and impaired muscle function are modifiable risk factors amenable to primary and secondary prevention strategies. The strategies that are most appropriate for each patient should be identified, by selecting interventions to correct — or at least attenuate — OA risk factors. We must also choose the interventions that are most likely to be acceptable to patients, to maximize adherence to — and persistence with — the regimes. Now is the time to begin the era of personalized prevention for knee OA.

Traditionally, osteoarthritis (OA) was diagnosed by the use of radiography, and joint arthroplasty was regarded as the only effective treatment. However, the results of the past 20 years of research have changed our thinking about the disease, and about how and when to treat it. We know today that OA often takes decades to develop and has a range of associated risk factors. We also know that considerable discordance exists between symptoms and structural signs of OA, and current evidence-based clinical guidelines recommend early treatment with education, exercise and weight loss. Between them, hip OA and knee OA are responsible for a major burden of disease, and when they are considered together, they are ranked number 11 of the 291 diseases listed by the WHO according to years lived with disability¹. Although OA was previously regarded as a disease of the elderly, its development starts much earlier than originally thought, and OA is ranked among the top 20 diseases in the 40–45 years age group².

The current level of knowledge regarding the nature of OA and effective treatments for the disease enable the consideration of preventive strategies and treatments for its first symptoms. This approach is similar to contemporary treatment of cardiovascular disease and diabetes mellitus, and can potentially prevent many years of pain and functional impairment in patients, as well as considerable expenditure on health care. Prevention

and early treatment require a reappraisal of the definition and diagnosis of OA. In this Review we outline the classic methods of defining OA, describe a modern framework for its definition, and suggest primary and secondary prevention strategies for three common OA risk factors — joint injury, impaired muscle function and obesity.

What is OA?

No single definition encompasses all instances of OA. Rather, structural signs of OA are considered to be common outcomes that are arrived at by a number of pathways, involving various risk factors. The discordance between structural signs and symptoms is substantial³. Symptomatic OA is influenced by comorbidities, pain-processing factors and other personal traits. The current conceptual model describes OA as a whole-person disease (FIG. 1) developing along a continuum from early to late stages (FIG. 2).

Imaging findings of OA

OA affects all the tissues of the synovial joint, which include cartilage, bone, ligament, tendon, synovium and meniscus⁴. The relative involvements of each of these tissues can vary from patient to patient, and also throughout the time course of the disease. In most OA research, the disease has been defined by radiography

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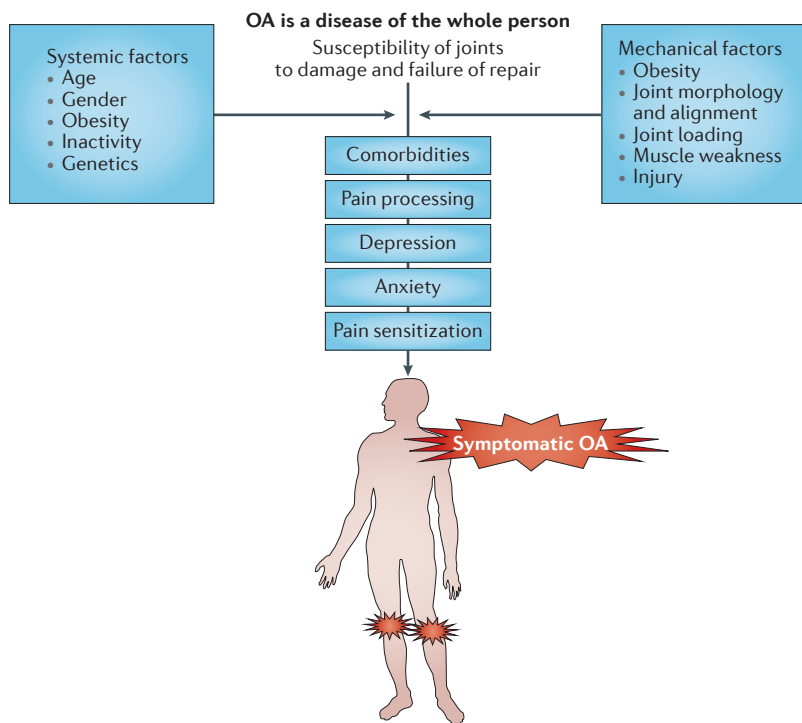
Key points

- Osteoarthritis (OA) is amenable to early prevention and treatment; not all patients with knee OA progress to severe pain or joint replacement, and patients at high risk should be identified
- Obesity is a major risk factor for OA, and weight loss is effective at reducing the risk of OA, but adherence to interventions is poor and should be addressed by personalized strategies
- Neuromuscular and proprioceptive training programs are successful in preventing 50% of major knee injuries during sport, which indicates that primary prevention of knee OA is possible
- Around 50% of individuals sustaining a major knee injury — with or without surgical reconstruction — develop knee OA, and secondary prevention could be valuable in patients with major knee trauma
- Impaired muscle function — a consequence of physical inactivity — is commonly seen after knee injury, is associated with knee pain, and is an independent risk factor for development of knee OA
- Biomechanical interventions, such as knee braces and exercise, show promise in altering contact stress and cartilage matrix content, suggesting ways to prevent or delay OA

without necessarily considering other structural findings or the symptoms experienced by the patient. This definition does not result in an accurate assessment of the disease, as the presence of radiographic OA is often discordant with the presence of other structural findings and related symptoms³.

A substantial proportion of patients with classic radiographic features of OA do not experience clinically relevant symptoms of the disease. Up to 50% of patients with radiographic knee osteoarthritis (RKOA)

— defined by the presence of bony enlargements (osteophytes) and the loss of cartilage (visualized by possible or definite joint-space narrowing of grade ≥ 2 on the Kellgren and Lawrence scale⁵) — do not experience regular pain⁶. The prevailing (but not unanimous) view is that the development of osteophytes, which are central to the diagnosis of RKOA, is a response to knee injury and instability. In this model, osteophyte formation helps to stabilize the joint by increasing the contact area, thereby reducing instability and pain. Stabilization of joints by osteophyte formation could explain the observation of asymptomatic RKOA. Up to 50% of patients with knee pain suggestive of OA do not have radiographic features of OA⁶. The use of highly sensitive MRI, which can detect bone-marrow lesions, synovitis and meniscal abnormalities, can identify abnormalities in a large number of these patients, but the clinical relevance of these lesions is not known. Indeed, in a large study of asymptomatic individuals without radiographic signs of OA, abnormalities thought to be associated with OA were detected in 89% of knees by MRI⁷. In a population-based study of ambulatory individuals aged 50–90 years, right-knee meniscal tears were identified by MRI in as few as 19% of women aged 50–59 years and as many as 56% of men aged 70–90 years⁸. Among people with RKOA, the prevalence of meniscal tears was 63% in symptomatic individuals and 60% in those who were asymptomatic. Of those with MRI-verified meniscal tears, 61% had not had any pain, aching or stiffness during the preceding month⁸. Neither RKOA nor meniscal tears seem to be effective markers of symptomatic knee OA.



Clinical findings of OA

Knee OA can be classified on clinical criteria alone (including pain, age, stiffness, crepitus, bony tenderness and bony enlargement), which make up the inclusion criteria for most clinical trials in this field⁹. The use of clinical criteria to diagnose OA is also recommended by the national clinical guidelines in Sweden and Denmark, which explicitly state that radiography is not needed for an OA diagnosis^{10,11}.

Attention should be focused on symptomatic OA (and the phenotypes of pain and function) to identify clinically relevant investigations and treatment strategies capable of reducing the huge burden of the disease. To this end, research is increasingly being directed towards studies of the symptoms of knee OA, usually in combination with structural changes. In parallel, attempts are being made to determine the importance of central and peripheral pain-processing mechanisms. Evidence is emerging of differences in the results of Quantitative Sensory Testing (a noninvasive technique to determine sensory and pain thresholds) and the regulation of genes that are involved in pain processing between subjects with RKOA with and without associated pain^{12,13}. Although pain and function are often closely related, physicians tend to focus on pain, whereas function and participation restrictions are reported to be equally important to many patients.

Figure 1 | **A conceptual model of OA.** OA is a disease of the whole person. Modifiable and nonmodifiable systemic and mechanical risk factors contribute to the development of joint vulnerability and eventually OA. Comorbidities and pain-related factors affect the development of symptomatic OA. Abbreviation: OA, osteoarthritis.

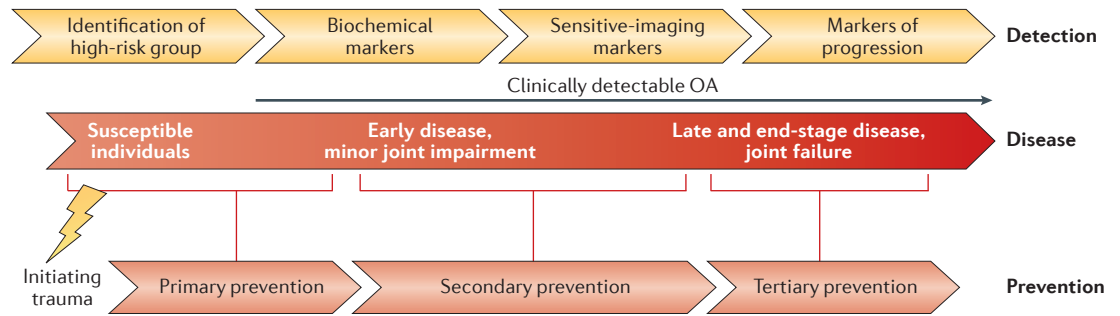


Figure 2 | **The OA continuum.** OA develops slowly, taking 10–15 years to develop from a known initiating trauma. Different techniques can be used to identify individuals at risk of OA and those with early-stage and late-stage disease. For knee OA, primary prevention includes the prevention of knee injury. Secondary prevention includes dietary intervention and exercise in individuals who are overweight, have impaired muscle function or prior joint injury, whereas tertiary prevention involves early treatment of OA to prevent progression of the disease. Abbreviation: OA, osteoarthritis.

Definitions of OA

Although a single definition of OA could help when describing the benefits and cost effectiveness of primary and secondary prevention strategies for knee OA, such a definition might not be possible, or even advisable. A more useful approach could focus on the stages of disease. Commonly, the natural history of OA is described as beginning with normal joint structures, lack of symptoms and normal joint and muscle functions, progressing to total loss of cartilage, which is accompanied by other structural changes, perceived instability and loss of muscle function, with severe pain at night and during activity, impaired physical function and reduced quality of life. This end stage is often called joint failure (FIG. 2), in an analogy with heart failure or kidney failure, and is treated by replacement of the joint with an artificial prosthesis.

Completion of the ongoing process of producing classification criteria for early knee OA should aid the performance of clinical studies in early stages of disease, and eventually the definition and assessment of new prevention and treatment strategies. This process could take inspiration from the field of osteoporosis research, in which, after years of debate about different definitions of osteoporosis related to bone density, the bold step was taken to move to a risk-based model for identifying ‘at-risk patients’ by assessing an individual’s 10-year risk of sustaining an osteoporotic fracture. This model would work well in OA as it makes allowances for the heterogeneous nature of the disease, and for the multiple and diverse risk factors that can lead to the development of symptomatic OA (FIG. 1). Although models exist to predict the onset of OA, and in particular knee OA, they need to be improved and validated before being used in clinical practice^{14–16}. These models will be useful not only for stratifying risk for prevention strategies, treatment and entry into clinical trials, but also for identification of the risk phenotype of each patient, to enable appropriate interventions. This approach would encompass the key principles of personalized medicine, which seems to be entirely appropriate for diseases such as knee OA, which is responsible for 83% of the burden of disease from OA overall¹⁷. In knee OA, the disease is heterogeneous in terms of risk factors and rates of progression, and no treatment works well for all patients.

Epidemiology of OA

Estimating the size of the problem of knee OA is difficult, because of the multiple definitions of the disease, and the general lack of data from people <50 years old. The largest body of data on knee OA is derived from population-based studies of RKOA. Ideally, we would know the prevalence and incidence of symptomatic knee OA defined by knee pain, alone or associated with clinical signs or radiographic changes, or both. The available data suggest a prevalence of symptomatic RKOA of 20% in individuals >65 years old and an annual incidence rate approaching 1% in women aged 70–89 years¹⁸. In a population-based sample from Sweden the prevalence varied from 8% to 26% in the group aged 56–64 years, depending on whether the definition of disease was based on the combination of pain and RKOA (8% prevalence), clinically defined OA according to ACR criteria (10% prevalence), RKOA alone (17% prevalence) or knee pain alone (26% prevalence)¹⁹. Although the prevalence of symptomatic RKOA, clinically defined OA and knee pain were fairly stable in association with age, the prevalence of RKOA alone was nearly 40% in the highest age group (75–84 years)¹⁹.

Studies of the burden of knee pain in the community have shown that knee pain is predictive of future health-care costs, and OA is associated with considerable costs to individuals and to health-service providers, accounting for >90% of lower-limb joint replacements performed in Western health-care systems²⁰. OA is also associated with mortality, especially from cardiovascular causes, and physical inactivity is an important mediating factor^{21–23}.

Prevention of knee OA

Primary and secondary prevention strategies are necessary to prevent increased rates of OA resulting from an ageing population and increasing rates of obesity and physical inactivity. Strategies that are developed for knee OA might not be transferable to other joints, because of anatomical and other differences.

Primary prevention strategies are intended to prevent the onset of specific diseases via risk reduction, by altering behaviours or exposures that can lead to disease, or by enhancing resistance to the effects of

exposure to a disease agent. Preventing knee injury and obesity during adolescence are examples of strategies that are relevant to knee OA. Secondary prevention includes the detection and treatment of risk factors for progression in individuals who are already at risk. Examples relevant to knee OA include the detection and monitoring of weight gain and impairments in proprioceptive acuity, dynamic joint stability and muscle function, and subsequent intervention with weight management and targeted exercise therapy in those who already have sustained a knee injury. OA is a heterogeneous disease with several different phenotypes and a large number of risk factors, which often interact with each other (FIG. 1). Three important risk factors, which show promise for both primary and secondary intervention, are obesity, trauma and impaired muscle function.

Epidemiology of obesity

Obesity and related diseases cost the UK economy >UK£3 billion per year, and this cost is expected to rise to £45.5 billion per year by 2050²⁴. The rates of obesity are increasing dramatically throughout most areas of the developed world as populations become more affluent and sedentary. Most worrying are the high — and also rising — rates of childhood obesity in industrialized countries, which occur before the skeleton is mature²⁵.

Association of obesity with incident knee OA

Obesity is well known to be associated with RKOA, with weaker associations for hand OA and possibly hip OA. Despite initial uncertainty as to whether the obesity was the cause or effect of the OA, prospective cohort studies have demonstrated that obesity precedes the onset of RKOA^{26–28}. Similar associations have been demonstrated for symptomatic RKOA^{26,29}. Data from the USA demonstrate that the lifetime risk of symptomatic RKOA increases by 30.3% in individuals who are obese compared with those who have normal BMI³⁰. The adverse effects of obesity are present from an early age; among 1,180 male medical students, each 8 kg increase in weight as a young adult (aged 20–29 years) was associated with a 70% increase in the risk of clinical knee OA >30 years later²⁸.

As well as being overweight or obese, weight gain is associated with the risk of receiving a total knee replacement^{31,32}. Few data exist on the association of obesity with knee pain. In a cohort of 594 women, BMI at baseline was associated with self-reported knee pain 14 years later³³. Furthermore, the association was independent of RKOA, suggesting the involvement of pain processing rather than structural joint changes³³. In this regard, proinflammatory cytokines originating from adipose tissue can act as pain modulators^{34,35}. The mechanism of the association between obesity and knee pain is multifactorial, involving mechanical load through the knee joint and levels of physical activity, as well as the systemic inflammatory load caused by cytokine production from adipose tissue. Fat mass, rather than lean mass, might drive the association³⁶.

Weight-reduction strategies

Interventions for weight reduction have been fairly ineffective at the population level, although evidence suggests that a number of successful strategies are available at an individual level. The results of clinical trials have demonstrated the ability of a number of interventions to reduce weight in the short and medium terms, and trials are now addressing the more difficult issue of maintaining weight loss over longer periods of time, as has been reviewed previously³⁷.

Dietary restriction has been shown to reduce weight, but macronutrient (protein, carbohydrate and fat) manipulation within the diet seems to have, at best, a minor effect on weight loss³⁷. However, for complications of obesity — such as diabetes and heart disease — macronutrient manipulation might well be important³⁸. Exercise in isolation is less effective than dieting in producing weight loss, particularly in women³⁹, but exercise is considered pivotal in maintaining weight loss, so diet and exercise are often combined.

Interventions using cognitive behavioural therapy (CBT) can lead to substantial weight loss and do not necessarily need to be intensive^{40–43}. The internet and social media are improving the affordability and accessibility of these techniques, so that they can reach a diverse population of overweight people³⁷.

The current gold standard of intervention to achieve weight loss is bariatric surgery. This technique has excellent effectiveness in terms of weight reduction and long-term persistence⁴⁴.

Although short-term weight loss of 7–10% of body weight is achievable with a number of different strategies, maintaining the loss is difficult. Up to 50% of individuals regain some of their lost weight by 12 months from the initiation of the strategy^{37,45}. In a diabetes prevention programme, 50% of those involved lost 7% of body weight at 6 months, but only 38% maintained this level of weight loss at a mean of 2.8 years⁴⁶. A number of factors are associated with the persistence of weight loss, some of which are irreversible (BOX 1). Others are amenable to modification, and should be taken into account when designing weight-loss strategies.

Weight loss and OA

A considerable number of randomized, controlled trials of weight loss have reported OA and joint pain as outcomes, but these trials recruited patients with existing OA and, as such, are tertiary prevention trials, and beyond the scope of this Review, except to state their effectiveness in reducing pain and improving function⁴⁷. The effects of weight loss on primary and secondary prevention of knee OA have been investigated in observational studies.

In a study involving 796 women, weight loss of around 5.1 kg reduced the risk of developing symptomatic RKOA over a period of 10 years, relative to women without weight loss (OR 0.46, 95% CI 0.24–0.86)⁴⁸. In a retrospective study³¹, historic weight gain from age 20–50 years was compared in 220 individuals aged 55–75 years with knee arthroplasty for primary OA and 415 individuals from the general population. For knee OA and arthroplasty,

Box 1 | Weight-loss maintenance and regain of lost weight: associated factors

Maintenance of $\geq 10\%$ weight loss for ≥ 1 year

- Ethnicity (non-Hispanic white vs Hispanic)
- Gender (female vs male)
- Age (adults aged 75–84 years vs 20–34 years)
- Low-calorie, low-fat diet
- High levels of physical activity (~1 h per day of brisk walking)
- Frequent self-monitoring of weight
- Eating breakfast
- Cognitive restraint (acting like a recently successful weight-loser for many years)
- Dietary consistency throughout the week rather than just on weekdays

Maintenance of $\geq 5\%$ weight loss for ≥ 5 years

- Ethnicity (African American vs white)
- Smoking
- History of type 2 diabetes mellitus
- Increased moderate physical activity over the 5-year period in comparison with activity before the weight-loss intervention
- Emotional support greater over the 5-year period than before the intervention
- Lower consumption of sugar-sweetened soft drinks reported at follow-up in comparison with those who regained weight

Maintenance of $\geq 5\%$ weight loss over 9 years

- Unmarried status (women)
- Low stress levels and health-promoting behaviours (men)
- Baseline type 2 diabetes and/or hypertension prior to weight loss (men)
- Lower levels of admitted previous alcohol use (men, in comparison with those who regained weight)
- Lower sugar consumption, more frequent intake of vegetables, and more frequent leisure activity (men, in comparison with overweight men and those who regained weight)

Maintenance of weight loss following bariatric surgery for ≥ 1 year

- Regular physical activity up to 10 years after surgery

Regain of weight after >1 year successful weight loss

- Reduced dietary disinhibition (periodic loss of control of eating)
- Depression
- Decrease in physical activity
- Increase in the percentage of calories from fat, compared with period of maintenance of weight loss
- Reduced dietary restraint

Regain of 5% weight loss after 9 years

- Stressful life, with use of tranquilizers in the year prior to weight loss (men)
- Low life satisfaction (self-reported, women)
- Social isolation (women)
- Poor sleep (women)
- Increased high-salt food intake compared with those who maintained weight loss (women)

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weight gain from normal BMI to overweight was associated with higher relative risk than persistent overweight, compared with normal weight over the same age range³¹. In the small group of individuals who lost weight, the risk of arthroplasty showed a nonsignificant reduction compared with individuals who maintained normal weight³¹. The results of other studies have shown increased risk of

knee OA or total knee replacement in association with weight gain, but these studies were underpowered to detect reduced risk with weight loss^{32,33}.

The evidence suggests that obesity leads to knee OA and pain, and that weight loss will reduce both clinical OA and knee pain. Weight loss is achievable with the help of various interventions, and although maintenance of reduced weight is difficult, modifiable predictors have been identified (BOX 1). In the current climate of progress towards personalized treatment of disease, interventions for weight loss should be targeted to the individual rather than enforcing homogeneous policies across the whole population.

Epidemiology of knee injury

Early intervention with a focus on the prevention of knee injury in young adults has great potential to reduce the burden of knee OA in the general population. Post-traumatic OA of the hip, knee or ankle is estimated to be responsible for 12% of the overall prevalence of symptomatic OA, with a financial burden of around 0.15% of the total US health-care direct cost outlay⁴⁹. The prevention of knee injuries will not only reduce the risk for the individual of life-long consequences in terms of symptoms, function and participation in work and recreational activities, but will also be cost-effective. The cost of implementing prevention programmes is small compared with the potential savings from avoidance of future orthopaedic surgery.

The great majority of knee injuries occur in sport, and sport-related injuries are more frequent in women than in men, which suggests that prevention of injury can be targeted to people at high risk. Although patients are often categorized as having an injury to the anterior cruciate ligament (ACL), these injuries are seldom isolated. On the contrary, concomitant injuries to the menisci, cartilage, bone or other ligaments are nearly always seen⁵⁰. The results of a population-based study from Sweden⁵¹ showed an incidence rate of 71 physician-diagnosed cruciate ligament injuries per 100,000 persons per year; other soft-tissue injuries were around 10 times as common. The highest incidence of injury was observed during adolescence, but knee injuries continued to occur throughout the adult lifespan⁵¹. The mechanisms of OA development following injury are multifactorial and incompletely understood. These mechanisms seem to involve not only the structures affected by injury, but also inflammatory responses and treatment factors relating to surgery and rehabilitation, as well as personal factors such as obesity and lifestyle, pain processing and genetics^{52,53}. Prevention strategies should be targeted not only at ACL injuries, but also at overall knee trauma to reduce the future burden from knee OA.

Around 50% of individuals who sustain an ACL injury develop RKOA in 10–15 years, whether or not they have reconstructive surgery^{52,54–56}. Because knee injuries often occur in young adults, these patients subsequently develop OA in their thirties and forties, when they have high demands and expectations of physical activity and participation in work, family and recreational life. As in other OA phenotypes, discrepancies

Box 2 | Characteristics of neuromuscular training

- The goal is the improvement of sensorimotor control and the functional stabilization of joints
- The rationale for the use of neuromuscular training is the existence of sensorimotor deficiencies, symptoms of pain and functional instability and functional limitation
- The targets for improvement are postural control, proprioception, muscle activation, muscle strength and coordination
- The exercises involve multiple joints and muscle groups, closed kinetic chains, and lying, sitting and standing positions
- The level of training is determined by the patient's sensorimotor control and quality of movement
- Training progresses by introducing more-challenging support surfaces, engaging more body parts simultaneously, adding external stimuli, and varying the type, speed and direction of the movement

are seen between structural findings and symptoms in those developing OA following a prior injury. Reports of symptoms following knee trauma including ACL injury are mostly restricted to patients who have had surgical reconstruction of the ACL. The relative contributions to the reported symptoms of the injury, the surgical reconstruction, rehabilitation and other surgical treatments are not known. Evidence obtained from a study of 1,197 patients with ACL reconstruction showed that although 66% of patients found their symptom state acceptable at 1–2 years after surgery, 22% were undecided and 12% considered themselves treatment failures⁵⁷. Thus, one-third of patients do not deem their symptoms to be acceptable, and similarly, patients with ACL reconstruction report more pain and worse quality of life than population norms⁵⁸. ACL injury also affects future physical activity level, with about one-third of those affected not returning to their prior level of sports participation, regardless of whether the injury is treated with surgical reconstruction or rehabilitation alone^{59–61}. Considering the interest and increasing participation rates in soccer, basketball and other sports with a high risk of joint injury, and the involvement of heavier players in many sports, the incidence of OA as a consequence of joint trauma is likely to increase in the future⁵³.

The identification of young people at risk of OA could involve screening for risk factors such as knee injuries requiring medical attention, surgery to the joint, persistent pain within the past month, overweight or obesity, physical inactivity, impaired muscle function and family history of OA. Most epidemiological studies of the incidence of OA have had a lower age limit of 50 for participants, but future studies should include people in their twenties, thirties and forties, to assess those who sustained major knee injuries as adolescents — around half of whom develop RKO within 10–15 years of the injury.

Primary prevention of knee injury

A meta-analysis including data derived from 27,000 individuals found that neuromuscular and proprioceptive training programs are successful in preventing around 50% of ACL injuries⁶². Principles of neuromuscular training for the prevention of knee injury are similar to those used in the treatment of knee injury

(BOX 2). These programmes typically take 10–20 min to perform, and commonly substitute for the regular warm-up session prior to sports practice 2–3 times weekly. The programmes usually also involve education in the awareness of high-risk positions. This form of prevention seems to be equally effective in all subgroups of individuals analysed⁶².

As with all behavioural changes, maintaining the new behaviour — in this case, including neuromuscular training in warm-up sessions prior to sports practice — is a challenge. Both the immediate and long-term effects are highly dependent on adherence to the training. In Norway, the use of physical therapists instead of coaches to train female handball players in a neuromuscular injury-prevention programme was associated with adherence during the specified intervention period⁶³. However, when the intervention period was finished, the injury rate increased and was at least as high as before the intervention started. An information campaign was then developed, targeting team coaches and managers in major cities around the country. The campaign involved an educational DVD and a website describing sport-specific exercise programmes, as well as a range of other activities, performed over a period of >10 years. The incidence of ACL injury in team handball was monitored and found to decrease to levels below those seen during the initial intervention period⁶³. In sports, many of the choices that determine the risk of injury to a player are made by the coach, so the implementation of injury-prevention programmes by coaches represents a valuable opportunity to effect change⁶³. The alternative, in which the players themselves have responsibility for preventive training, is ineffective.

Evidence shows that neuromuscular training performed for 15–20 min, 2–3 times per week, prevents 50% of ACL injuries. The current challenge is to increase uptake of such training (which shows great variation across sports and countries) in high-risk groups such as children and adolescent players. In this respect, the inclusion of injury-prevention programmes during physical-education classes in schools could have a substantial public-health effect. Guidance on well-tested interventions, along with additional information, is easily accessible on the internet, to help organizations, politicians, insurance companies, schools and other stakeholders to facilitate uptake^{64,65}.

Secondary prevention of knee OA

Individuals who sustain a knee injury in youth sports are at increased risk of being symptomatic, having impaired physical function, and being overweight or obese 3–10 years later, compared with uninjured controls matched for age, sex and sport⁶⁶. These findings suggest that risk factors predictive of OA in the general population are also present at a younger age in those with prior knee injury.

Compared with uninjured individuals, knee injuries are known to increase the risk of OA, and orthopaedic knee surgery is associated with the risk of OA and joint replacement at a younger age^{54,67}. The group of patients with injury overlaps with the surgery group, but not

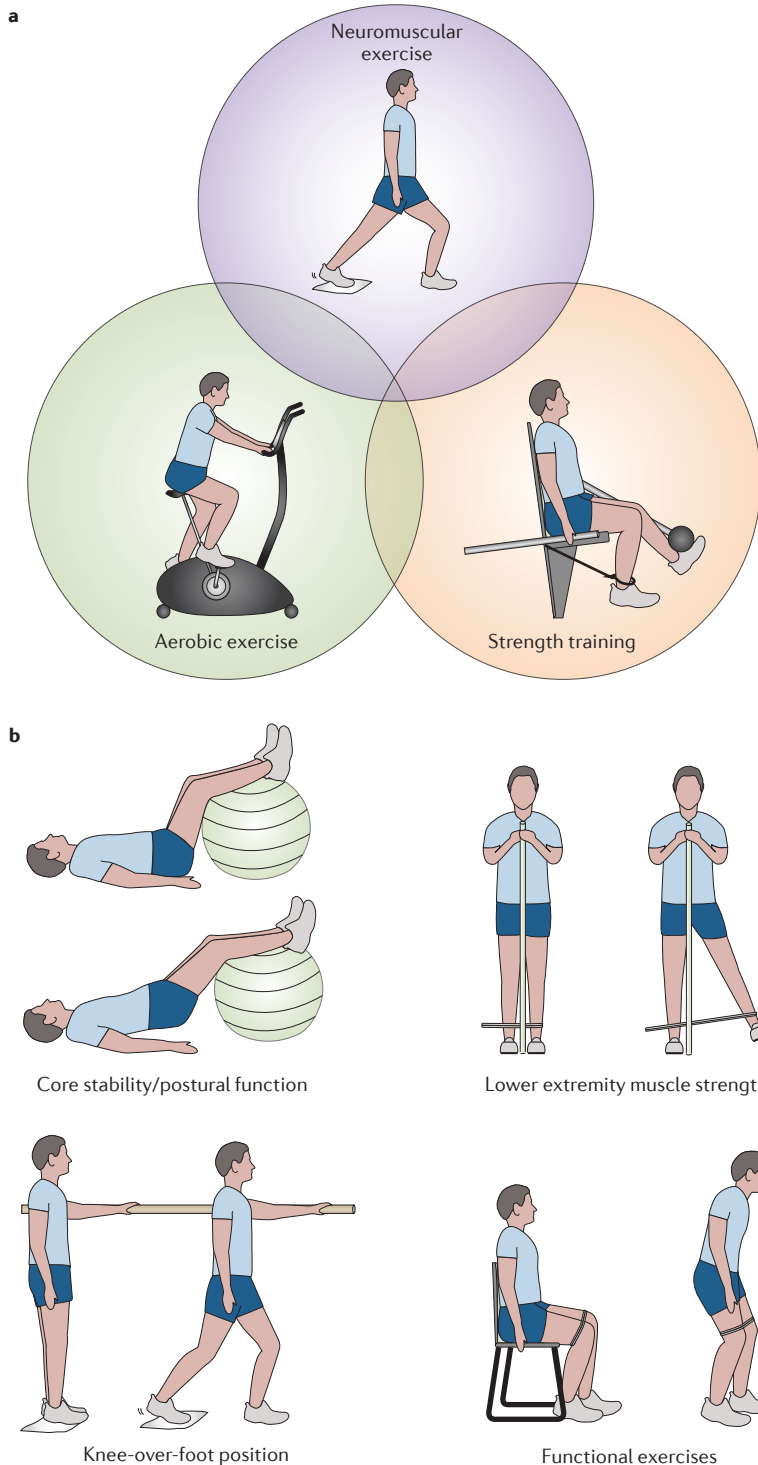


Figure 3 | Neuromuscular exercise. a | Whereas aerobic exercise aims to improve cardiovascular fitness, and strength training aims to increase muscle strength and muscle mass, neuromuscular exercise aims to improve sensorimotor control and obtain functional joint stabilization. The rationale for the use of neuromuscular training is the existence of sensorimotor deficiencies, symptoms of pain, functional instability and functional limitation. **b** | The targets for improvement are postural control, proprioception, muscle activation, muscle strength and coordination. The exercises involve multiple joints and muscle groups, closed kinetic chains, and lying, sitting and standing positions. Good movement quality with appropriate positioning of the hip, knee and foot in relation to each other is emphasized. The level of training is determined by the patient’s sensorimotor control and quality of movement. Training progresses by introducing more-challenging support surfaces, engaging more body parts simultaneously and adding external stimuli, as well as varying the type, speed and direction of movement. Examples of external stimuli include throwing a ball, catching a ball and sudden, unexpected movements.

groups in whom secondary prevention could be valuable. Although the causes of OA vary in different patients, the consensus is that OA is a mechanically driven disease, which is evident in individuals who have had injury or surgery — or both — in whom the joint structure is affected, so that the joint is less stable and more vulnerable. As an example, relative to joints without surgery, removal of meniscal tissue increases local contact pressures and the risk of future OA⁷⁰.

In addition to advice on achieving a healthy lifestyle, including maintaining a healthy body weight and regular physical activity, prevention strategies for those who are at risk of knee OA owing to injury or surgery should focus on biomechanical interventions with the ability to improve joint stability and decrease pain. As with the prevention of injury, neuromuscular exercise therapy can be used for this purpose. Neuromuscular exercise therapy is based on biomechanical principles, targets the sensorimotor system, stabilizes the joint while in motion and improves the patient’s trust in their knee (BOX 2, FIG. 3)⁷¹. Neuromuscular exercise therapy, like aerobic exercise and strength training, also provides effective pain relief in individuals with established OA^{72–74}. The first neuromuscular exercise program developed for use in patients with OA was published in 2010⁷⁵. Meta-analyses of the effectiveness of neuromuscular exercise should include consideration of additional outcomes such as perceived instability, tendency to give way, confidence in the knee and biomechanical outcomes.

Exercise therapy is different from physical activity with regard to definition, purpose and goal. Although physical activity is good for general health, and is defined as “any bodily movement produced by skeletal muscles that requires energy expenditure”⁷⁶, exercise therapy is good for the joint at risk of OA and is defined as “A regimen or plan of physical activities designed and prescribed for specific therapeutic goals. Its purpose is to restore normal musculoskeletal function or to reduce pain caused by diseases or injuries.”^{71,77} Neuromuscular

completely. For example, arthroscopic partial meniscectomy (APM) is the most commonly performed arthroscopic knee procedure, and is most often performed in middle-aged individuals without any prior high-impact trauma⁶⁸. Middle-aged patients undergoing APM have a sevenfold increased risk of developing symptomatic RKOA, compared with controls matched for age, sex and BMI⁶⁹. Individuals who have had major knee trauma, or orthopaedic surgery, make up easily identifiable target

exercise therapy is more effective than strength training alone in improving outcomes following ACL injury⁷⁸, and in many countries is the main component of ACL rehabilitation⁷⁹. However, strength training is also important in knee-injury rehabilitation, because muscle weakness is common following injury and is an independent risk factor for the development of OA⁸⁰.

Access to rehabilitation differs across countries and health-care systems. In some countries, patients with surgical reconstruction of the knee are not offered any structured exercise therapy at all, but are left to perform more general physical activities on their own. The available knee-ligament registries are focused on surgical patients, so the effect of exercise alone following a knee-ligament injury cannot be determined. The only high-quality, randomized study in young, active adults (comparing individuals treated with rehabilitation and early ACL reconstruction to those treated with rehabilitation alone and optional delayed ACL reconstruction) showed no difference in pain, other symptoms, function, quality of life, return to sport or RKOA at 2 years or 5 years^{61,81}. The results of a randomized study in 45 middle-aged patients with partial medial meniscectomy who were at high risk of OA suggest that neuromuscular exercise can improve cartilage matrix content⁸².

Exercise therapy is an active approach involving the sensorimotor system — including the muscles — to improve biomechanics; passive approaches are also available to improve joint biomechanics. Most commonly, knee braces and shoe modifications have been studied, alone or in combination. Typically, valgus braces (which force the knee in a medial direction) and lateral-wedge foot orthotics (which force the foot towards a more pronated position) have been tested in patients with established medial knee OA. This combination, or the brace alone, decreases pain and somewhat shifts the load in the knee from the medial to the lateral side^{83–89}. This change in load or contact stress might delay or prevent the onset of OA. In a randomized study in patients with patellofemoral OA, bracing was associated with pain relief and a decreased volume of bone marrow lesions in the affected compartment⁹⁰. These strategies could be used to prevent future OA, but poor compliance is currently a problem^{88,89}, and further development of devices and clinical studies are needed.

Personalizing prevention strategies

Motivation and adherence are key components in successful lifestyle changes. Ultimately, the responsibility for achieving a healthy lifestyle lies with the individual, and surveys show that large parts of the population are willing to make the required changes. However, the role of the clinician in providing motivation and support cannot be overemphasized.

In the clinician's office

Clinicians with positive attitudes and beliefs, who take time to explore the goals and barriers that patients perceive to be important, are more successful in achieving lifestyle changes in their patients than less-engaged clinicians. However, this approach is time-consuming

and rarely feasible in a busy practice. Referral to patient education and self-management programmes is, therefore, an attractive option to inform patients about the disease that they are at risk of or have early symptoms of, as well as their future prospects, and the effects, advantages and disadvantages of available treatment options.

Patient education

Patient education is often delivered in groups to enable interaction between participants, but is also available to individuals via the internet. Shared-decision-making tools enable patients, carers and clinicians to participate jointly in the choice of care pathway⁹¹. A choice of educational packages should be provided, to enable patients to have a choice and a personalized education. Checklists of known barriers to change and strategies to overcome them have been developed^{92,93}. Motivating factors for patients include the presence of social support, opportunities for organized exercise conducted by a professional, the availability of an exercise partner, and familiarity with exercise tasks⁹⁴.

Personalized exercise and weight loss

Although different types of exercise have similar pain-relieving effects^{74,95}, exploratory analyses suggest potential benefits to targeting deficits in individual patients with specific exercises⁹⁶. A patient suffering from varus thrust during walking (which is related to joint instability and lack of confidence in the knee) is likely to benefit from neuromuscular exercise, whereas an obese patient with muscle weakness is likely to benefit from strength training⁹⁶. Strategies for weight loss and exercise, as well as the use of appliances for biomechanical modification, should be tailored to the individual patient, rather than using a 'one size fits all' approach.

Conclusions

Knee OA is a common disease, which is predicted to become more prevalent as longevity and rates of obesity and physical inactivity increase. The current armoury of nonsurgical treatments for knee OA is aimed at providing relief from the symptoms of the disease, and no validated disease-modifying drugs are being marketed. The employment of prevention strategies is, therefore, essential to prevent an epidemic of knee OA.

Not all patients with RKOA experience knee pain, and most of those with RKOA will not progress to require surgical joint replacement. Early identification of individuals who are at risk of developing knee pain and OA is essential, to target prevention strategies more effectively. Neuromuscular exercise programmes are successful in preventing half of the knee injuries that occur during adolescence, suggesting that primary prevention of knee OA is possible. Appropriate prevention strategies, including weight loss and exercise programmes, should be identified for each patient by selecting interventions to correct, or at least attenuate, risk factors for OA. These interventions must also be acceptable to the patients, to maximize adherence to — and persistence with — the regimes. Now is the time to start the era of personalized prevention for knee OA.

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Author contributions

Both authors researched data for the article and contributed to discussion of content and writing the article, as well as reviewing and editing the manuscript before submission.

Competing interests statement

E.M.R. receives royalties for textbook chapters from Munksgaard and Studentlitteratur and is an associate editor of *Osteoarthritis and Cartilage*. N.K.A. has received honoraria from Bioberica, Flexion, GlaxoSmithKline, Novartis, Pfizer, Rottapharm, Servier and Smith and Nephew, held advisory board positions (which involved receipt of fees) with Bioventus, Merck Sharp and Dohme, Nicox and Q-MED, and received research grants from Bioberica, Roche and Servier.