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Editorial
Risk factors of knee osteoarthritis − excellent evidence but little has been done

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About one in four people over the age of 55 have persistent knee pain and one in 10 of these people have painful disabling knee osteoarthritis (OA)[1]. The disease increases with increasing longevity and obesity[2,3]. More than 50 treatments are available; almost all are symptomatic therapies[4]. However, the benefits of these treatments are only marginal over placebo[4,5], and often outweighed by their side effects[4]. Currently there is no effective structure modification treatment. The majority of patients have to live with the disease for the rest of their lives, with few being able to receive total joint replacement due to cost and other issues[6]. OA is irreversible with current medical treatments!

What else can we do for this most common and disabling arthritis? Given the outstanding researches in the past two decades into the epidemiology of knee OA, prevention is possible. We welcome Blagojevic and her colleagues' current meta-analysis[7] in this issue of the journal (page xxx). The study summarised the effect sizes of major risk factors, including modifiable risk factors (such as obesity, joint injury and occupational risk) and non-modifiable risk factors (e.g., Heberden's nodes, age and female gender). Unlike the results from an individual observational study, the meta-analysis provides a pooled effect size taking into account variation between studies. The results are therefore more generalisable. The important message from this study is no longer restricted to the relative risk estimates *per se*. It is the possibility and potential public impact that we may achieve by modifying these risk factors. According to the odds ratio (OR) and 95% confidence interval (CI) pooled for obesity (OR = 2.63, 95%CI 2.28−3.05)[7], for example, in a population with 25% people who are obese, 29% knee OA could have been prevented by reducing body mass index (BMI) from more than 30 to less than 25. This is calculated using population attributable risk percent (PAR%) = $Pe(OR-1)/[Pe(OR-1)+1] \times 100\%$, where Pe is the percentage of exposure[8]. The size of the benefit may vary from population to population with a 95% CI between 24% and 34%. The impact increases with increasing prevalence of obesity, until 2025 when the prevalence of obesity reaches 60%[9], the benefit due to the weight reduction is enormous − 49% (95%CI 43−55%) knee OA could have been avoided! Similar population risk of knee OA attributable to obesity was estimated by Felson and Zhang in their excellent narrative review a decade ago, where the total population risk and the risk due to obesity were used to calculate the PAR%[10]. The method may be extended to any study which reports the relative risk or OR according to above formula, and a meta-analysis may be used to combine the results to increase the power and generalisability of the estimate. Unfortunately, after 10 years, little has been done for this and at the population level to prevent the disease. Much of the time and resource have been spent on the identification of a "magic bullet" which in fact does not exist for this condition. As a result, the incidence of knee OA is rising[2,3], as is the prevalence of the disease, resulting in horrendous economic burdens to the society.

In addition to obesity, there are number of other risk factors that can be modified such as joint injury and occupational risk, as reviewed by Blagojevic *et al.* (in this issue)[7]. Given an OR of 3.86 (95%CI 2.61−5.70)[7] and a population risk of 10% for knee injury[11], for example, 22% (95%CI 14−32%) knee OA could have been further prevented. The benefits obtained from preventing different risk factors may be additive under the assumption of independence. Theoretically there is an opportunity that we may prevent the disease completely, should all risk factors be eliminated. It is a shame that this systematic review only provided the effect sizes for BMI and knee joint injury. Other modifiable risk factors such as occupational risk, muscle strength and diet have not been quantitatively reviewed.

There are some other limitations for Blagojevic *et al.* systematic review. Firstly, the relative risks may not necessarily be independent. This is because meta-analysis can only summarise data available from individual studies where relative risks may not be adjusted with all putative risk factors, therefore the OR is not exclusive. Secondly, results from cohort and case control studies should always been treated separately, as they are prone to different selection biases. The community-based cohort study would give the best estimate for the relative risk. The "protective" effect of smoking detected in case control studies cannot be ratified by the result from cohort studies because of the selection bias in the case control study design. In a case control study, cases and controls are often selected from a hospital. Controls are normally patients from other departments such as patients with respiratory, renal, cardiovascular diseases, diabetes and cancer that are highly associated with smoking. The negative association between smoking and knee OA should not be interpreted as smoking is a *PROTECTIVE* factor for knee OA, but a "RISK" factor for respiratory, renal or cardiovascular diseases! I would never use the word "protective" for any negative finding

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before I understand what is exactly going on with the association. Thirdly, although this is a systematic review, due to its extensive scope – attempting to cover all risk factors in one manuscript for the development of knee OA, the literature search might have missed some studies; especially those which only included the target risk factor as a confounding factor for the adjustment purpose, not a primary risk factor for the purpose of risk estimation.

Given the extensive literature in epidemiology of knee OA, we would like to encourage more meta-analyses for modifiable risk factors (e.g., BMI, joint injury, occupational risk and muscle strength). We would also like to know the effect size of biomechanical risk factors, such as mal-alignment. Although these may not be directly modifiable, the extra risk due to them may be reduced by changing the biomechanical stress for the knees, e.g., wearing knee braces and insoles. Although we cannot do much about genetic and constitutional risk factors, we are able to work out the size of the interaction between genetic and exposure, hence to modify this effect. Nutrients (such as vitamins) have been suggested beneficial to the joints. Several prevention trials are now ongoing. We are expecting some better ideas how nutrients would contribute to the prevention of knee OA soon. Analysis of existing epidemiological data on the effect size of healthy diet is also useful. All together, knee OA is preventable and the potential benefit of the prevention is huge. As knee OA shares some of its risk factors (e.g., overweight) with other joint OA and other chronic conditions, such as cardiovascular diseases and diabetes. The benefit of weight reduction if overweight or prevention of overweight is multiplicative. In brief, extensive epidemiological investigation has confirmed that obesity, knee injury and occupational risk are three major modifiable risk factors for the development of knee OA. The modification of these three factors at the population level may lead to the effective control of knee OA. The sooner we put the primary prevention in place, the quicker we can reduce the burden of the disease.

Conflict of interest

There are no financial interests, direct or indirect, that might affect the content of this editorial. The manuscript has been read and approved by the author, the requirements for authorship have been met. This is an original manuscript that has not been reported elsewhere.

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