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Can we prevent OA? Epidemiology and public health insights and implications

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Abstract

This narrative review discusses the potential of prevention of OA in different stages of the disease. The theoretical background for primary prevention (i.e. prevention of occurrence of definite structural or clinical OA in subjects free of the disease) and secondary prevention (i.e. prevention of progression of the disease in subjects with pre-clinical pathological changes to the joint) is provided and evidence for effective strategies is discussed. Since direct evidence for the prevention of OA development and progression is scarce, indirect evidence enhancing our current knowledge on the potential of OA prevention is additionally discussed. Also, implications of preventive strategies for study design and public health are considered. Prevention of OA has great potential, but as deliberated in the current review, there are still large gaps in our current knowledge and the implications of preventive strategies for the development and progression of OA require consideration.

Key words: prevention, osteoarthritis, risk factors, incidence, progression

Rheumatology key messages

- Research on the prevention of osteoarthritis is still in its infancy.
- Despite the availability of potential targets, primary prevention of osteoarthritis has hardly been studied.
- Secondary prevention of osteoarthritis is hampered by a lack of knowledge on modifiable risk factors.

Introduction

OA can affect every synovial joint and is characterized by structural changes to joint tissues, for example cartilage, bones and capsules. Pain and stiffness are the most common symptoms, resulting in a considerable impact on activities of daily living. Although the prevalence of hand/finger OA is substantial, hip and knee OA are thought to be responsible for the main burden of the disease. Ranked by years lived with disabilities, hip and knee OA are ranked 11th out of 291 diseases listed by the WHO [1]. Due to the ageing population and the obesity epidemic, OA is expected to become the fourth leading cause of disability by 2020 [2].

At present there is no cure for OA [3]. Treatment is focused on reducing physical disability and controlling pain. This narrative review aims to identify potential options for OA prevention.

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We delineate the primary prevention (i.e. measures aiming to prevent the development of definite structural or clinical OA in subjects free of the disease) and secondary prevention (i.e. measures aiming to prevent progression). In each section, the current knowledge on effective preventive interventions is discussed. This is supplemented with potential directions for future preventive interventions, based on the available evidence on risk factors of the disease, and their implications for study design and public health. The current review does not consider tertiary prevention (i.e. prevent and/or postpone the occurrence of OA sequelae in those with established OA), as it is thought to be very closely linked to the clinial treatment of OA rather than true prevention of the disease.

Primary prevention of OA

Although its urgency has been highlighted for many years [4–6], very little is known on how to apply primary prevention for OA development. Given the discordance between radiographic signs and symptoms of OA, subjects free of structurally defined OA could still fulfil a clinical diagnosis of OA and vice versa. Therefore, primary prevention of OA is defined as the prevention of the development of definite structural OA [e.g. Kellgren and Lawrence (KL) grade $\geqslant$2], clinical OA (e.g. defined by

the ACR criteria) or both in subjects free of structural and clinical OA.

According to the Society for Prevention Research, some basic principles should be considered when designing a preventive trial. Among others, the Society for Prevention Research states that (primary) preventive measures should be applied in an early stage of the disease, to those at high risk for disease development, and should avoid causing harm. The preventive intervention itself should target modifiable risk factors, specify clear goals, allow flexible protocols to comply with individual needs, be available in the local community and target the risk factors with a multidisciplinary approach [7].

In theory, primary prevention of OA would be most effective in a high-risk population free of structural and clinical OA, targeting modifiable risk factors over a prolonged period [8]. For this, knowledge on risk factors for the development of OA is crucial. For the development of knee and hip OA, numerous systematic reviews provide strong evidence for a variety of risk factors. To select a group of individuals at high risk for future knee OA, one could select women [9], overweight or obese individuals [9, 10], individuals with a previous knee injury or surgical procedure [9–11], those with low upper leg strength [12, 13] or those with with knee malalignment [14]. For hip OA development, those at high risk are individuals with a heavy physical work load or occupations that require heavy lifting [10, 15], individuals physically active at high intensity or for prolonged durations [13, 16], individuals with a previous hip injury [10], individuals with cam deformities [17] or dysplasia [18], or overweight/obese individuals [19, 20]. Although studied far less, the female sex [21], low forearm strength [13], overweight/obesity [21, 22] and a history of manual labour with high impact on hand/fingers [21] will put individuals at increased risk for hand OA development. In selecting a group at high risk for future OA, a combination of the listed factors will identify individuals at the highest risk for OA development, but will limit the number of eligible individuals.

Obviously, not all risk factors are suitable for the application of preventive interventions, since not all are modifiable. To prevent OA development, either risk factors themselves need to be prevented (e.g. joint injury or occupational heavy lifting) or the risk factors need to be reversed (e.g. low muscle strength, increased body weight or malalignment). In theory, that is, because very little evidence is available for the true preventive effects of these adaptations on OA development. Actually, only for the prevention of joint injuries are effective interventions available that should, in the long run, diminish the incidence of OA [23–25]. For other risk factors, such as overweight/obesity, low muscle strength and knee malalignment, well-known, widely applied and effective interventions that positively affect risk factors in asymptomatic individuals are available, for example diet [26], strengthening exercise [27] and braces [28]. Nevertheless, no studies have been performed to evaluate the long-term effects of such an intervention on subsequent OA development. Overweight/obesity is thought to be linked to OA development through overload of the joint (especially true for the knee joint, but less for the hip joint) and through low-grade systemic inflammation (all joints, but especially the hand/finger joints). In subjects without knee OA, but with obesity, it is known that weight loss (e.g. through bariatric surgery) reduces the joint stress [29]. Moreover, weight loss as little as 5% significantly reduces the low-grade inflammatory status of the body [30]. Other indications for preventive effects of these interventions come from estimations or observational data. A classic example is the paper by Felson *et al.* [31] from 1996, where a reduction in body weight from the obese group (BMI $\geqslant 30\,kg/m^2$) to the overweight group (BMI $\geqslant 26$ and $<30\,kg/m^2$) or from the overweight to the normal weight group (BMI $<26\,kg/m^2$) was calculated to reduce the incidence of symptomatic knee OA by 21% in men and 33% in women. Also, measures such as population-attributable fractions provide insightful, but indirect evidence for the potential preventive effects of counteracting risk factors. Population-attributable fractions calculated by Silverwood and colleagues indicated that 5% of new cases of knee pain/OA are related to previous injuries and 25% to being overweight or obese [9]. So for knee OA development, reducing the prevalence of overweight/obesity has probably greater benefits than the prevention of knee injuries will have; this is also the case because the prevalence of overweight and obesity is much higher than the prevalence of previous knee injuries.

Among others, the *Standards of Knowledge for the Science of Prevention* by the Society for Prevention Research highlights one key issue that has major consequences for the feasibility of primary prevention of OA: the intervention should avoid causing harm [7]. Although one might argue that harm should always be avoided when treating individuals, patients that do suffer from discomfort caused by any disease are probably likely to accept increased risk for side effects of any intervention when the intervention has the potential to reduce the discomfort (risk–benefit ratio). On the other hand, subjects free of any complaints will be reluctant to be exposed to potential side effects while treated for a disease that is not causing any discomfort at the time preventive measures are undertaken. Moreover, as potential preventive interventions, such as weight loss and muscle strengthening, will require behavioural changes that demand long-term interventions, the risk for unwanted side effects is high. Together with the absence of the potential to experience any effect of primary prevention by the target population in the absence of any disease activity, the willingness to undergo preventive strategies forms a major challenge when designing a preventive trial for OA. However, from exercise and weight loss trials among subjects with OA, it is known that in general there are very few adverse events reported in exercise studies. They usually include mild strains and muscle soreness, but might put the participants at increased risk for trips and falls [32]. For weight loss interventions, only weight loss $>20\%$ in 6 months or $>30\%$ within 12 months are indicated to require consultation with a medical doctor [32].

To the authors' knowledge, there has been only one published randomized controlled trial, evaluating a lifestyle intervention aimed at reducing body weight among overweight women free of both clinical and radiographic knee OA at baseline, primarily focused on the prevention of knee OA [33]. This study failed to show any preventive effects of the lifestyle intervention on knee OA development, mainly due to limited contrast in weight loss between the intervention and control group [33]. Nevertheless, in a *post hoc* analysis, the preventive effects of 5 kg or 5% weight loss on incident radiographic and clinical knee OA have been shown [34]; only 5 kg or 5% weight loss during the first year resulted in a 3-fold reduction in incident clinical knee OA after ±6.5 years (21 *vs* 7%) and a 2.5-fold reduction in radiographic knee OA development (16 *vs* 6%) in the high-risk population of middle-aged overweight and obese women. Given the high burden to society and the health care system, more high-quality trials studying the preventive effects of potentially effective interventions among subjects at high risk are urgently needed [8, 35].

Another major issue to be resolved for the feasibility of future preventive trials is the selection of outcome measures. OA is a very slowly progressing disease, for which the diagnosis requires the presence of substantial symptoms and structural changes to the joint. Validated diagnostic measures include the KL criteria that assess structural changes on radiography and the ACR criteria that combine both structural features and disease symptoms [36, 37]. Among different populations at risk, reported incidence numbers using these validated criteria vary between 1 and 4% per year [38–40]. These low annual incidence numbers would require unrealistic follow-up durations for preventive trials that aim to achieve clinically relevant differences between their preventive and control interventions. Runhaar *et al.* [33] counteracted this issue in the only available preventive trial by combining the incidence of KL $\geqslant$2, the ACR criteria and joint space narrowing of $\geqslant$1.0 mm into one single primary outcome; knees fulfilling one or more of these criteria were defined as having incident knee OA. Since the overlap between structural changes in symptoms is known to be low, this combination of incidence measures resulted in an overall incidence of 17% after 2.5 years of follow-up among the population of middle-aged overweight and obese women [33]. Although such a combined outcome measure seems appealing, validation against future definite knee OA development should still take place.

Rather than using validated diagnostic criteria as outcomes for preventive trials, also surrogate markers (e.g. joint space narrowing on radiography) or hallmarks of the disease (e.g. MRI techniques to quantify cartilage volume, cartilage morphology or bone marrow lesions) can be considered. However, MRI studies among individuals free of structural knee OA (KL grade 0) showed a high prevalence of structural OA features, without significant differences between BMI groups, questioning the specificity of these signs [41]. Moreover, since longitudinal data on surrogate markers and hallmarks of the disease in subjects at risk for OA development are limited, what change in these measures could be deemed clinically relevant within asymptomatic individuals free of structural changes, and thus should be the prevention target and used for sample size calculations, is still unknown.

Given the discussed challenges when targeting specific high-risk groups of individuals for the prevention of future OA development, population-based approaches might be the way forward to reduce the incidence and hence the burden of OA on society. Already in 1985, epidemiologist G. A. Rose discussed the superiority of population-based approaches to prevent diseases over individualized approaches focused on high-risk individuals from a community perspective [42]. Although strategies targeted at high-risk individuals will lead to interventions appropriate to the individual, will enhance motivation by the individuals and the physicians, and will have a favourable risk–benefit ratio, it will also have many disadvantages such as high costs for screening, over-diagnosis and the potential of targeting only a population at high risk while in fact those at minimal risk actually cause the highest number of cases, due to the high prevalence of such a population [42]. Rose's population-based approaches attempt to control the determinants of incidence, which potentially has far greater effect on a population level than the individually targeted approaches [42]. Due to its prevalence and its strong association with the development of OA in multiple joints, obesity probably is the most important risk factor to target with population-based approaches, targeting the prevention of weight gain in all and the reduction of body weight in those with overweight/obesity. Obviously, given the well-known risk for other chronic diseases due to the prevalence of obesity (e.g. cardiovascular disease, cancer and type 2 diabetes), OA development would not be the only reason to target the prevention and reduction of excessive body weight [43, 44]. In favour of population-based approaches, one can probably appreciate that in theory a reduction of 5% body weight in all individuals has far greater effects on the health status and the burden on health care than a 10% reduction of body weight among those with a BMI $\geqslant$30 (obesity), given the fact that the prevalence of obesity is only about 25% in Western societies [45]. Another advantage of the population-based approach is the fact that it is behaviourally appropriate; for example, when targeting body weight, one is not advising an individual to change habits and adopt a healthy lifestyle within an environment that elicits unhealthy behaviours (e.g. fast food, sugary beverages, alcohol consumption, etc.), but rather aiming to make the desired behaviour the social norm [42]. Since the publication of Rose's theories on population-based approaches, interventions on unhealthy habits (e.g. smoking, alcohol usage and high fat intake) using more general, upstream policy-based interventions have been shown to be more effective than the downstream interventions targeting individuals (counselling, education, medication prescriptions) [46]. Moreover, these more comprehensive interventions are indicated to be more powerful, more rapid, cost-saving, more equitable and tending to

Table 1 Overview of policy actions and barriers for the prevention of overweight and obesity

Target	Potential strategies	Barriers
Improve the food environment to stimulate healthy choices	Fiscal food policies, mandatory nutrition panels on the formulation and reformulation of manufactured foods, implementation of food and nutrition labelling, and marketing restrictions and advertising bans for unhealthy foods	Food industry aims for maximal profit, not necessarily for optimal public health
Improve the physical activity environment to facilitate higher levels of physical activity	Urban planning policies, transport policies and organizational policies on the provision of facilities for physical activity	
Diminish social inequality	Trade agreements between countries, personal income tax regimes and social security mechanisms	
Influencing eating and physical activity behaviours	Directly influence behaviour through directly affecting the setting in which people live their lives, such as schools (e.g. nutrition education and policy, parent outreach and social marketing), home environment (e.g. reducing television time, role modelling by parents and creating opportunities for physical activities), workplaces and community (e.g. availability and price of healthy food choices, quality of food, and portion sizes)	Computer-based work dominating most occupations and school education is highly dependent on the internet and computer. The habit of snack consumption. Stress caused by the increasingly competitive society
Supporting health services and clinical interventions in primary care	Increase number of dieticians and nutritionists, subsidize weight-loss medication, provide professional and organizational support and training, and offer financial incentives	To physicians: a lack of time to address obesity during routine office visits, a lack of reimbursement, inadequate training and low self-efficacy in handling patients of excess weight. To patients: stigmatization, a lack of financial incentive, difficulties in accessing weight management services

Summarized from Chan and Woo [44].

reduce disparities [46]. In a neat overview, Chan and Woo [44] presented the complex issues around designing and implementing public health approaches for the prevention of overweight and obesity. Based on the framework of Sacks *et al.* [47], these authors discuss that policy actions for effective obesity prevention strategies should target the food, physical activity and the broader socioeconomic environments, should aim at improving eating and nutritional habits, and should support health care services and clinical interventions [44]. Table 1 summarizes the presented strategies for each of these targets and their potential barriers.

In 2015, the Canadian Task Force on Preventive Health Care published a guideline with recommendations for the prevention of weight gain and use of behavioural and pharmacological interventions to manage overweight and obesity in normal-weight and overweight/obese adults in primary care, applicable to most Western societies [43]. Based on systematic searches of the literature, the task force postulated different recommendations for the prevention of weight gain and the treatment of excessive body weight in primary care. Unfortunately, no recent high-quality studies were identified that supported any strategy to prevent short- or long-term weight gain among persons with normal weight [43]. For people with obesity, the task force recommends 'that practitioners offer or refer to structured behavioural interventions aimed at weight loss. Structured interventions are intensive behavioural modification programs involving several sessions over weeks to months. Recommended interventions include behaviourally based interventions focused on diet, exercise or lifestyle changes, alone or in combination. Lifestyle changes include counselling, education or support, and/or environmental changes in addition to changes in exercise and/or diet' [43]. Although evidence is available for the effectiveness of pharmacological interventions (e.g. orlistat or metformin), the task force recommends against the use of these due to the increased risk for adverse events and the incorporation of behavioural components in combination with the pharmacological interventions in the identified studies, whereby the effectiveness of the pharmacological interventions alone could not be determined [43]. In conclusion, as overweight and obesity are highly multifactorial conditions, involving complex interactions between genetic factors, hormones and environmental and social factors [44], the solutions to prevent or to counteract these conditions are complex. Experts call for high-quality knowledge on the individual's motivation for behaviour changes and for the development of effective support mechanisms and counselling tools for primary care

to cope with the obesity epidemic [43, 44]. That effective population-based weight loss strategies will prevent the subsequent onset of OA is expected, but remains to be seen. Adding OA-specific patient-reported outcome measures or even standardized radiography to population-based cohorts and intervention studies aimed to treat the onset or prevalence of obesity might be an efficient way forward in the field of research on the primary prevention of OA development.

Contrary to what is suggested for the uptake and effectiveness of a healthy lifestyle [46], for the prevention of joint injuries (the other strong modifiable risk factor for OA development) much of the available evidence comes from trials focusing on more personal and individually targeted, downstream interventions. Although evidence supports the effectiveness of several injury prevention strategies [23, 48, 49], only 4% of the interventions available in literature ($n = 6$) focused on upstream changes to the rules and regulations that govern sport [50]. So although efficacy is proven for several specific targeted preventive strategies, this lack of more general, upstream policy-based interventions to diminish the number of sport-related joint injuries could limit the effectiveness of injury prevention strategies on a population level.

Secondary prevention of OA

Secondary prevention focuses on measures to detect OA early, to prevent symptom occurrence once the first structural lesions have developed, and to halt or decelerate the progression of structural lesions. Compared with the risk factors for incident knee OA, the risk factors for OA progression and the magnitude of association are not well established. Except for structural lesions, such as joint malalignment, many studies have found a few strong risk factors, such as sex and BMI, were not associated with the risk of OA progression. This paradoxical phenomenon could be partly explained by conditioning on intermediate stage of OA [51, 52]. In a systematic review published in 2015, Bastick and colleagues concluded that there is only strong evidence for knee pain, presence of Heberden nodes, varus alignment and high levels of serum markers hyaluronic acid and TNF-α as risk factors for knee OA progression [53]. In addition, although symptomatic OA is a major factor leading to the decision to seek medical care and an important antecedent to disability, most previous studies have focused on the risk factors for structural lesions. Only a few population-based observational studies have been conducted to describe the pattern of incident symptomatic or clinical OA at three major joint sites (i.e. hip, knee and hand) [54–56], and to identify their risk factors [55, 57]. As a result the underlying causes of symptomatic OA are still not well understood, and there is an urgent need to shift OA research toward patient-centred outcomes, that is, symptomatic or clinical OA and its sequelae [58]. All these challenges hinder the development of effective strategies for secondary prevention.

Nevertheless, previous studies have shown that severity of radiographic OA is strongly associated with the presence of symptoms, such as pain [59]. Thus, it is not unreasonable to adopt the same strategies of primary prevention, such as lowering body weight, avoiding joint injury, avoiding frequently carrying or lifting heavy objects, and minimizing knee-bending activities, for the secondary prevention of OA.

To date, few studies have been performed to assess risk factors for progression or symptom occurrence of hand and hip OA, making it difficult to recommend the effective secondary prevention strategies for OA in these two joints. However, as mentioned above, one may argue that a primary prevention programme aiming to prevent the occurrence of radiographic OA at hand or hip joints, such as lowering weight, avoiding joint injury or weight lifting, may also have a potentially beneficial effect on the occurrence of symptoms and progression of structural lesions.

In conclusion, although risk factors for incident OA in different joints are known and primary preventive strategies focusing on the occurrence of OA have been advocated for many years, such as lowering the prevalence of overweight/obesity or reducing the risk of joint injury, there is a paucity of evidence on effectiveness of primary prevention of OA from well-conducted randomized clinical trials. Such kinds of studies are urgently needed. Currently, population-based approaches that target obesity, as the largest risk factor for OA, are probably the most effective measures available that are expected to have positive effects on the incidence of OA and other diseases that challenge the health care systems worldwide. Knowledge on the secondary prevention of OA is hampered by the limited knowledge on risk factors for symptomatic OA progression, especially for joints other than the knee.

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