The epidemiology of osteoarthritis: Manchester and beyond

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The paper describes the contribution made to the understanding of the epidemiology of osteoarthritis by the Arthritis Research Campaign Epidemiology Unit. Kellgren and Lawrence defined the condition radiographically and produced the widely used Atlas of Standard Radiographs of Arthritis. They documented the age- and sex-specific prevalence of osteoarthritis. Based on studies in occupational groups, they proposed that local biomechanical stress was linked to causation. Philip Wood focused on osteoarthritis as a syndrome of pain and disability. During the directorship of Alan Silman the emphasis has been on osteoarthritis as a public health problem.

Rheumatologists have not always enthused about osteoarthritis. Jonas Kellgren, rightly feted at this jubilee gathering, made lasting contributions to osteoarthritis studies and yet in 1961 could write about the condition that 'it is one of those dull commonplace disorders that are hard to study with enthusiasm' [1]. It was not such an exciting experience for patients either. Roy Acheson, another great British pioneer of population-based studies of osteoarthritis, whose New Haven studies in America were contemporaneous with Lawrence and Kellgren's descriptions of the condition in English communities, considered that 'it has generally been considered a dull and inevitable accompaniment of advancing years' [2]. If you are going to have a rheumatic disease, it seems, at least get something more exciting than osteoarthritis. However, the sense that the rheumatological community was neglecting something more worthy of attention was best captured by Dixon's characterization of osteoarthritis as 'the Cinderella of rheumatology' (quoted in [3]).

In this brief review, I want to consider some ways in which epidemiological studies during the past 50 yr have helped to repair that neglect and have highlighted osteoarthritis as a clinical, social and public health problem of great and increasing importance in our ageing society. The Arthritis Research Campaign (arc) Epidemiology Unit in Manchester has not only made a major contribution to the current picture, but the unit's three phases of development under separate and distinctive leaders serve to typify three different approaches to osteoarthritis studies. The structure and the emphasis of this article is based around these and is intended to focus on the particular developments inspired directly or indirectly by the work of the unit.

Phase 1: The Kellgren and Lawrence years. Osteoarthritis as a disease

In her contribution to this anniversary meeting, Deborah Symmons has described how rheumoid and osteoarthritis gradually developed distinctive and separate identities during the first half of the 20th century, as they emerged from the single pot of inflammatory arthritides. By the time that Kellgren and Lawrence had settled firmly into the biomechanical, non-inflammatory mode, and was seen as a pathological disease that resulted from 'the joint's inadequacy to meet the mechanical stress placed upon it' [1]. Indeed, so emphatic were they in this anti-inflammatory depiction of the disease that they consistently called it 'osteoarthrosis' in their publications on the topic.

Armed with this model, they then set about the first task of epidemiology, as depicted by Kellgren in his 1961 Honeyman Gillespie lecture 'Osteoarthrosis in patients and populations'. This lecture—the terms of which precluded the mentioning of experiments on animals—was published in the British Medical Journal in 1961 [1] and remains a classic introduction to osteoarthritis epidemiology. The task was 'the definition and quantitation of the abnormality' [1]. The X-ray was to be the basis for this, with the presence of pathological processes of osteoarthritis (the loss of cartilage, the sclerotic thickening of the bone around the joints, and the formation of new bone to scaffold and stabilize the degenerating joint) being deduced from the radiographic appearances (narrowing of joint space, subchondral opacification of bone, and osteophytes). Kellgren and Lawrence's creative contribution was to standardize both the identification of these features (by the use of the atlas reproduced in this supplement) and the classification of their severity (by a numerical grading system). This Kellgren and Lawrence grading [4] was their most enduring contribution to osteoarthritis studies, and is still used today.

The pair then took this standard quantitative approach and applied it to the next task of epidemiology: to describe the occurrence and distribution of disease in populations. They X-rayed joints in their community studies. Defining the presence of disease as there being at least one joint affected by definite radiographic osteoarthritis (Kellgren and Lawrence grade 2, which means a definite osteophyte is present), they found that the prevalence of osteoarthritis increases steadily with age, until at ages above 65 yr the prevalence reaches 100% [5].

Does this mean that osteoarthritis the disease, as diagnosed radiographically, is an inevitable consequence of ageing, that cartilage, for example, will inevitably decay away within the lifespan of humans? Population-based studies since Kellgren and Lawrence's time have shown that this is not the case. These studies have added to the picture provided by the early Manchester studies because the numbers of older people were sufficient to stratify and analyse up to the oldest ages. David Felson's group, for example, reported on the prevalence of Kellgren and Lawrence grade 2-plus radiographic knee osteoarthritis from an American population. Although radiographic osteoarthritis of the knee is common in this population and the prevalence increased
from 28% in those aged 60–69 yr to 45% in those aged over 80 yr, this still meant that most over 80-yr-olds were unaffected by the condition [6]. At any major joint site, many people in the oldest age-groups will not have osteoarthritis on X-ray. It is not therefore an inevitable consequence of ageing. This conclusion opens up the possibility of prevention and takes us, as it did Kelgren and Lawrence, to the third task of epidemiology, to identify what causes the disease of osteoarthritis.

Given Kelgren’s depiction of osteoarthritis as joints failing under strain, there are two basic models of cause. In the first model, a joint has developed abnormally or become abnormal as a result of damage or injury. Osteoarthritis then arises from normal stress acting on a joint that has lost some of the biomechanical qualities which would normally enable it to absorb the stress. In the second model, a normal joint is put under unusual stress or load over time, and develops osteoarthritis. Added to both of these models is a third factor, the presence of a generalized susceptibility to osteoarthritis, which might be genetic or metabolic, for example, and which interplays with local factors of stress or injury to produce osteoarthritis at certain joint sites.

The possibility that abnormal development in a joint can give rise to osteoarthritis change is evidenced by the well-described problem of premature osteoarthritis in the hips of pedigree heavy breeds dogs such as German shepherds and rottweilers. This has been traced to the high incidence of congenital dysplasia of the hips in these breeds. In humans too, cohorts of young people with acetabular dysplasia have been followed up and have a high risk of developing early osteoarthritis of the hip [7]. However, the question as to whether mild forms of dysplasia continue into adulthood and give rise to osteoarthritis of the hip in the older population is controversial. Clinical and epidemiological studies continue to highlight that a small proportion of all cases in older adults are attributable to this cause [8], but it is unlikely to be a major cause of hip osteoarthritis in the population as a whole [9].

However, Lawrence and various of his international collaborators did raise the possibility that geographical variations in congenital hip problems might be one explanation of the geographical variation that they noted in hip osteoarthritis across the world. Further studies since then, supported by the arc Epidemiology Unit, in Hong Kong [10] and Nigeria [11], and in Japan by the UK Medical Research Council's Environmental Epidemiology Unit in Southampton, which conducted a series of case-control studies during the 1990s, led by David Coggon and Cyrus Cooper and funded by the arc [14, 16, 17]. These investigated physical activities across a range of occupations, rather than using occupational job title as a proxy for biomechanical stress. Heavy lifting and walking for both hip and knee joints, and bending and kneeling for the knee, were identified as risk factors. The associations were stronger the longer the time spent in jobs involving such activities, but the proportion of all osteoarthritis that can be attributed to such activities is small. The lack of strong associations between lower limb osteoarthritis and leisure and domestic activities, such as sport and walking, suggests that these may not be common causes of the problem in the population as a whole.

There is one exception to this, the biomechanical stress of obesity. Both hip and knee osteoarthritis have been consistently linked with overweight, particularly the knee, and work from the Framingham study in America [13] and a range of arc-sponsored investigations in the UK [14, 18, 19] have estimated both the relative and the attributable risks to be substantial. Those with a body mass index in excess of 30 have a five-fold risk of definite radiographic knee osteoarthritis, and it is estimated that one-third of knee osteoarthritis in obese people is attributable to the obesity. Although it is reasonable to suppose that the effect of overweight on lower limb joints is a simple one of excess biomechanical stress on these joints, this is unlikely to be the whole picture. Firstly, it remains a puzzle as to why the ankle joint is relatively spared in all this; whether through evolutionary selectivity [20] or some other general mechanism, the ankle points clearly to there being some additional factor (protection at the ankle or susceptibility at the knee or hip) which is necessary to the development of osteoarthritis in obese people—the mechanical stress of obesity does not inevitably harm the joint. Secondly, there is the puzzle of the link (observed in some [21, 22] but not all studies) between obesity and hand osteoarthritis, which is difficult to characterize as biomechanical and which has led to the proposal that obesity might act through a more general metabolic mechanism. One such mechanism has been highlighted in recent studies of groups of babies born in the same year and followed regularly into adulthood. The combination of low birth weight
and subsequent overweight during adult life carried the highest risk for hand osteoarthritis at the age of 53 yr, suggesting that the trajectory of weight gain carries susceptibility to osteoarthritis generally [21].

Such susceptibility might underlie the observation that osteoporosis and osteoarthritis are inversely related [22]. High bone density might increase the risk of osteoarthritis whilst at the same time protecting against osteoporosis. This might be a general association or one that acts locally at different joint sites. However, epidemiological studies have identified a conundrum: in general those factors considered to be protective against osteoporosis (high bone mineral density, hormone replacement therapy) are linked with a higher risk of onset of osteoarthritis [23] but are protective against radiographic progression of established radiographic osteoarthritis [24]. This is not unreasonable if osteoarthritis is seen as a dynamic process of damage and repair [25]—the osteophyte as both sign of disease and evidence of active repair of the problem. Such concepts and studies clearly identify a new era of epidemiological studies of radiographic osteoarthritis which are distinctive from the designs of Kellgren and Lawrence in being longitudinal. They are distinguishing between risks for onset and progression of the disease and between the different risks which there might be for the appearance and change over time of different radiographic features of osteoarthritis (for example [26]).

Although Kellgren and Lawrence did not go down these pathways, they were well aware of the idea of generalized susceptibility to the disease. In particular they took the logical idea that generalized susceptibility would mean that there would be clustering of multiple joint involvement in individuals in the general population—since a susceptibility would act at more than one joint site, even if additional local factors were needed to convert that susceptibility into actual disease. They were aware of the clinical description of people with multiple site joint osteoarthritis: more likely to be female and middle-aged and to have consistent involvement of the hand joints. They demonstrated the existence of this syndrome at the population level [27], and this finding has been confirmed and explored further since that time. A notable example was the study by Egger et al. [28] of patterns of hand involvement in osteoarthritis. Women with one distal interphalangeal joint affected by radiographic osteoarthritis were compared with women who had no osteoarthritis in that joint. Given osteoarthritis in one such joint, the odds of the following joint involvement were elevated: same joint in the other hand (symmetrical involvement, odds ratio = 39), other distal interphalangeal joints in the same hand (row involvement, odds ratio = 10), and proximal joints in the same digit (ray involvement, odds ratio = 3).

The reverse argument, however, does not hold. Such clustering does not imply a generalized disease—it could be that environmental factors act at a number of joint sites (occupational stresses, for example, in the different joints of the hand). Kellgren and Lawrence had looked further at this by investigating one specific joint involvement were elevated: same joint in the other hand (symmetrical involvement, odds ratio = 39), other distal interphalangeal joints in the same hand (row involvement, odds ratio = 10), and proximal joints in the same digit (ray involvement, odds ratio = 3).

The crucial relevance of this approach to osteoarthritis becomes clear when we look at the relationship between symptoms and radiographic disease. Sidney Cobb, an American who was carrying out population studies of the rheumatic diseases before both Lawrence and Acheson, observed that ‘it has long been recognised that many persons have X-ray evidence of osteoarthritis without symptoms’ [38]. This finding has been confirmed in many epidemiological studies since, including those of Kellgren and Lawrence [39]. The ‘prevalence staircase’ described by Peat [40]

Phase 2: The Wood years. Osteoarthritis as a syndrome of pain and disability

Kellgren and Lawrence were certainly very concerned about pain and disability [1], but they approached it as an important aspect of the radiographic disease. Wood’s contribution, together with that of the arc unit’s then deputy director Lisa Badley, was to place the patient’s actual problems at the centre of things and to pioneer the development of a classification of these in their own right through the World Health Organization’s International Classification of Impairments, Disabilities and Handicaps (ICIDH) [36, 37]. This classification has changed its name over the years but the central organizing principles remain the same and their application to osteoarthritis is clear. The radiographic disease represents the basic pathological impairment, and joint pain is the basic patient-perceived impairment. Disability is any restriction of usual functioning that either or both of these impairments might bring (e.g. inability to walk a certain distance in a certain time), whilst handicap refers to the crucial idea that any actual impact that impairment and disability have depends on the circumstances of the individual’s personal and social life. Does the inability to walk a certain distance, for example, actually restrict the person from doing the things they wish to do in reasonable comfort?

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summarized data from the studies as follows. In the general population aged over 55yrs, some 25% will have radiographic knee osteoarthritis but only about half of these will have experienced significant knee pain in the past year. In addition, among all those in this age-group who have experienced such knee pain in the past year, only about a half will have radiographic osteoarthritis. Even among those who have disabling knee pain, only about two-thirds will have definite X-ray changes of osteoarthritis. There is no doubt that there is an association between symptoms, disability and radiographic osteoarthritis of the knee, particularly at the severe end of the spectrum, but the clinical and radiographic syndromes of knee osteoarthritis in the population are not equivalent despite some overlap. Among older people with knee pain in the population, as groups from Bristol and Nottingham have separately shown [41, 42], the strongest predictors of disability are not the severity of the X-ray changes at the knee but other factors, such as quadriceps strength and the presence of depression. This is a clear example of Wood’s template. Disease impairment (the biomedic model) alone does not explain the impact on patients’ lives, which will involve many other influences—biological, psychological, social—which shape the illness and its effect on the individual.

But why does local disease pathology not equal pain? One explanation is that the radiograph is an inadequate tool for identifying osteoarthritic change. Certainly, the gap which Cobb and others all identified between symptoms and X-ray has narrowed at the knee because of the recognition of the importance of disease in the patello-femoral joint, a site not represented in the radiographic views taken in early studies [43]. Furthermore, studies involving magnetic resonance imaging of the bone and periaricular structures are suggesting other potential sources of chronic joint pain in older people which might be early indicators of later radiographically visible changes [44]. Despite all this, it is likely that the severity and nature of chronic joint pain in older people will never be completely explained by local changes in or around the site of pain. This is now accepted to be the case in low back pain, and reflects the findings of basic pain researchers such as Wall and Melzack [45], who described how excitatory and inhibitory stimuli from the central nervous system—emotions for example—can modulate and mould the perception of peripherally located pain.

Experiments to induce pain in areas distant from the affected joint in people with osteoarthritis and their age- and gender-matched non-osteoarthritis controls suggest that general sensitivity to pressure-induced pain is enhanced in the presence of local osteoarthritis [46]. Jinks has described that knee pain sufferers from the general population have an increased likelihood of other sites of joint pain compared with those without knee pain, the odds increasing with the total number of other sites of pain [47]. Finally, cross-sectional and longitudinal studies of older people show that, in addition to the presence of severe radiographic osteoarthritis and obesity, factors such as low levels of exercise, poor general health, anxiety and depression, pessimistic and catastrophizing ideas about pain and osteoarthritis, and low social class and education levels are all associated with more frequent or more disabling chronic joint pain [42, 48]. Apart from the important fact that there is a strong pathological model of joint disease at the centre of all this, the features of the clinical syndrome of osteoarthritis are no different from those of other chronic pain syndromes, such as back or neck pain and widespread pain, except in terms of the age-group affected.

**Phase 3: The Silman years. Osteoarthritis as a public health problem**

Whether we conceive the problem in terms of the clinical or pathological syndrome, the era of Alan Silman at the unit, together with the work of his deputy director Deborah Symmons, has encouraged a different course to be pursued which considers both aspects to be of importance when set in the context of osteoarthritis as a public health problem. These years have seen, both from the Manchester unit and from osteoarthritis epidemiologists elsewhere in the UK and internationally, attention focused on rigorous studies of potentially preventable causes of both syndrome and disease. In particular, these modern studies have filled one notable gap left from the Kellgren and Lawrence years: the addition of longitudinal studies to the osteoarthritis canon.

One measure of the public health impact of a condition is the level of health-care consumption associated with it. Using data from Morbidity Surveys of General Practice in England and Wales, which identify the reasons for which people have consulted their general practitioners during a year of study, musculoskeletal conditions are the second commonest reason for such consultations behind respiratory problems, and are the most frequent chronic conditions for which consultation is sought [40]. In the older age group, osteoarthritis as diagnosed by the general practitioner is the most frequent reason for musculoskeletal consultations—and this does not include repeat consultation by the same individuals during the course of the year.

Kadham has recently highlighted the extent to which this is not a set of people who consult exclusively about osteoarthritis [49]. Consultants about this problem are more likely than the rest of their age and gender-matched peers to be consulting for four or more other complaints. Comorbidity clearly increases the public health importance of osteoarthritis. The other component of osteoarthritis as a public health problem is demography. Osteoarthritis is strongly related to age, and by 2030 it is predicted that the proportion of the population who will be aged 60yr and over will have increased from 20% to 33%. This means at current rates that the numbers of people with disabling osteoarthritis will have increased substantially.

How to tackle the problem? The first option, proposed by Dieppe [50], would be to focus on the group of people with the advanced pathological disease, and to ensure that there are resources and interventions to diagnose and treat them. Dieppe cautions against medicalizing the rest, who have the clinical syndrome and whose aches and pains, although needing positive approaches, can be regarded as part of life. The difficulty with this approach is threefold. Firstly, Birrell and colleagues [51] point out that demographic increases alone would have major effects on the number of hip replacements needed and that this would be radically increased if joint replacement rates seen in Sweden were applied to the UK on the assumption that too few operations are performed in the UK at present. This might be reasonable if costly. The second problem is illustrated by data from population studies such as the French survey reported by Boutron et al. [52]. Such large studies of older population samples now inevitably include significant numbers of people who have already had joint replacements. Although longitudinal studies indicate that this group function better after the operation, their health status remains substantially lower than that of age- and gender-matched peers in the rest of the population. The significance of this is that, as life expectancy increases, postoperative disabilities will represent a continuing and important impact on the health of older people. The efficacy of joint replacement as a treatment of disabling disease is not an argument against trying to prevent people getting to the stage of needing a joint replacement in the first place. Thirdly, a study of hip pain consultants in primary care undertaken by the Manchester are unit in collaboration with the UK Primary Care Rheumatology Society has shown that, although a substantial proportion of older people with hip pain already have significant radiographic disease by the time of their first consultation, only 25% of them have progressed to replacement 5yr later [53]. Some of this might represent delay on surgical waiting lists, but it does mean that at least 75% of older people presenting to primary care for help with knee pain represent a
potential target for secondary prevention of progression of pain and disability.

Population studies must consider also those who do not access medical care. Estimates from one study suggest that half of those aged 50 yr and over who have chronic severe disabling knee pain do not recall having consulted their general practitioner about the problem in the previous 12 months [54]. Although they may be accessing alternative sources of care or may have consulted further back in the past, they represent another group of people whom it would be reasonable to target in order to prevent progression to a stage where joint replacement might be considered. One weakness in the argument for secondary prevention is the absence of long-term intervention studies. However there is sufficient evidence about the short-term benefits of exercise, physical therapy, weight loss, mechanical aids and adaptations, treatment of comorbidity, and pain management [55], to suppose that secondary prevention is a worthwhile model for primary care in addition to the diagnostic and referral function for those at the severe end of the spectrum.

But the reality is that prevention at the population level cannot depend on patients presenting to health-care, and the Alan Silman era, although osteoarthritis has not been its main focus, has emphasized a return to the original tenets of the unit, which were to identify ways to prevent musculoskeletal diseases starting in the first place. The current state of osteoarthritis epidemiology is that there are a number of targets for such primary prevention: shift the population’s weight downwards, increase appropriate exercise and maintain activity into older ages but also concentrate on reducing injuries and occupational hazards to the joints, improve education levels, reduce social isolation in older people and ensure adequate sources of social support. It is likely that these targets will affect both radiographic and clinical syndromes (for example [56, 57]), and, what is more, they are not risks unique to osteoarthritis. One of the most powerful messages for public health from osteoarthritis epidemiology is that investment in these areas of primary prevention will carry benefits far beyond the coronary disease and cancer which present the major rationale for such prevention targets at present. It also means for future epidemiology that barriers between disciplines need to be dismantled. These topics have been addressed for years by gerontologists and epidemiologists in the field of ageing. Independence at age 76 yr in a Swedish cohort, for example, was predicted by measures of walking speed and muscle strength at the age of 70 yr [58]. Ensuring that musculoskeletal health is preserved by the time we enter our 70s is probably the strongest public health message to emerge from the epidemiological studies of osteoarthritis since Kellgren and Lawrence first set out with their caravan on the population trail. Kellgren’s 1955 message is still relevant now: ‘In rheumatism, as in other form of diseases, prevention is ultimately likely to be more effective than cure’.

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