Chapter 2
Epidemiology of osteoarthritis

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Definition of osteoarthritis

> *“ A group of overlapping disorders with different aetiologies but similar biologic, morphologic and clinical outcomes. The disease processes affect articular cartilage, subchondral bone, synovium, capsule and ligaments. Ultimately, cartilage degenerates with fibrillation, fissures, ulceration and full thickness loss of joint surface. ”*
>
> *Nigel Arden*

This definition is itself developed from one coined by the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association for the development of criteria for classifying and reporting osteoarthritis in 1986 [1]. It also made the distinction between subclinical, non-symptomatic defects in articular cartilage, which is poorly innervated, and the clinical syndrome, which includes pain, that may develop from such defects [1].

> *“ Knee osteoarthritis is characterised clinically by usage-related pain and/or functional limitation. It is a common complex joint disorder showing focal cartilage loss, new bone formation and involvement of all joint tissues. Structural tissue changes are mirrored in classical radiographic features. ”*
>
> *The European League Against Rheumatism*

> *“ A heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins. ”*
>
> *American College of Rheumatology*

A specific definition of knee osteoarthritis was developed in 2010 for the European League Against Rheumatism (EULAR) evidence-based recommendations for the diagnosis of knee osteoarthritis [2]. The EULAR recommendations, which emphasise that knee osteoarthritis may associate with osteoarthritis at other joints due to shared genetic and constitutional risk symptoms, also highlight that the definition of knee osteoarthritis may change based on the different levels of care needed and the clinical requirements [2].

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Classification of osteoarthritis

In 1957, Kellgren and Lawrence developed a classification system that sets out a series of radiological features that are considered evidence of osteoarthritis, and divides the disease into five grades (Figure 2.1) [3]:

- 0 – None
- 1 – Doubtful
- 2 – Minimal
- 3 – Moderate
- 4 – Severe

Grade 0 indicates a definite absence of osteoarthritis changes on a single anteroposterior X-ray, while grade 2 represents definite osteoarthritis, albeit of minimal severity [3]. Although the system is widely used, it has limitations, particularly when assessing individual radiographic features.

Radiographic classification of osteoarthritis

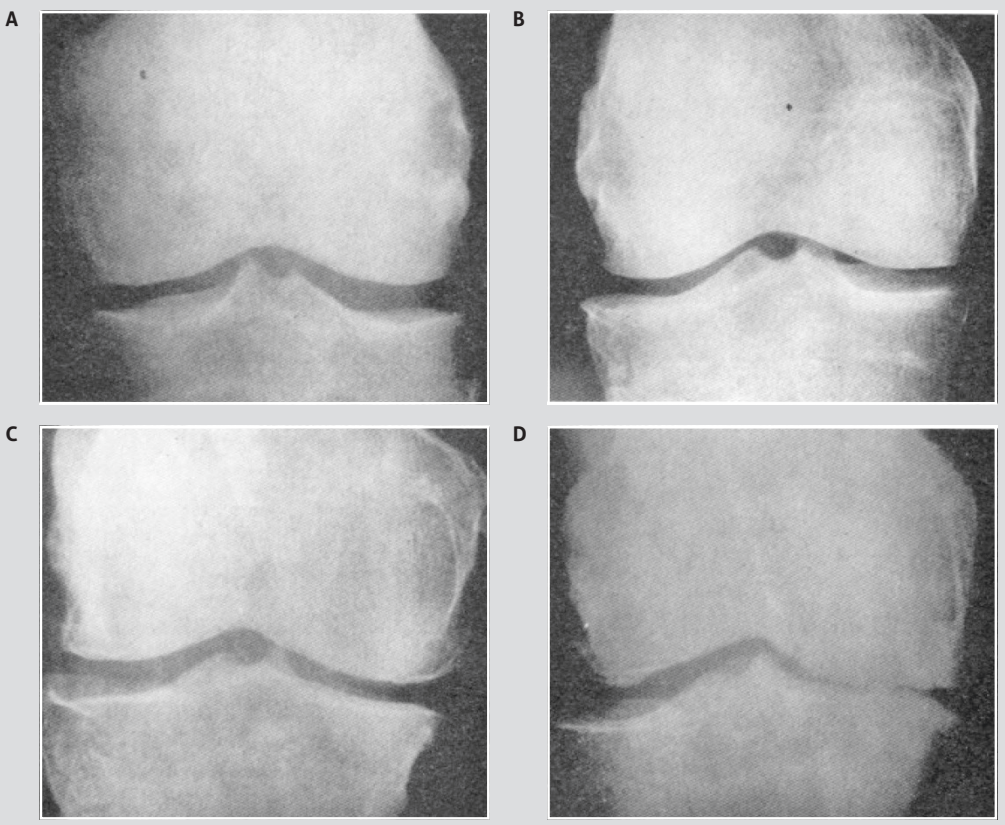

Figure 2.1 Radiographic classification of osteoarthritis.
A, Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping.
B, Grade 2: definite osteophytes and possible JSN.
C, Grade 3: moderate multiple osteophytes, definite JSN, some sclerosis, possible bone end deformity.
D, Grade 4: large osteophytes, marked JSN, severe sclerosis definite deformity of bone ends. Image from Kellgren & Lawrence [3].

The radiological features of knee osteoarthritis were refined by the Osteoarthritis Research Society International in 2007 [4], and divided into: the presence of marginal osteophytes in the medial femoral condyle, medial tibial plateau, lateral femoral condyle and lateral tibial plateau (Figure 2.2) [5] and joint space narrowing (JSN) of the medial compartment and lateral compartment. Each of these are graded for degree of change:

- 0 – Normal
- 1 – Mild change
- 2 – Moderate change
- 3 – Severe change

Femoral osteophytes

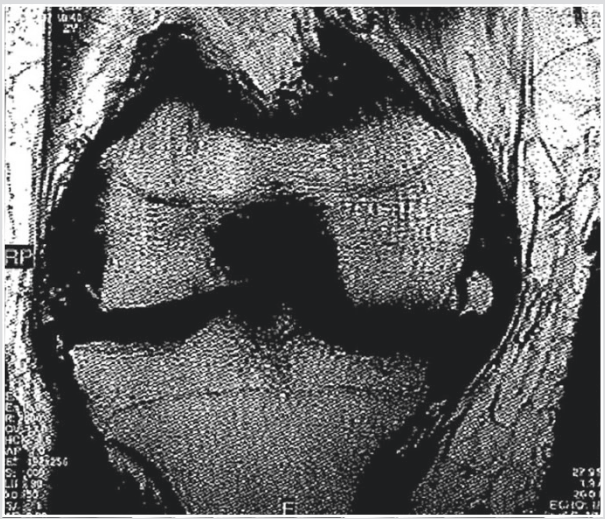

Figure 2.2 Femoral osteophytes. This coronal magnetic resonance image of an osteoarthritis knee is a T1-weighted spin-echo image that shows femoral osteophytes on the medial and lateral aspects of the joint. The bright signal within the osteophytes is produced by marrow fat. Reproduced with permission from Myers [5].

Recently, a Delphi exercise was undertaken to develop definitions of osteoarthritis on magnetic resonance imaging (MRI), which suggested that, while MRI changes of osteoarthritis may occur in the absence of radiographic findings, MRI changes in isolation and single MRI changes, are not diagnostic of osteoarthritis [6]. Nevertheless, a definition of tibiofemoral osteoarthritis on MRI was developed (Figure 2.3, see page 22) [7], which was either the presence of two features from group A, or one group A feature plus at least two group B features, where:

- Group A, after exclusion of joint trauma within the last 6 months and exclusion of inflammatory arthritis:
  - Definite osteophyte formation
  - Full thickness cartilage loss
- Group B:
  - Subchondral bone marrow lesion or cyst not associated with meniscal or ligamentous attachments
  - Meniscal subluxation, maceration or degenerative (horizontal) tear
  - Partial thickness cartilage loss (where full thickness loss is not present)
  - Bone attrition

Magnetic resonance imaging of the knee: remodelling and sclerosis

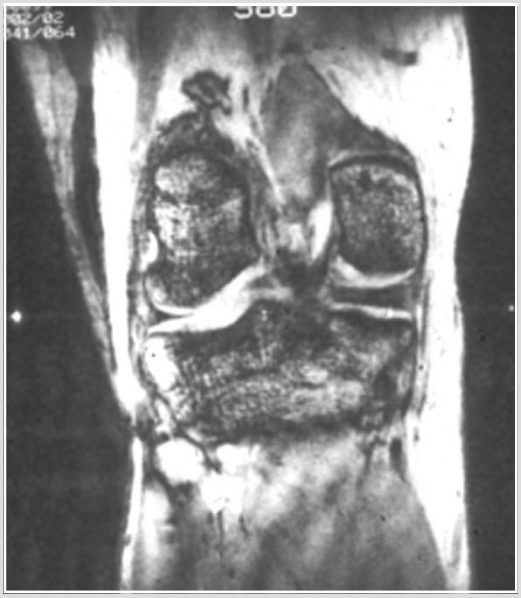

Figure 2.3 Magnetic resonance imaging of the knee: remodelling and sclerosis. This magnetic resonance image reveals considerable subchondral bone remodelling and sclerosis. Posteriorly, the cartilage of the lateral compartment is thickened with thinning and irregular cartilage in the medial compartment. Reproduced with permission from Altman [7].

A composite model was created using the above features to assess the ability of MRI to detect radiographic osteoarthritis compared with Kellgren and Lawrence (KL) grade 2, which yielded a C statistic of 0.59, which was described by the authors as "disappointing" [6]. Nevertheless, MRI retains the potential to diagnose osteoarthritis earlier than the current reference standard of radiography [6].

Prevalence and incidence of osteoarthritis

The prevalence of osteoarthritis has been assessed in a number of studies spanning several decades. van Saase et al examined the prevalence of mild and severe radiological osteoarthritis in a single Dutch village, finding that increased radiological osteoarthritis is strongly linked to age, regardless of whether small or large weight-bearing joints are considered, and holds for both men and women (Figure 2.4) [8].

The highest prevalence for osteoarthritis is seen in the cervical spine, the lumbar spine and the distal interphalangeal joints (DIP) [8]. Severe radiological osteoarthritis is uncommon under age 45 years, and the prevalence does not exceed 20% in the elderly aside from in the cervical and lumbar spine and DIP and, in women, the joints of the hands and the knees [8]. Significant sex differences are seen in the knees, in the hips among those aged at least 65 years and in the DIP of the hands [8]. Comparison with other populations shows that, although there are substantial differences between populations for individual joints, the slope of the majority of lines is similar for individual and groups of joints, with no one population having a low or high prevalence of osteoarthritis for all joints [8].

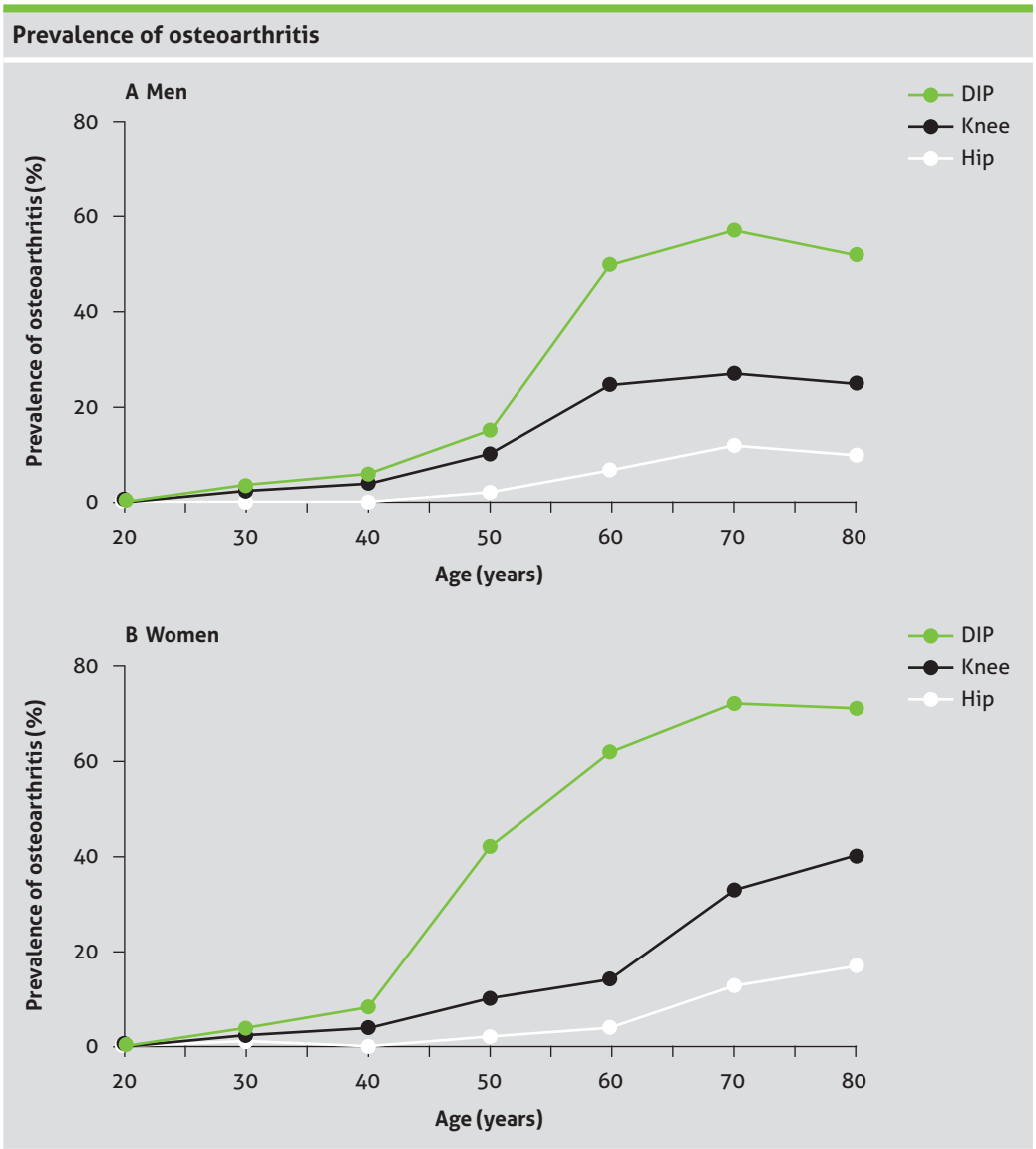

Figure 2.4 Prevalence of osteoarthritis. A random sample of a Dutch village demonstrated the high prevalence of radiological osteoarthritis, which increases progressively with age. Mild radiological osteoarthritis is more prevalent in women (**B**) than in men (**A**), while severe radiological osteoarthritis is substantially more prevalent in women. DIP, distal interphalangeal joints. Data from van Saase et al [8]. © 1989, reproduced with permission from BMJ Publishing Group Ltd.

The incidence of osteoarthritis increases with age, and women have higher incidences than men, especially after age 50 (Figure 2.5, see page 24) [9]. The incidence of knee osteoarthritis is twice that of hand or hip osteoarthritis, and the female:male sex ratio for hand, hip and knee osteoarthritis is approximately 2:1. The trend of increasing osteoarthritis incidence continues until age 80 after which there is a levelling off or decline in the rates for all joints, which may be linked to sedentary activity in older age groups [9].

The lifetime risk of undergoing total hip replacement (THR) or total knee replacement (TKR) is lower than that of developing symptomatic knee or hip osteoarthritis [10]. The mortality-adjusted lifetime risk of undergoing THR at age 50 years is estimated, using 2005 data, at 11.6% for women and 7.1% for men, while the risks of undergoing TKR are 10.8% and 8.1%, respectively [10]. The risk decreases with increasing age for THR and TKR in both men and women, such that, at 80 years of age, the lifetime risk of THR is 3.8% for women and 2.7% for men, while that for TKR is 3.3% and 2.7%, respectively [10].

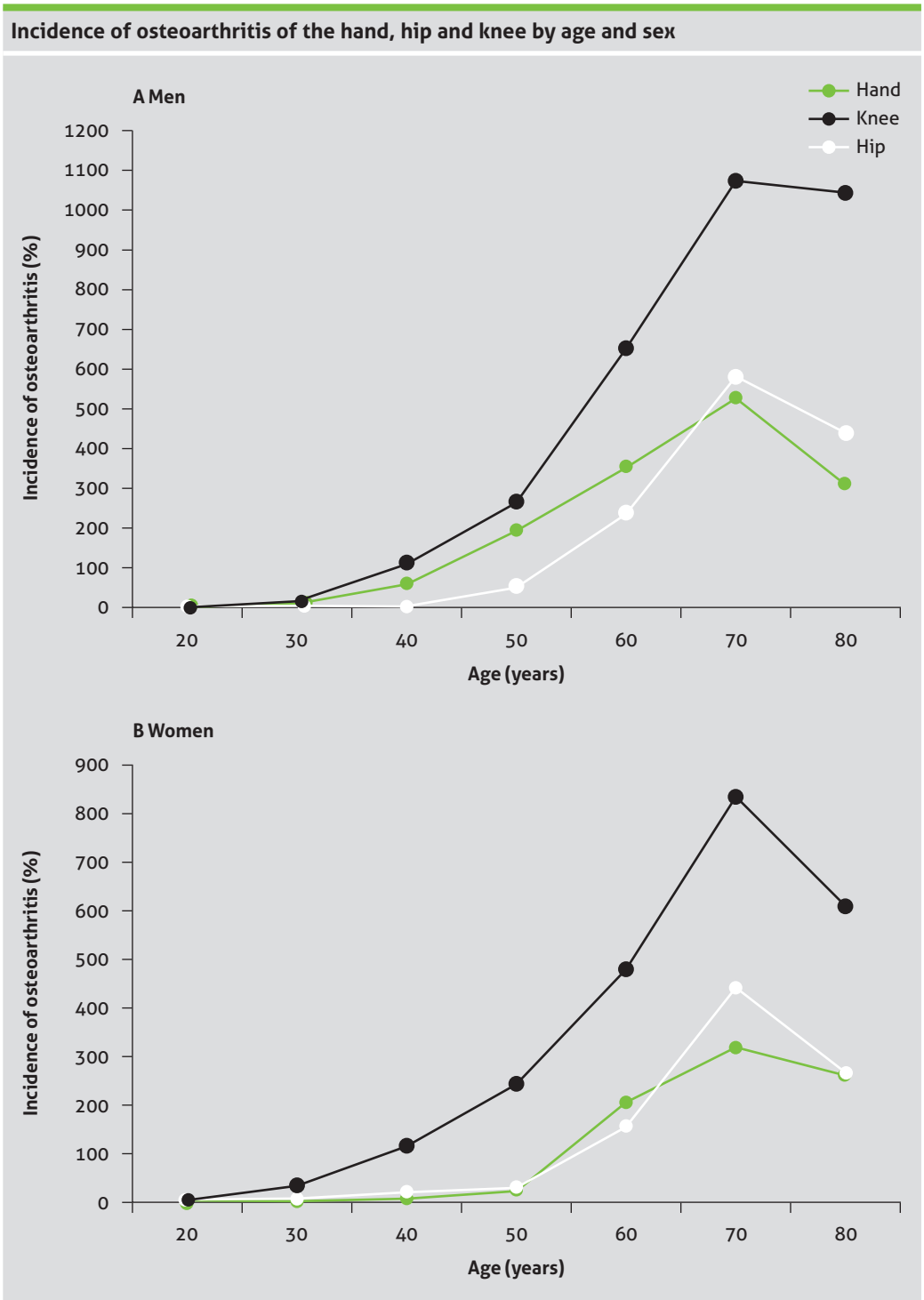

Figure 2.5 Incidence of osteoarthritis of the hand, hip and knee by age and sex. The data represents incidence in members of the Fallon Community Health Plan, 1991–1992. **A**, The equivalent figures for men were 5 per 100,000 person-years and 619 per 100,000 person-years. **B**, Among women, the incidence rates for knee osteoarthritis ranged from 0 per 100,000 person-years among those aged 20–29 years to 1082 per 100,000 person-years for those aged 70–79 years. The overall age- and sex-standardised incidence rate for knee osteoarthritis was 240/100,000 person-years (95% CI 218–262). Adapted from Oliveria et al [9].

Interestingly, the rates of primary TKR have increased substantially over the last two decades, much more so than for THR (Figure 2.6) [11]. This may reflect the more recent maturation of TKR as an efficacious treatment for osteoarthritis, or be because the number TKRs performed each year is below that which would be appropriate for the burden of osteoarthritis of the knee [11].

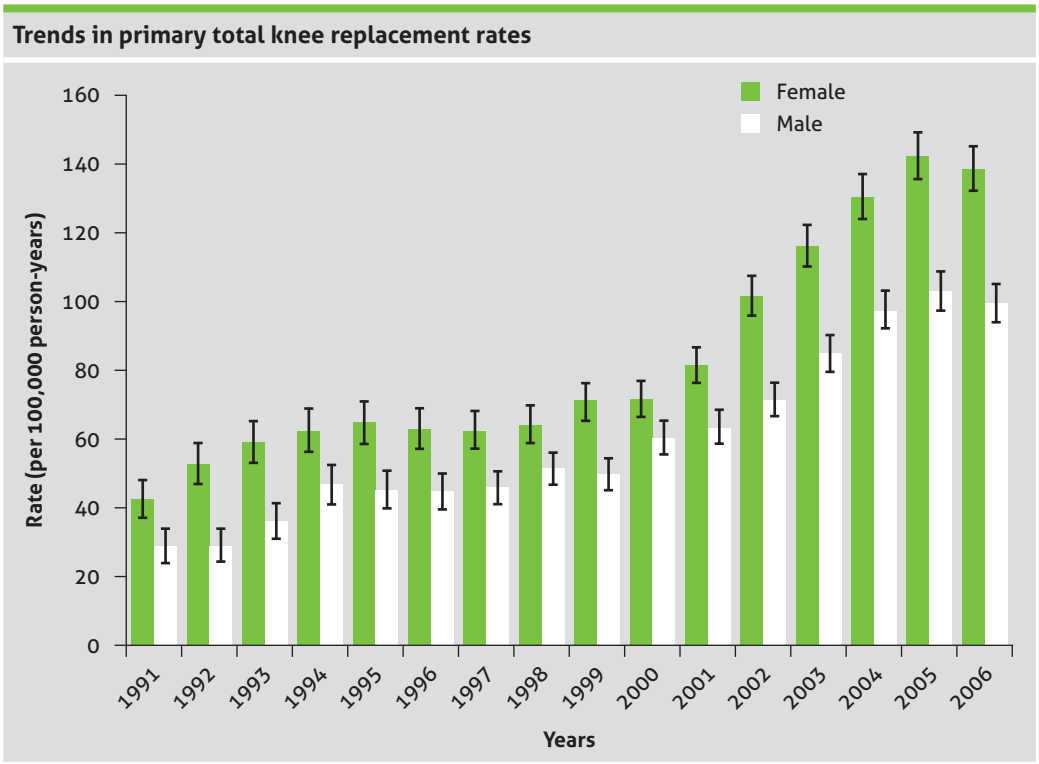

Figure 2.6 Trends in primary total knee replacement rates. During the study period (1991–2006), the estimated age-standardised rates of primary total knee replacement (TKR) increased from 42.5 (95% CI 37.0–48.0) to 138.7 (95% CI 132.3–145.0) in women and from 28.7 (95% CI 23.9–33.6) to 99.4 (95% CI 93.9–104.8) in men. Interestingly, there was a marked plateau in TKR rates from the mid-1990s, followed by a sharp rise from 2000. Data from Culliford et al [11]. © 2012, reproduced with permission from The British Editorial Society of Bone and Joint Surgery.

Aetiology and risk factors

In order to understand the influence that risks factors for osteoarthritis have on the pathogenesis, a conceptual framework for the disease has been developed in recent years that consists of the following tenets (Figure 2.7) [12–18]:

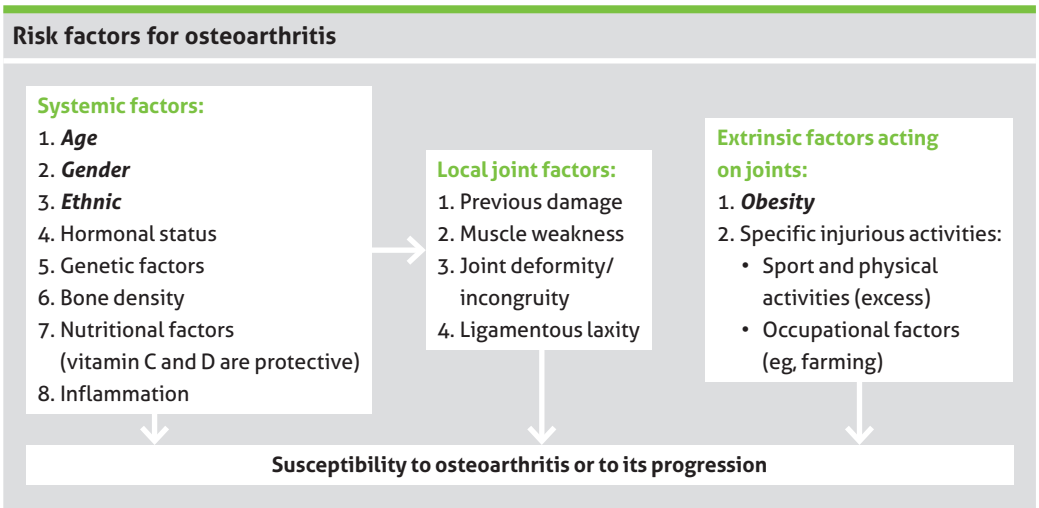

Figure 2.7 Risk factors for osteoarthritis. Several systemic factors have been identified as risk factors for knee osteoarthritis, which may act by increasing the susceptibility of joints to injury, via direct damage to joint tissues, or by impairing the repair process in damaged joint tissue. Local biomechanical factors are, in contrast, believed primarily to determine the exposure of individual joints to injury and to excess loading that leads to joint degeneration. Adapted from [16–18].

- Cartilage, bone, muscles, ligaments and other joint tissues and structures function as a biomechanical organ system that maintains proper movement and prevents excessive joint loading;
- Systemic factors that increase overall susceptibility to joint degeneration, and local biomechanical factors that impair the optimal functioning of a joint both play an important role in determining the risk of developing osteoarthritis; and

- Systemic factors interact with mechanical factors operating within the local joint environment to determine which joints develop osteoarthritis and how rapidly the disease progresses in an affected joint.

It is suggested that several of the pathological features of osteoarthritis, including proliferative bone changes, may represent attempts to repair the injured joint [19]. For example, osteophytes may arise from a reactive response of cartilage and bone to abnormal mechanical loading, thus reducing instability to protect the damaged joint [12]. Systemic and local factors may act in a joint-specific manner to determine whether such a response is normal or aberrant, and whether it succeeds or fails in protecting the joint [12]. There are a number of factors associated with osteoarthritis of the knee, hip and hand.

Age

The age-related increases in osteoarthritis prevalence and incidence are particularly pronounced in the commonly affected joints, such as the knee, hip and hand. It is thought that the relationship between age and the risk of osteoarthritis is mediated by age-related increases in a range of systemic and biomechanical risk factors [12].

Sex

Female gender amplifies the age-related increase in osteoarthritis risk in the hands and knees, as well as osteoarthritis in multiple joints, such that, after 50 years of age, the prevalence and incidence is significantly greater in women than men [9,20]. While hip osteoarthritis appears to progress more rapidly in women [21,22], there appears to be no gender impact on knee [23,24], or hand osteoarthritis progression [12].

Ethnicity

The prevalence of osteoarthritis and patterns of affected joints vary among racial and ethnic groups [25]. Osteoarthritis is, in general, more prevalent in Europe and the USA than other parts of the world [26]. Osteoarthritis of the knee is more common in African-American women than white women [27], but that is not the case for the hip [28]. Osteoarthritis of the hip is more common in European whites than in Jamaican blacks [29], African blacks [30] or Chinese [31]. The Beijing Osteoarthritis Study indicated that hip and hand osteoarthritis was less frequent among Chinese than in whites in the Framingham Study, although the prevalence of radiographic and symptomatic knee osteoarthritis was significantly higher in Chinese women than in white women [32,33].

Menopause

As the increase in the age-related rise in osteoarthritis occurs following menopause, it would suggest that sex hormones, particularly oestrogen deficiency, play a role in the systemic predisposition to osteoarthritis [12]. While many studies have looked at the possibility of lowering osteoarthritis risk through oestrogen use, any associations may be misleading, as oestrogen use is linked to a healthy lifestyle and osteoporosis, which lowers the risk of osteoarthritis [12].

Genetic factors

Genetic vulnerability appears to account for approximately half the variability of susceptibility to hand, hip and knee osteoarthritis in women [34–40] and men [38,39]. These studies suggest that not only are multiple genes likely to be involved in osteoarthritis susceptibility but also that environmental factors have an important role in progression [12]. The search for candidate genes has focused on genes encoding type II collagen (the primary collagen in articular cartilage), structural proteins of the extracellular cartilage matrix, the vitamin D and oestrogen receptor genes, as well as encoding bone and cartilage growth factors [41].

Obesity

Obesity is one of the most well-established and strongest risk factors for knee osteoarthritis [13], and precedes the development of knee osteoarthritis by many years [42–44]. In addition, obesity accelerates the progression of knee osteoarthritis [45,46]. The primary mechanism for the impact of obesity of knee osteoarthritis is likely to be excess weight on overloading of the joints during weight-bearing activities, leading to breakdown of cartilage and damage to ligaments and other support structures [12]. Metabolic factors, such as circulating adipocytokines, adiposity-linked glucose and lipid abnormalities and chronic inflammation, may also play a role in the pathogenesis of osteoarthritis [12].

Mechanical and occupational factors and trauma

Acute knee injuries, including meniscal and cruciate ligament tears in the knee, fractures and dislocations [12], substantially increase the risk of any subsequent osteoarthritis, as well that of more severe disease [45]. In addition, the risk of osteoarthritis is increased by weekly participation in sports for a decade or longer after leaving school [44]. Specifically, repetitive and excessive joint loading due to specific physical activities increases the risk of developing osteoarthritis in the stressed joints [12].

Congenital and developmental diseases

The risk of developing osteoarthritis is substantially increased as a result of congenital abnormalities that result in abnormal load distributions within the joint [47]. As the mechanical alignment of the knee, as determined by the hip/knee/ankle angle, is an important determinant of load distribution of the knee during ambulation [48], varus and valgus malalignment are found with a high frequency in knees with evidence of osteoarthritis involvement of the medial and lateral components, respectively [49]. Osteoarthritic knees with varus malalignment have a three- to fourfold increased risk of further joint space narrowing in the medial compartment, which is similar to the increased risk of further lateral compartment joint space narrowing in osteoarthritis knees with valgus malalignment [50]. Discoveries about the pathophysiology of the disease have led to a potential division of the disease into distinct phenotypes (see Table 1.1) [51]. In addition to improving our understanding of the disease, classifying the different clinical and structural phenotypes of osteoarthritis allows for more direct targeting of treatments, depending on where the predominate structural changes are, eg, cartilage, bone or synovial tissue. However, there is currently no consensus on the subgrouping of osteoarthritis into these phenotypes [51].

Disease course and determinants of osteoarthritis progression

There are a number of biomarkers under investigation for the assessment of osteoarthritis progression, as the identification of rapid progressors would assist in the development and targeting of therapies. Imaging technologies such as MRI appear promising in the assessment of disease progression, and combining biochemical and MRI-based biomarkers may offer effective diagnostic and prognostic tools for identifying osteoarthritis patients at high risk of progression (Figure 2.8) [52]. While cartilage roughness is a good diagnostic marker, with an area under the receiver operating characteristics curve (AUC) of 0.80, and cartilage homogeneity performs well as a prognostic marker, with an AUC of 0.71, an aggregate marker of cartilage matrix breakdown and cartilage volume, thickness, area, congruity, roughness and homogeneity performs well both diagnostically and prognostically, at respective AUCs of 0.84 and 0.77 [52].

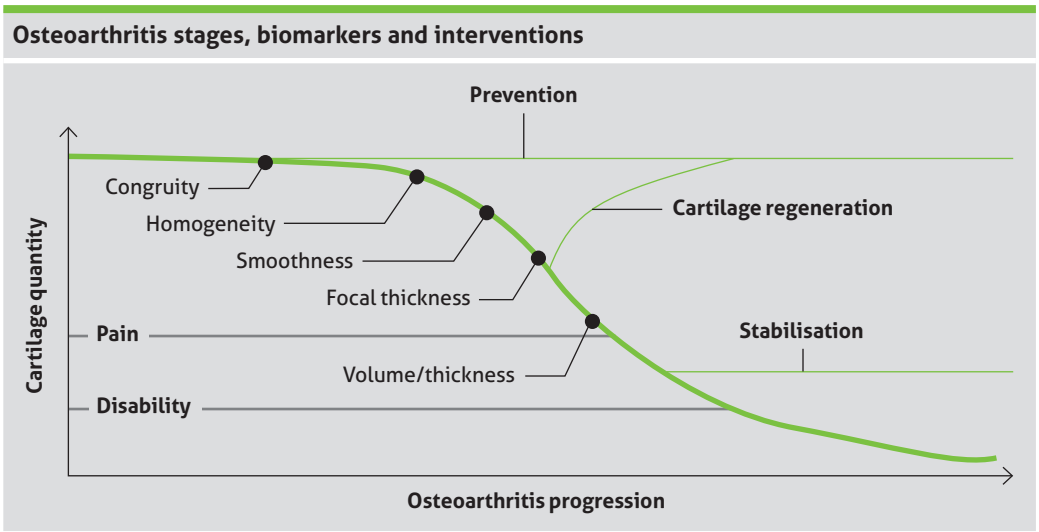

Figure 2.8 Osteoarthritis stages, biomarkers and interventions. Figure courtesy of Dr C Cooper.

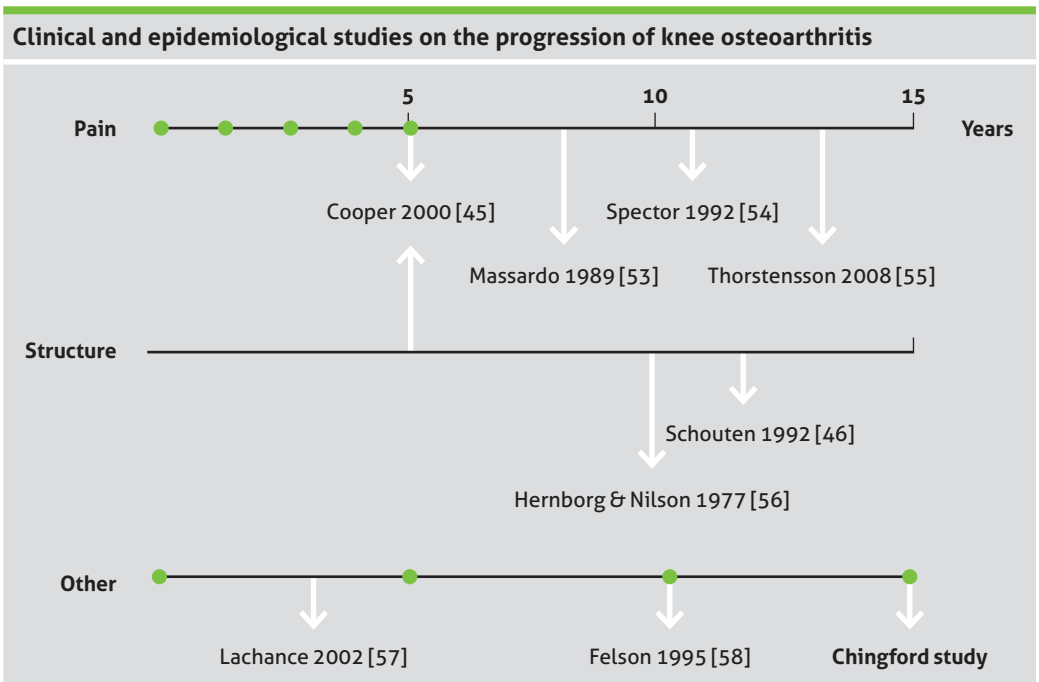

Figure 2.9 Clinical and epidemiological studies on the progression of knee osteoarthritis. Circles represent the timings of the visits for the Chingford study. Figure courtesy of Dr K Leyland. Data from [45,46,53–58].

There have been a number of studies that have examined the progression of osteoarthritis over follow-up periods of up to 15 years, including the recently published Chingford study (Figure 2.9) [45,46,53–58].

The evolution of knee osteoarthritis is slow, it typically takes several years and can remain stable for several years [21]. Radiographic deterioration is seen in a third to two-thirds of osteoarthritis patients and radiographic improvement is unusual (Table 2.1) [45,46,53,54,59–65].

Natural history of knee osteoarthritis

Study	N	Measure	Years	Deterioration (%)
Hernborg & Nilson (1977) [56]	94	C	15	55
		R	15	56
Danielsson (1970) [59]	106	R	15	33
Massardo (1989) [53]	31	R	8	42
Dougados (1992) [60]	353	C	1	28
		R	1	29
Schouten (1992) [46]	142	R	12	34
Spector (1992) [54]	63	R	11	33
Spector (1994) [61]	58	R	2	22
Ledingham (1995) [62]	350	R	2	72
McAlindon (1999) [63]	470	R	4	11
Cooper et al (2000) [45]	354	R	5	22
Felson (2004) [64]	323	R	2.5	28

Table 2.1 Natural history of knee osteoarthritis. C, Clinical; R, Radiographic. Table adapted with permission from Dennison & Cooper [65]. Data from [45,46,53,54,59–64].

Odds ratio of incidence and progression of knee osteoarthritis

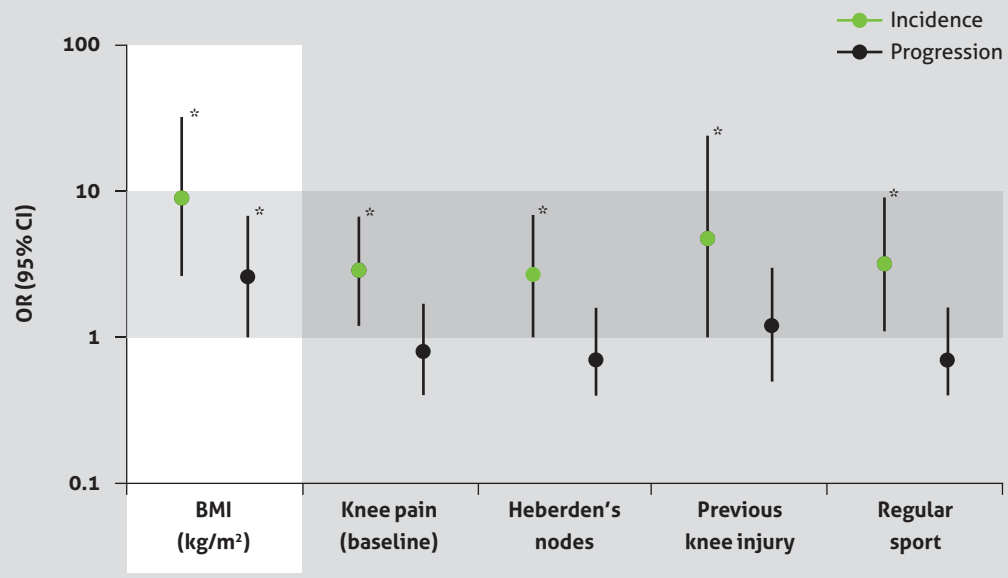

Figure 2.10 Odds ratio of incidence and progression of knee osteoarthritis. The odds ratio (OR) was calculated over 5 years among patients with Kellgren and Lawrence grade 1+ disease. OR are adjusted for age and sex in all cases. In addition, OR for BMI, knee pain and Heberden's nodes are mutually adjusted. OR for knee injury and sports participation are adjusted for age, sex, BMI, knee pain and Heberden's nodes. Obesity was a strong predictor of incidence knee osteoarthritis ($P<0.001$) and a significant predictor of progression ($P<0.05$). BMI, Body mass index; CI, confidence interval. *Significant increase in risk. Data from Cooper et al [45].

While there are several factors significantly associated with the incidence of osteoarthritis, only obesity is significantly individually linked to the progression of grade 1+ disease (Figure 2.10) [45]. In addition, the coexistence of Heberden's nodes with knee osteoarthritis increases the risk of knee deterioration by almost sixfold [21].

The Chingford study looked at the progression of individual KL grades over 15 years (Table 2.2) [66], which revealed that approximately half of knees had a KL grade of 0 throughout, while two-fifths worsened by at least one grade. Knees with baseline KL grade 1 had a higher percentage of progression, at almost three-quarters, than knees with any other KL grade at baseline. Less than 2% of knees were scored as having regressed to a lower KL grade by year 15 [43].

Progression of individual Kellgren and Lawrence grades over 15 years

Baseline Kellgren and Lawrence grade	N	Year 15 Kellgren and Lawrence grade					
		0	1	2	3	4	5
0	905	60.1% (548)	9.9% (90)	15.7% (142)	12.5% (113)	0.1% (1)	1.2% (11)
1	57	19.3% (11)	5.3% (3)	40.4% (23)	29.8% (17)	0.0% (0)	5.3% (3)
2	60	0 (0.0%)	1.7% (1)	50.0% (30)	41.7% (25)	0.0% (0)	6.7% (4)
3	26	0.0% (0)	3.8% (1)	15.4% (4)	65.4% (17)	11.5% (3)	3.8% (1)

Table 2.2 Progression of individual Kellgren and Lawrence grades over 15 years. Data from Leyland et al [66].

The prevalence of long-term knee pain is dependent on whether there was any pain at baseline (Figure 2.11) [67]. The presence of knee osteoarthritis increases the risk of persistent pain by 3.70-fold, while reported knee injury increases the risk of persistent pain 4.13-fold and intermittent pain 4.25-fold [44]. Interestingly, there is a discrepancy between the presence of radiographic osteoarthritis and corresponding pain, which may be due to KL grade being a predictor only of persistent, and not intermittent pain.

Prevalence of self-reported knee pain

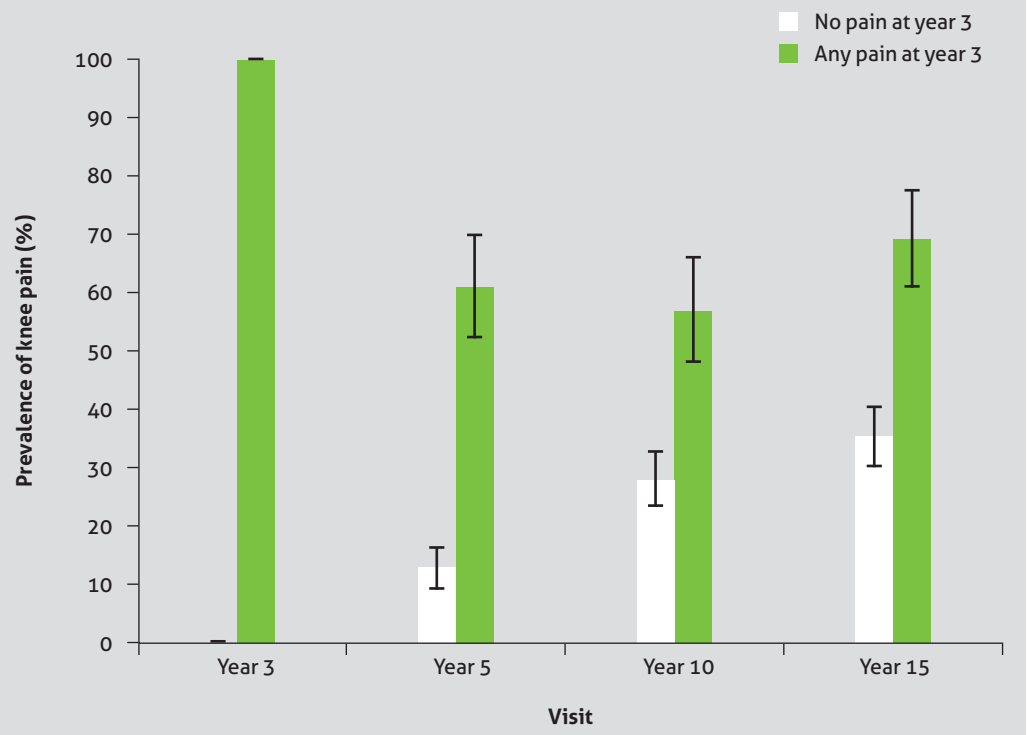

Figure 2.11 Prevalence of self-reported knee pain. Bars show the means with 95% confidence intervals. Individuals without knee pain at baseline (year 3) had an increase in pain prevalence with duration of follow-up, such that, at year 15, the prevalence was 35.2% for those reporting any days of pain. Data from Soni et al [67].

Another important consideration in the assessment of osteoarthritis is the presence of comorbidities. It is estimated that older osteoarthritis patients have an average of 8.7 chronic medical diseases [68]. The three most common comorbidities are obesity, hypertension and high cholesterol levels (Figure 2.12) [69].

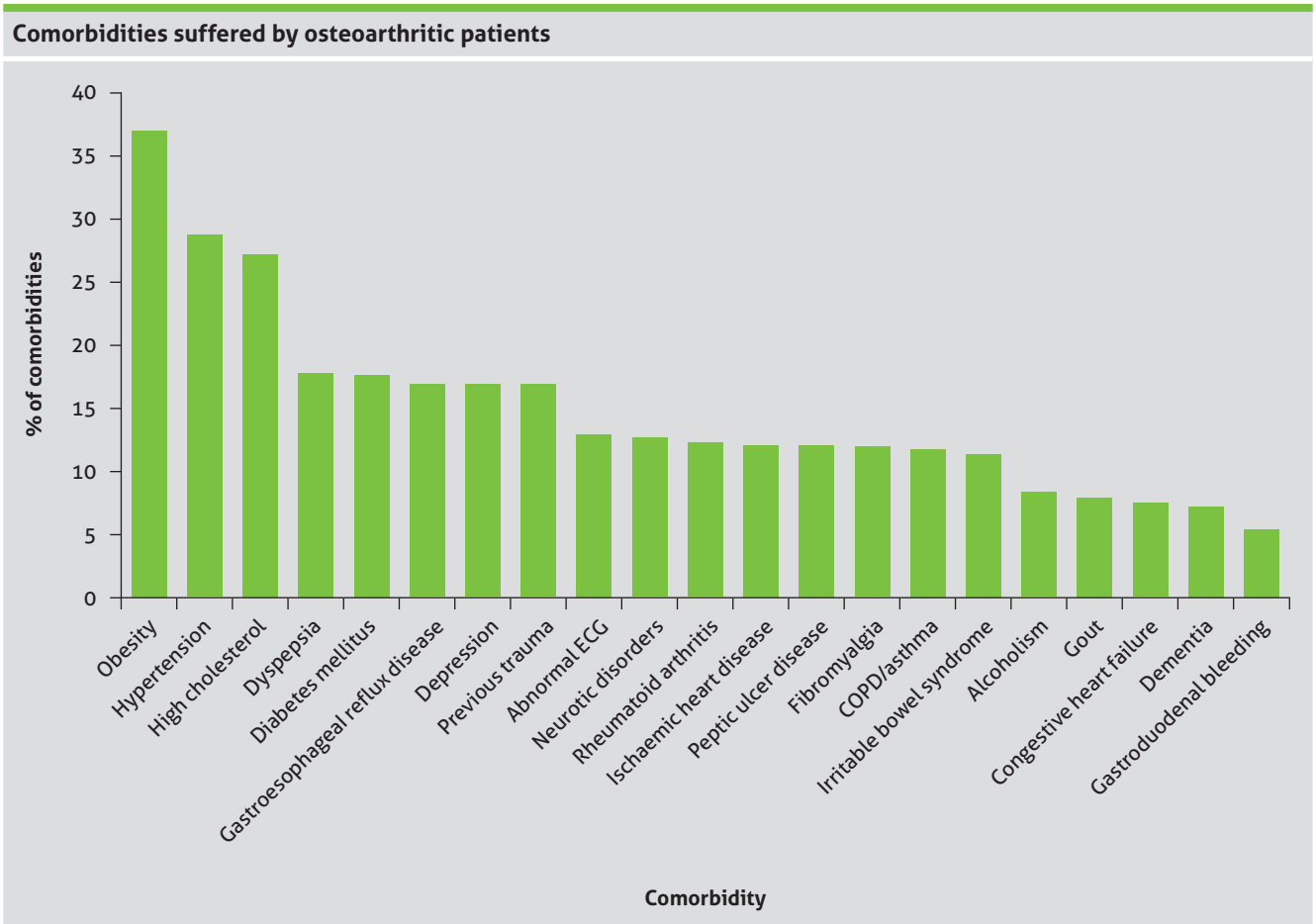

Figure 2.12 Comorbidities suffered by osteoarthritic patients. COPD, chronic obstructive pulmonary disorder; ECG, electrocardiography. Data from Datamonitor [69].

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