

# The global burden of rheumatoid arthritis in the year 2000

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## 1. Introduction

Rheumatoid arthritis (RA) is a systemic auto-immune disease. Symmetrical inflammatory polyarthritis is the primary clinical manifestation. The arthritis usually begins in the small joints of the hands and the feet, spreading later to the larger joints. The inflamed joint lining or synovium extends and then erodes the articular cartilage and bone, causing joint deformity and progressive physical disability. Extra-articular features include nodules, pericarditis, pulmonary fibrosis, peripheral neuropathy and amyloidosis.

An extensive review of epidemiological studies by Abdel-Nasser et al (1) found that among adult white populations of Europe and America, the prevalence of definite or classical RA by the 1958 ARA or 1987 ACR criteria (see below), is approximately 1%. The corresponding incidence of RA among white populations is about 0.03% per annum. The prevalence and incidence of RA are higher in women than men. The prevalence and incidence increase with age and peaks at about age 70 then declines.

RA was estimated to be the 40<sup>th</sup> leading cause of non-fatal burden in the world in 1990, accounting for 0.7% of total Years lived with Disability (YLD), around the same percentage as obsessive-compulsive disorders and meningitis (2). In the Version 2 estimates for the Global Burden of Disease 2000 study, published in the World Health Report 2002 (3), RA is the 31<sup>st</sup> leading cause of YLDs at global level, accounting for 0.8% of total global YLDs. This paper summarises the data and methods used to produce the Version 2 estimates of RA burden for the year 2000.

## 2. Case and sequelae definitions

Agreement on the criteria for the inclusion of an individual as a case of RA has not been easily achieved. Early epidemiological studies included patients with systemic lupus erythematosus and ankylosing spondylitis. The problem in defining RA has been the lack of a distinct clinical, laboratory or radiological marker. It is important to distinguish RA from arthropathies such as ankylosing spondylitis and psoriatic arthritis. At the other end of the spectrum, there is a need to exclude 'benign self-limiting polyarthritis' - the occurrence of a short-lived episode of inflammatory polyarthritis with no obvious cause that remits spontaneously without sequelae. In practice this is difficult given the lack of follow-up data.

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Classification criteria for RA were first proposed by the American Rheumatism Association (ARA) in 1958 (4). The separation by these criteria into possible, probable, definite and classical RA has been used for the majority of published studies of RA. The 1958 criteria included a number of histological features which were not applicable in the populations setting. An adaption - called the Rome criteria - excluding these features was produced for epidemiological studies (5) (Tables 2.1 and 2.2) and broadly reflected the actual use of the ARA criteria in field studies. The time when a sufficient number of criteria are reached should be considered the onset of RA. The Rome criteria also account for past arthritis (Table 2.2).

**Table 2.1 Rome Criteria for active rheumatoid arthritis**

Criterion	
1	Morning stiffness
2	Pain on movement or tenderness in a joint <sup>a</sup>
3	Soft tissue swelling in a joint <sup>a</sup>
4	Soft tissue swelling of another joint <sup>a</sup>
5	Symmetrical soft tissue joint swelling simultaneously <sup>a</sup>
6	Subcutaneous nodules <sup>a</sup>
7	X-ray changes <sup>b</sup>
8	Positive rheumatoid factor
3-4 criteria positive	Probable rheumatoid arthritis
5-6 criteria positive	Definite rheumatoid arthritis
7-8 criteria positive	Classical rheumatoid arthritis

a Must be observed by a physician but does not include terminal interphalangeal joints

b Can include juxta-articular osteoporosis

**Table 2.2 Rome Criteria for inactive rheumatoid arthritis**

Criterion	
1	Past history polyarthritis
2	Symmetrical deformity of hand or feet joints
3	Radiological change
4	Positive rheumatoid factor
2 criteria positive	Positive-possible RA
3-4 criteria present	Positive-definite RA

Anxieties about the specificity of these criteria led to development of another criteria set, the New York Criteria (6) (Table 2.3). These latter criteria never achieved the same acceptance possibly because there was no cut-off point given for a 'positive'. A cut-off point of at least three positive New York Criteria is, however, more specific but less sensitive than 'definite' RA for the 'Rome' Criteria (7). The 1958 ARA criteria were revised in 1987 by the American College of

Rheumatology (ACR) (Table 2.3) (8). These criteria have also been modified for use in population studies (9).

There has been considerable debate and investigation of the relative merits of the current criteria (10;11). Because the revised ACR criteria were derived using hospital patients, there may, in practice, be very little difference between Rome and the 1987 ACR criteria in clinic patients (12). It is very unlikely that the unmodified ACR criteria would perform as well in population studies, where it is necessary to distinguish early RA from other causes of joint inflammation.

**Table 2.3 The 1987 revised ARA/ACR criteria for the classification of rheumatoid arthritis\***

Criterion	Short Title	Definition
1	Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement. At least 3 joints.
2	Arthritis of 3 or more joint areas	Areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3	Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP or PIP joint.
4	Symmetric arthritis	Simultaneous involvement of the same joint areas [as defined in (2)] on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable with out absolute symmetry).
5	Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor in juxta-articular regions, observed by a physician.
6	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor or any method for which the result has been positive in <5% of normal control subjects.
7	Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

\*For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded.

Because of the relatively high prevalence of RA, a cross-sectional study may give reasonably reliable estimates from a relatively modest sample size (around 2000) depending on the degree to which age breakdowns are required. The problem comes from deciding on the inclusion criteria. In most series, the number of active cases who would satisfy any criteria set are small and many of the cases will be either in remission because of drug therapy or due to natural history. Further there may be no objective evidence of disease presence such as joint deformity or radiological evidence of joint destruction. In reality most apparent *point* prevalence estimates include a variable and unstated proportion of past cases (13).

Non specific musculoskeletal diseases as well as other types of arthritis, such as reactive arthritis, gout, Lyme arthritis and others, should also be included in the global burden of disease estimates in the “other musculoskeletal conditions” category, but must be distinguished from definite RA, and should be attributed a disability weight different from that of RA. For this reason, the case definition for RA has been chosen as definite or classical RA on the Rome criteria, or where that is not available, on the ARA or revised 1987 ACR criteria. The Rome criteria were chosen because they have been the most widely used. For future studies a version of the 1987 ACR criteria modified for population studies is recommended.

**Table 2.4 GBD 2000 case and sequelae definitions for rheumatoid arthritis**

Cause category	GBD 2000 Code	ICD 9 codes	ICD 10 codes
Rheumatoid arthritis	U126	714	M05-M06

Sequela	Definition
Cases	Definite or classical RA by Rome , 1958 ARA or 1987 ACR criteria

### 3. Population prevalence and incidence studies

The incidence and prevalence of RA generally rises with increasing age until about age 70, then declines (14-16). Around twice as many women as men are affected. The prevalence of RA is generally lower in developing countries, with few or no cases found in some African surveys (17). The prevalence in native American groups can be considerably higher (18-20). There may be a link to urban living as a study in Soweto (21) showed a prevalence of RA among urban blacks equivalent to that in white Europeans, while rural black groups have showed much lower prevalences (17;22).

In most countries it is not possible to estimate the incidence, prevalence or outcome of rheumatic diseases from national health information systems. There are some exceptions. The Scandinavian countries, in particular Finland and Sweden, have registers of those entitled to reimbursable medication and these registers can be linked, for example, to registers of death and malignancy. In the UK a network of primary care physicians record the reason for every consultation. However such data sources are unverified diagnoses which may be subject to bias. This analysis thus uses, whenever possible, representative community-based surveys which employ recognized diagnostic criteria for RA as summarized in Table 2.4.

Appropriate surveys were identified by a MEDLINE search using the words rheumatoid arthritis, incidence, prevalence, occurrence and epidemiology; and by examining other reviews on the epidemiology of RA, particularly the comprehensive review by Silman 1997 (23). Where more than one survey for an area was identified, preference was given to those with a random or stratified population sample; those where the sample size was over 500; those which gave the age- and sex-specific rates; and those which were done most recently. Where appropriate, the exact estimates obtained in a published study are used. In other situations, where the sample size was small and some age or sex groups had no cases, estimated rates were adjusted and smoothed using known age distributions from larger studies in regions of similar level of development. For developing regions, there are generally very few studies, and these are often of small sample size.

In 1981 the World Health Organization (WHO) and the International League of Associations for Rheumatology (ILAR) planned a Community Oriented Programme for Control of Rheumatic Disease (COPCORD) (24). The aims of the project were to qualify the prevalence of rheumatic disease; to identify possible risk factors; and to educate local primary health care workers in the prevention and treatment of common rheumatic complaints. The epidemiological studies consist of three phases: (1) administration of a simple screening survey, (2) those reporting rheumatological problems receive a second detailed and specific questionnaire, and (3) those indicating rheumatic complaints in the second survey are given a clinical examination by a consultant rheumatologist using confirmatory laboratory or radiological investigations.

The first surveys in the Philippines (25), Indonesia (26), and Malaysia (27) used a variety of questionnaires because of cultural differences. It was then decided that a "core" questionnaire should be adopted which would provide basic data on complaints, disability and treatment. This was completed in February 1992 and has been used in Shanghai (28), and Thailand. In 1992 a number of COPCORD surveys were initiated in South America. Since the GBD 1990 study, results from a several additional COPCORD studies have become available for China, Thailand, India, Pakistan, Australian Caucasians, Kuwait, Mexico, Brazil, Chile, Vietnam, Bangladesh, and Australian Aboriginals (see Table 3.2 below). Additional studies are ongoing.

### 3.1 Incidence

Incidence data on RA have been collected mostly in populations of Anglo-Saxon origin (1). The incidence of RA ranges from around 20-300 per 100,000 adults per year (Table 3.1).

**Table 3.1. Incidence studies for rheumatoid arthritis**

Region	Study population	Ref.	Years	Type of study	Sample size	Diagnostic criteria
EURO A	East Anglia, England.	(29)	1990-1991	Prospective population-based register of inflammatory arthritis. Notification system from GP and hospital.	210 cases notified	1987 ACR criteria
AMRO A	Rochester, Minnesota	(30)	1955-85	Medical records with diagnosis of arthritis.	1878	1987 ACR criteria

### 3.2 Prevalence

Available data on RA prevalence derive particularly from studies performed in the USA and Europe, with minimal information on other parts of the world. These studies have been recently reviewed (1;17). The prevalence of RA in most industrialized countries varies between 0.3 and 1% and a reasonable overall prevalence for definite RA is of 0.8 per cent adults (aged 15+). The prevalence in developing countries is variable; with some studies showing lower prevalence rates and others similar levels to those in developed countries (Table 3.2).

**Table 3.2. Prevalence studies for rheumatoid arthritis**

Region	Study population	Ref.	Years	Type of study	Sample size	Diagnostic criteria	RA prev. per 100,000
EURO A	Oslo, Norway.	(31)	1991-94	County patient register and postal population survey.	1333 (register) 10000 (survey)	1987 ACR criteria (definite cases)	437 (18-79)
	East Anglia, UK	(9)	1999-2000	Age-sex stratified random sample from 11 GP registers	7050	Modified 1987 ACR criteria (definite cases)	M 440 F 1160
EURO B/C	Sofia, Bulgaria	(32)	1965-66	1 in 10 age-stratified random sample from electoral register.	4318	CIOMS (Rome) criteria + X-ray/serology later	M 246 F 695
	Belgrade, Yugoslavia.	(33)	1990-91	Participants randomly selected and surveyed.	2184	1987 ACR criteria	M 87 F 183
AMRO B/D	Jamaica.	(34)	1962-63	Cultivators living in small hillside huts, Tavern district.	600	CIOMS (Rome) criteria –	(35-64) M 1901

				Random sample of 600 from 2234.		definite cases (active and inactive disease)	F 2247
	Gguaynabo, San Juan, Puerto Rico.	(35)	1961-63	All population screened, no stratified sampling. Door to door survey.	3885	1958 ARA criteria	(18+) M 161 F 417

**Table 3.2 (continued): Prevalence studies for rheumatoid arthritis**

AFRO	SE Liberia (Cavalla) and west Nigeria (Igbo-Ora and Isheri).	(36)	1965- 67	Cavalla plantation – systematic sample from registration cards of employees (mainly male). The employee and all over 5 years living in house selected. Igbo-Ora – Households randomly selected.	1037 (stratified for age and gender)	1966 ARA criteria	M 3051 F 2885
	Lesotho	(37)	1985	Adults over 15 years from 8 villages selected at random	1070	ARA criteria for active RA (probable and definite combined) or Rome criteria for inactive RA	M 1786 F 4575
	Orlando East, Soweto, Johannesburg	(21)	1975	15 blocks of house randomly selected from street map.	946	modified Rome criteria (used in the rural survey Beighton 1975)	M 2538 F 3672
	Tswana people of Phokeng, Johannesburg	(38)	?	6 blocks of 60 homes randomly chosen. Clinical examination.	1183	modified Rome criteria 1961, ARA 1958 criteria 'definite & probable' RA	M 1608 F 408
EMRO	Oman.	(39)	1987 (Jan –Dec)	House to house population survey and survey of health institutions in 10 representative areas.	1925 (1350 subjects actually seen)	1987 ACR criteria	M 208 F 519
	Al Qassim region, central Saudi Arabia.	(40)	?	Region stratified by population density and random samples selected from each of 3 strata.	5891	1987 ACR criteria	M 186 F 221
	Urban Iraq.	(41)	summer 1975	Whole adult population of Rawa & every 1/3 household by street address in selected areas in the other 9	6999	1958 ARA criteria	M 455 F 1546

towns for 10  
representative towns

SEARO B	Central Java	(42)	1982-83 (rural) 1984 (urban)	Household survey of those over 15 years of age in population of 4683 rural and 1071 urban subjects. Medical examination for those with peripheral joint pain.	5754 (4683 rural and 1071 urban)	1958 ARA criteria	M 113 F 259
	Thailand	(43)		COPCORD survey		1987 ACR?	M 0 F 232
SEARO D	Bhigwan village, India	(44)	1996	COPCORD Survey	4056	1987 ARC criteria and clinical definition	M 133.4 F 800
WPRO A	Wakayama, Japan	(45)					
	Kamitonda, Wakayama, Japan	(46)	1965- 1996	Longitudinal population-based study.	3000	Rome definite and classical	M 250 F 300

**Table 3.2 (continued): Prevalence studies for rheumatoid arthritis**

WPRO B	Hong Kong.	(47)	1991-1992	Household survey of in 2 housing blocks (for low income Chinese families and elderly).	2000 interview ed, 70 examinations.	modified 1987 ACR criteria	M 111 F 550
	Kinmen island.	(48)	1974	Total village name list, 17 years +.	30,000 interview ed, 5629 examinations.	1958 ARA criteria for definite RA (C.I.O.M.S. Rome)	M 183 F 414 (18+)
	Philippines	(49)		COPCORD survey		1987 ACR	166

### 3.3 Time trends in rheumatoid arthritis

Future changes in the incidence and prevalence of RA are difficult to predict. Recent studies indicate a decline in its prevalence, particularly among women(50). On the other side, RA is expected to increase in the next 10 years in Europe and North America as a function of their ageing population. The net result of these opposite trends, however, is unpredictable and prospective figures should be gathered through specific studies.

Due to the paucity of data on time trends in prevalence or incidence of rheumatoid arthritis, these have been assumed to be stable over time, and prevalence studies over the last 30 years used to assess regional prevalence rates of rheumatoid arthritis.

### 3.4 Risk factors for the development of RA

RA tends to run in families. One of the genetic components of seropositive RA has been mapped to a short gene sequence now known as the shared epitope. This appears to be the marker for RA disease severity rather than susceptibility (51). The prevalence of the shared epitope varies considerably between populations. This may, in part, explain the different patterns of RA seen around the globe.

Little is known about the environmental triggers for RA. Infection may play a part in some individuals. There are complex interactions between the female sex hormones and RA. The onset of RA is rare during pregnancy and RA is more common in nulliparous women. The oral contraceptive pill, or some other factor associated with its use, appears to protect against the development of the severe RA. Again the frequency of the pill use, nulliparity and breast-feeding varies considerably between communities and may influence the epidemiology of RA. Smoking and obesity are also risk factors for RA (52).

### 3.5 Mortality and case fatality

RA is associated with a reduced life expectancy. As expected, mortality is generally lower in population-based studies of RA in comparison with studies reporting patients in the clinical setting who usually suffer from a more severe form of the disease. On the other hand, there is some evidence from a pair of population surveys that mortality amongst community based RA patients in

developing countries is very high (42) and this may, in part, account for the low prevalence in some of these countries. Mortality is related to severity of RA as expressed by functional status, health status and health status perception, radiological damage, and extra-articular manifestations. Co-morbidity, formal education, socio-economic and marital status, but not race, may affect survival. The provision of treatment has been rarely considered a factor influencing mortality until recently. However it should now be considered since more aggressive therapy can affect outcome and there is evidence, for example, that methotrexate therapy improves life expectancy in RA (53).

A study which analysed the national mortality statistics of Australia from 1950-81 showed no improvement in survival for men with RA in that period and a small decline in survival for women with RA which was confined to the over-75 age group (54). A recent study from the Mayo clinic reported no improvement in mortality from RA over the last 4 decades (55). It has been estimated that between 3 and 7 years are taken off the life of a person with RA. The main causes of excess deaths are infection, renal and cardiovascular disease (54). A recent study from Norway confirmed a significant excess mortality for females with RA because of cardiovascular disease (56) and similar results have been reported from elsewhere. The excess cardiovascular deaths in RA are probably attributable to the cumulative inflammatory burden of the disease.

In those with an onset before the age of 50 men have a worse prognosis than women; while in those over the age of 50 women fare worse (57). A lifespan reduction of 5 years for a 50 year old corresponds to a relative risk of death of 2.0. Pincus et al (58) reported a relative risk of mortality for RA of 1.6. A relative risk of 1.5 was used in GBD 1990 for ages from 15 onwards, a relative risk of 1 was assumed for children. Based on the recent evidence, we use the relative risk of mortality for RA set out in Table 3.3. For juvenile arthritis, this corresponds to annual case fatality rates in the range 0.1-0.2 per 1,000 for developed countries through to 3-4 per 1,000 in sub-Saharan Africa.

**Table 3.3 Relative risk of mortality for rheumatoid arthritis cases**

Age group	Males	Females
0-24	2.00	2.00
25-64	1.60	1.75
65+	1.35	1.50

Problems associated with studies of mortality in RA include classification of patients with non-standardised criteria and lack of the "RA" diagnosis in death certificates. Small numbers of deaths are recorded in vital registration systems with underlying cause given as rheumatoid arthritis. For regions with low adult and child mortality rates ('A' regions), the average RA crude death rate is 0.3 per 100,000 males and 0.6 per 100,000 females. The rates are around 50% higher in the WPRO A region. Crude annual case fatality rates (deaths per 1,000 prevalent cases for which RA given as underlying cause) range from around 0.6 in some developing regions to over 2 in some high prevalence regions. The global average case fatality rate is around 1 per 1,000 prevalent cases for both males and females. These case fatality rates do not include the cardiovascular deaths and other deaths for which RA is an underlying cause.

## 4. Juvenile idiopathic arthritis

Juvenile arthritis encompasses a range of disorders in children and adolescents aged 15 and below, which can be classified into groupings including infectious arthritis, reactive arthritis, connective tissue diseases, and congenital and developmental diseases (17;59). The most common of these diseases is now called juvenile idiopathic arthritis (JIA), an umbrella term which describes children with an inflammatory arthritis of unknown origin which has persisted for at least 6 weeks (60). There are 7 subsets of JIA. In the past numerous other terms including juvenile chronic polyarthritis, juvenile chronic arthritis (JCA), juvenile rheumatoid arthritis (JRA) and Still's disease have been used for this group of patients.

### 4.1 Classification criteria

The original Taplow criteria for juvenile chronic arthritis (JCA) (61-63) were modified by a World Health Organization/European League against Rheumatism (WHO/EULAR) workshop to eliminate the need for histopathological confirmation of inflammatory synovitis (64). Using these EULAR criteria for JCA criteria, cases are defined by onset of disease before age 16, minimum duration of arthritis of 3 months and further classification by pattern of disease at onset. The definition of JCA includes juvenile ankylosing spondylitis and juvenile psoriatic arthritis but specifically excludes children who are sero-positive for rheumatoid factor (i.e. those who have a true childhood onset of RA). The EULAR criteria are similar to those proposed by the ARA in 1977 for JRA (65). However the ARA criteria for JRA require a disease duration of 6 weeks and excludes children with juvenile psoriatic arthritis and ankylosing spondylitis while including those positive for rheumatoid factor. In studies which have used both JCA and JRA criteria, JCA prevalence is usually higher because it includes more categories. Most recently, ILAR (60) has developed criteria for juvenile idiopathic arthritis which encompass both seropositive and sero-negative forms of arthritis in children.

### 4.2 Incidence and prevalence

The prevalence of JCA and/or JRA has been estimated in several studies both in the USA and Europe (17). Using EULAR criteria, the incidence of JCA ranges from around 20 to 50 per 100,000 per year (Table 4.1). Laaksonen (62) analysed 544 children who satisfied the Taplow diagnostic criteria and estimated the prevalence rate was 40 per 100,000 children aged under 15. Other studies carried out in the USA during the 1970s, estimated prevalence rates of JRA ranging from 16 to 110 per 100,000 (66;67). Gare *et al.* conducted a population based study in Sweden and estimated the prevalence of JCA as 0.56 per 1000 (68). Manners and Diepeveen (69) measured point prevalence of JCA in an entire urban Australian community in which case ascertainment was based on clinical examination by a rheumatologist. The resulting point prevalence in 12 year olds was 40 per 100,000, most of which were mild cases. The definition of prevalence used in the study included cases either in remission or currently active. The study would not have picked up children in remission with no residual deformities. Mielants *et al* (70) found a prevalence of 167 per 100,000 with definite JCA and 301 per 100,000 with probable JCA, but 80% of these children were in remission at the time of the study. Assuming on average, the diagnosis was 3-5 years previously, this corresponds to an instantaneous average remission rate of about 0.4.

**Table 4.1. Incidence and prevalence studies for juvenile arthritis**

Region	Study population	Ref.	Years	Type of study	Sample size	Diagnostic criteria
<b>PREVALENCE</b>						
EURO A	5 counties, Sweden	(71)	1984-88	Population study in 5 southwestern counties	389,976	EULAR criteria for JCA
<b>INCIDENCE</b>						
EURO A	UK, 23 centres.	(72)	1989-1995	UK National diagnostic register for pediatric rheumatology.	4948 cases registered	EULAR criteria for JCA, including seropositive polyarticular disease
AMRO A	Rochester, Minnesota	(73)	1960-93	Medical records screened.	1878 medical records with diagnosis of arthritis	revised ARA 1977 criteria (<16 years at diagnosis)
AMRO B/D	San José, Costa Rica.	(71)	1993-1995	Two-year longitudinal study of referrals to National Children's Hospital	189 Hospital	EULAR criteria for JCA

Gare and Fasth (74) conducted a total population study during 1984-1988 with mean observation = 5 years, using EULAR criteria for JCA. The reported annual incidence rates of JCA by age and sex are listed in Table 4.2.

**Table 4.2. Incidence per 100,000 for juvenile chronic arthritis cases(74)**

Age group	Males	Females
0-4	7.4	17
5-14	8.2	12.8
15+	6.4	14.1

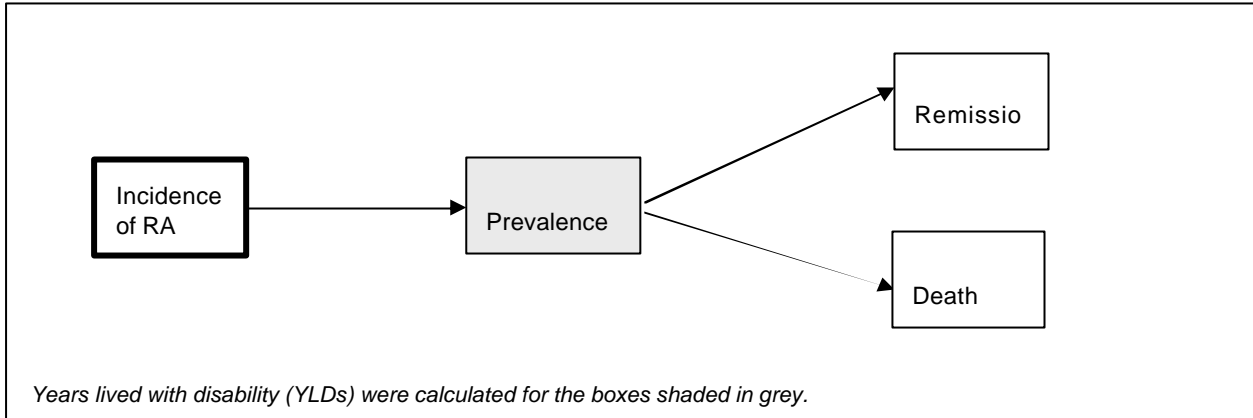
### 4.3 Duration and severity

Longitudinal studies of juvenile arthritis with up to 20 years follow up have shown that 20 to 40 per cent will be significantly disabled (75-78), but more recent studies give proportions below 20 per cent (79;80). Greater disability is associated with five or more joints (i.e. polyarticular) involved at onset and female sex. Baum and Gutowska (81) reviewed data from several European and American clinics and estimated the overall case fatality rate at 1.1 per cent. A more recent study of 11,000 North American cases found a lower case fatality rate of 0.3 per cent.

## 5. Disease model for rheumatoid arthritis

There is only one study of RA where both incidence and prevalence rates have been measured for a population: the Rochester 1955-1985 study in the USA (30). A disease model was developed for

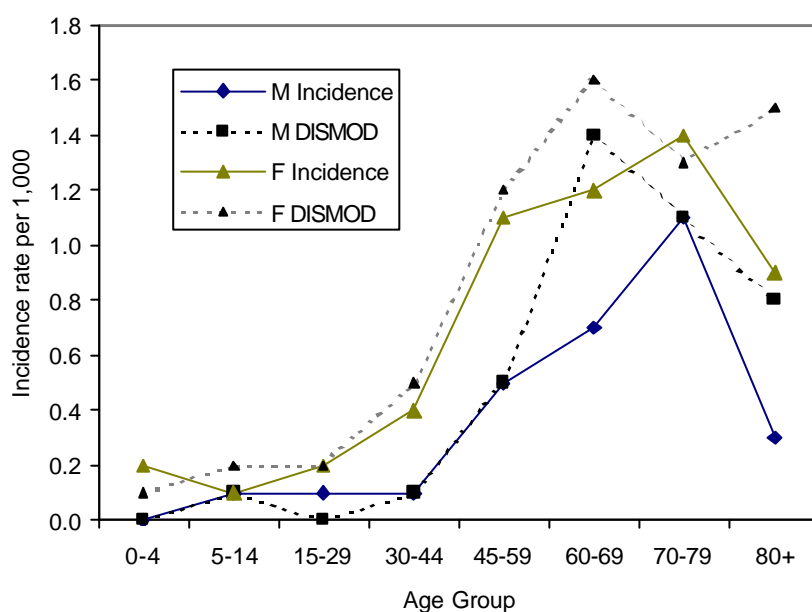
rheumatoid arthritis using this data together with DISMOD 2 (an epidemiology software program available from the WHO website at [www.who.int/evidence/dismod](http://www.who.int/evidence/dismod)), in order to check consistency with estimates of mortality RR and remission rates. The disease model is shown in Figure 5.1.



**Figure 5.1: Rheumatoid arthritis disease model.**

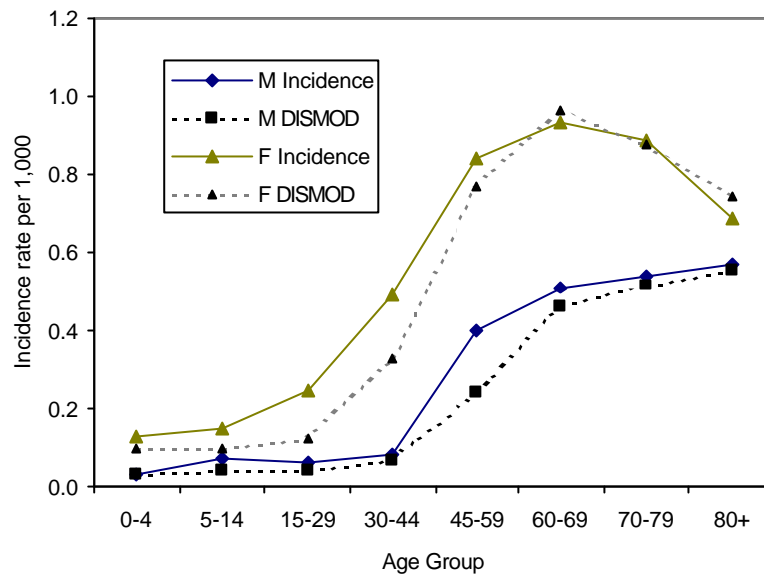
The GBD 1990 study used instantaneous remission rates of around 0.1 to model disease duration, resulting in average durations of around 8 years. Ahern and Smith (82) state that spontaneous remission can occur, particularly when the onset is explosive, but that most patients will experience fluctuating symptoms with slow progression of damage. Although drug treatment slows the disease process, few patients go into lasting remission (83). Prevoo et al (84) found that the remission rate was 15% over 4 years. This corresponds to an instantaneous average remission rate of 0.04. For juvenile arthritis, a remission rate of 0.1 was assumed. Relative risks of mortality used in DISMOD 2 are shown in Table 3.3.

The observed prevalence rates from the Rochester study were input to DISMOD 2 together with remission rates and mortality RRs. The resulting calculated incidence rates are shown in Figure 5.2, together with the incidence rates observed in the study. There is reasonably good agreement, suggesting that the remission and RR assumptions are acceptable.



**Figure 5.2. Comparison of modelled and observed RA incidence rates, Rochester USA.**

There is not a single study with both incidence and prevalence estimates in any other region. However, there is a UK incidence study (the Norfolk Arthritis Register) and incidence estimates for Oslo in 1997. The Oslo prevalence rates were input to DISMOD 2 with the same remission and mortality assumptions as for Rochester and incidence rates calculated. Figure 3 compares the calculated incidence rates for Oslo with those observed in Norfolk. There is surprisingly good agreement, suggesting that the UK and Norwegian data are consistent, and that the remission and mortality assumptions are reasonable. These assumptions were used for other regions of the world estimate RA incidence rates and average durations from RA prevalence rates. Data and assumptions are further described in Section 8.



**Figure 5.3. Comparison of observed RA incidence rates in the UK with modelled incidence rates based on prevalences in Oslo 1997.**

**Table 5.1. Comparison between GBD 1990 and GBD 2000 disease models**

	GBD 1990	GBD 2000
Stages/Sequelae	Definite or classical RA cases by 1958 ARA or 1987 ACR criteria	Definite or classical RA cases by Rome criteria, 1958 ARA or 1987 ACR criteria
Incidence rates	DISMOD 1 used to estimate from prevalence rates	DISMOD 2 used to estimate from prevalence rates
Remission	0.112	0.04 (15% over 4 years)
Case fatality	RR=1.5	See Table 4.1
Severity distribution	0.174 (treated) 0.233 (untreated)	0.174 (treated) 0.233 (untreated)

## 6. Health state descriptions and disability weights

RA is a more disabling disease (although not necessarily more painful) than lower limb osteoarthritis. The disability starts early and rises in a linear fashion (85). Within ten years of onset, at least 50% of patients are unable to hold down a full-time job (83). Those whose disease starts early (before the age of 45) are more likely to become severely disabled than those whose disease starts at older ages (70+).

There is no cure for RA. Drug treatment falls into five categories:

- 1 Non-steroidal anti-inflammatory drugs - of which the cheapest is aspirin - which relieve pain and stiffness.
- 2 Second-line agents such as injectable gold, methotrexate and sulphasalazine - which slow the disease process and reduce the acute phase response. They have a high side-effect profile and require careful monitoring.
- 3 Steroids - which produce symptomatic benefit, require no monitoring, but have serious long-term consequences.
- 4 Immunosuppressive drugs - which are needed for the small proportion of patients with systemic disease.
- 5 The new biologic agents - directed against inflammatory cytokines . The exact place of these agents in the treatment of RA has yet to be established

In addition to drug treatment, orthopaedic surgery is able to offer great relief to those particularly in the second and third decade of disease, who have been severely disabled. Physiotherapy and adaptations to the home may also reduce disability. It is estimated that, with current management applied optimally, the burden of disability due to RA might be further reduced by 25% in developed countries. There is some recent evidence that methotrexate may reduce mortality (53).

In low income countries, the appropriate infrastructure to provide adequate supervision of second-line drug therapy; and to provide skilled orthopaedic surgery is often absent. In addition, steroid therapy is often freely available and used indiscriminantly. Thus it is estimated that the burden of disability due to RA might be reduced by 40% if medical input were increased.

The GBD 1990 study estimated disability weights for treated and untreated RA as shown in Table 6.1. The proportion of cases treated was assumed to range from 80% in the EME, to around 50% in China, India and LAC, down to 20% in Sub-Saharan Africa. This resulted in disability weights ranging from 0.185 in the EME to 0.221 in SSA. The Netherlands disability weights study (86) estimated disability weights for three levels of severity of RA. These were defined in terms of EQ-5D+ health state descriptions 122211 (mild), 222221 (moderate), and 50% 222331 and 50% 333331 (severe).

Hakala et al (87) examined the severity of RA in a population study using 1987 ARA criteria and found that less than 10% of the subjects had severe disability due to RA, and about two-thirds had mild or moderate disability due to RA. Gare and Fasth (88) also found that among the cohort of 124 JCA patients who were followed up in a prospective population study, 30.6% were in remission, 20.2% had inactive disease, 18.6% were active, and 30.6% were stable. This information was used in the Australian Burden of Disease study (89) to estimate an average disability weight (see Table 7.1), which is somewhat higher than the GBD 1990 weight. Pending revision of GBD 2000 disability weights, using health state valuations from the WHO World Health Survey, to be carried out in 2002, we use the GBD 1990 disability weights to estimate global RA burden.

Rheumatoid arthritis causes erosion initially of the cartilage and then of the bone leading to joint destruction, deformity and subsequent disability. If erosions occur in RA (majority of cases) they will do so in the first one or two years and possibly earlier. We thus use the average GBD 1990 disability weight, rather than model progression through the various levels of severity - which would result in discounting of YLD contribution for more severe cases.

**Table 6.1 Disability weights for rheumatoid arthritis**

<b>Stage/sequela</b>	<b>GBD 1990</b>	<b>Netherlands Study</b>	<b>Australian BOD Study</b>
Cases	0.174 (treated) 0.233 (untreated)	0.27 (mild) 0.31 (moderate) 0.94 (severe)	0.231 (based on Dutch weights)

**Table 7.1 Data and assumptions used to estimate regional prevalence rates for adults**

AFRO	<p>Small studies from Nigeria, Liberia, South Africa plus others. These were old, but showed much higher prevalence than those used in 1990. Also showed male prevalence higher than female, while the pattern was opposite in every other region and in disease literature.</p> <p>Prevalence of probable plus definite RA ranges from 2 to 5 times higher than definite plus classical RA prevalence. Prevalence estimates for Africa based on 20% of prevalence for probable plus definite RA.</p> <p>The low sex ratio probably reflects problems with case finding or sampling in females, given high female/male sex ratio observed in all other regions. We adjusted female prevalences to give a F:M ratio of 1.5:1, lower than the ratio in any other region, to best reflect both the studies and the general disease patterns.</p>
AMRO A	Prevalence data from Rochester, MN used with DISMOD to estimate incidence and durations.
AMRO B and D	No new prevalence studies (Jamaica, Puerto Rico, Costa Rica) but numbers from older studies were lower than those from 1990. Estimated prevalence to be 80% of 1990 prevalence numbers (based on the few data points) to reflect the lower values found in the studies.
EMRO	In 1990, MEC was one of lowest prevalence regions, but new studies for Oman, Saudi Arabia, Iraq showed it as one of the highest, much higher than 1990 rates. We estimated prevalence rates similar to AMRO A.
EURO A	Prevalence from Oslo study, consistent with UK incidence data.
EURO B and C	No new studies. Overall prevalence was similar to that for FSE in GBD 1990.
SEARO B/ WPRO B2	No new studies. Prevalence estimates similar to that for OAI in GBD 1990
India (SEARO D)	In 1990 India was one of the lowest prevalence regions but a more recent study has given much higher rates. Because this was a study in one rural village, we have been conservative and assumed that incidence rates are not higher than in AMRO A..
WPRO A	Few studies in this region. Prevalence rates for USA were used for Australia and New Zealand and separate rates estimated for Japan (for which only a very incomplete set of age-specific rates were available). Since Japan rates were lower, but not from a national study, we assumed national rates for Japan were similar to those for EURO A, which are significantly lower than AMRO A, but not as low as the few age-specific rates from the Japanese study.
China (WPRO B1)	Based on studies for Hong Kong, Qemoy (island of China), Taiwan. Resulting prevalences were consistent with those estimated for China in GBD 1990.
WPRO B3	Recorded RA mortality is high. No prevalence studies. Assumed high prevalence (similar to AMRO D).

## 7. Regional incidence, prevalence and mortality estimates

Table 7.1 summarises the data and assumptions used to estimate regional prevalence rates. For those regions with no available RA prevalence or incidence studies, prevalence rates were assumed to be similar to other selected regions, comparable in terms of level of development and/or RA mortality rates. An estimate derived from a different region is more likely to be correct than the assumption that the condition does not exist in the region with no data of its own. In some instances, there are sufficient data from a region to indicate whether it is likely to be a high or low prevalence

area for RA, but not to give a clear age pattern. In these cases, age patterns have been based on those seen in other regions. This process can also be used to decide where further work is needed. It is not necessary for a comprehensive set of surveys to be conducted in every country. A few large, high quality surveys are needed from representative areas.

Table 7.2 summarizes juvenile arthritis incidence and prevalence estimates for developed and developing regions. Table 7.3 summarizes the resulting subregional incidence, prevalence and cause-specific mortality rates for rheumatoid arthritis, in terms of crude rates per 100,000 persons. For the three developed regions, the overall prevalence rates for persons aged 50 years and over are around 11-12 per 1,000 or 1.1%. Table 7.4 gives similar rates for each subregion, age-standardized to the World Standard Population (90).

**Table 7.2 Estimated incidence and prevalence rates for juvenile arthritis**

Region	Incidence per 100,000		Prevalence per 100,000	
	Males	Females	Males	Females
EURO A, B1, C, WPRO A				
0-4	3	13	6	28
5-14	7	13	33	79
AMRO A				
0-4	2	20	4	43
5-14	7	15	30	103
AFRO, EMRO, EURO B2, SEARO D, WPRO B3				
0-4	2	4	4	8
5-14	4	8	14	29
WPRO B1, B2, SEARO B				
0-4	0	2	0	4
5-14	2	4	4	14

**Table 7.3. Rheumatoid arthritis: crude rates for WHO epidemiological subregions, 2000.**

Subregion	Incidence/100,000		Prevalence/100,000		Mortality/100,000	
	Males	Females	Males	Females	Males	Females
AFRO D	14	22	124	197	0.3	0.7
AFRO E	14	22	117	188	0.3	0.8
AMRO A	35	72	336	801	0.3	0.6
AMRO B	20	63	209	754	0.4	0.9
AMRO D	18	59	183	654	0.5	1.2
EMRO B	16	36	156	368	0.2	0.3
EMRO D	15	37	142	381	0.2	0.3
EURO A	41	88	365	979	0.2	0.6

EURO B1	31	78	351	1006	0.2	0.5
EURO B2	16	39	153	417	0.2	0.4
EURO C	36	89	379	1142	0.2	0.5
SEARO B	15	31	108	262	0.4	0.5
SEARO D	17	37	160	376	0.2	0.2
WPRO A	29	67	315	799	0.5	0.9
WPRO B1	20	45	194	457	0.2	0.3
WPRO B2	13	29	96	259	0.4	0.6
WPRO B3	18	58	179	620	0.5	1.2
World	21	48	201	521	0.2	0.5

**Table 7.4. Rheumatoid arthritis: age-standardized rates for WHO epidemiological subregions, 2000.**

Subregion	Age-std. Incidence/100,000		Age-std. prevalence/100,000		Age-std. mortality/100,000	
	Males	Females	Males	Females	Males	Females
AFRO D	25	38	233	347	0.3	0.7
AFRO E	25	39	231	346	0.3	0.8
AMRO A	30	58	284	621	0.3	0.6
AMRO B	24	69	264	852	0.4	0.9
AMRO D	25	71	268	856	0.5	1.2
EMRO B	22	48	232	530	0.2	0.3
EMRO D	22	48	223	523	0.2	0.3
EURO A	29	59	255	614	0.2	0.6
EURO B1	31	74	349	936	0.2	0.5
EURO B2	22	47	219	513	0.2	0.4
EURO C	33	75	347	925	0.2	0.5
SEARO B	23	41	181	358	0.4	0.5
SEARO D	23	47	223	498	0.2	0.2
WPRO A	21	46	220	502	0.5	0.9
WPRO B1	22	47	216	477	0.2	0.3
WPRO B2	23	41	179	357	0.4	0.6
WPRO B3	25	73	270	846	0.5	1.2
World	25	52	244	562	0.2	0.5

## 8. Global burden of rheumatoid arthritis in 2000

General methods used for the estimation of the global burden of disease are given elsewhere (91). The tables and graphs below summarise the global burden of RA estimates for the GBD 2000 and compare them with the RA estimates from the GBD 1990 (2).

**Table 8.1 Rheumatoid arthritis: global total YLD, YLL and DALY estimates, 1990 and 2000.**

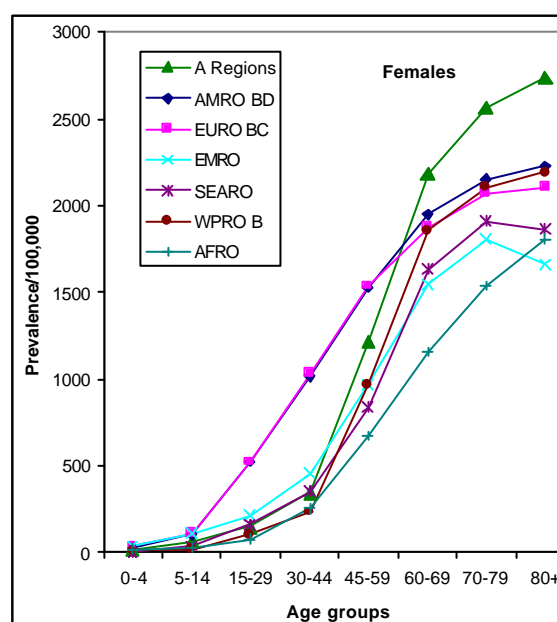
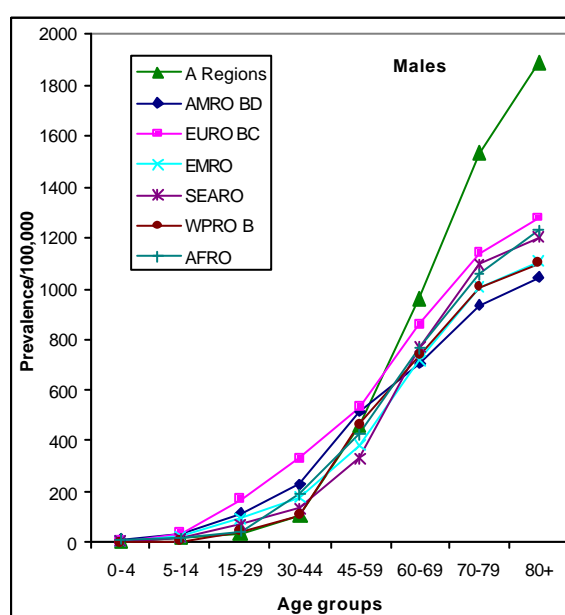
	Males	Females	Persons
<b>YLD('000)</b>			
<i>GBD1990</i>	859	2,309	3,168
<i>GBD2000</i>	1,274	3,214	4,488
<b>YLL('000)</b>			
<i>GBD1990</i>	39	79	118
<i>GBD2000</i>	46	102	148
<b>DALY('000)</b>			

GBD1990	898	2,388	3,286
GBD2000	1,320	3,316	4,636

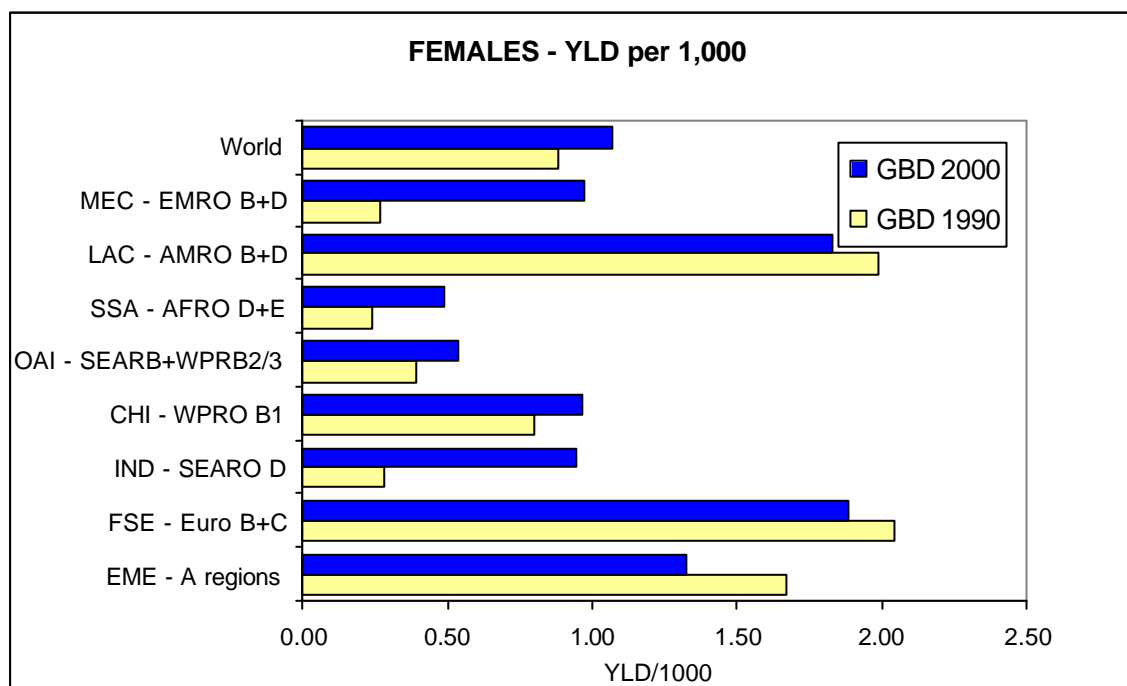
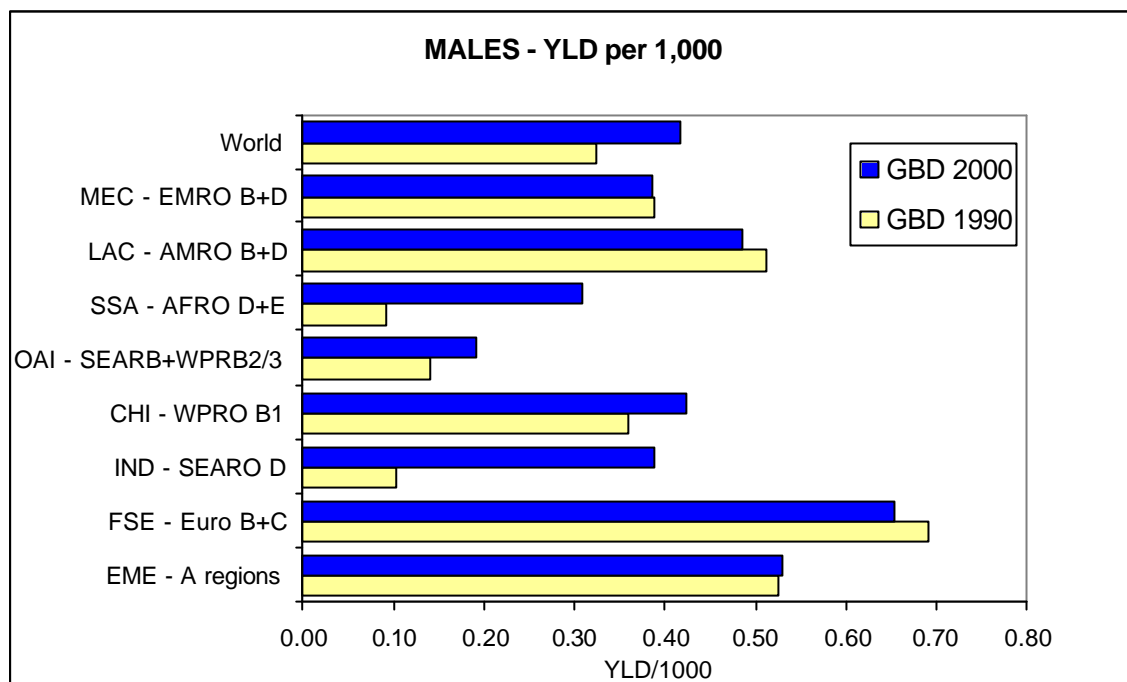
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**Table 8.2. Rheumatoid arthritis: YLD, YLL and DALY estimates for WHO epidemiological subregions, 2000.**

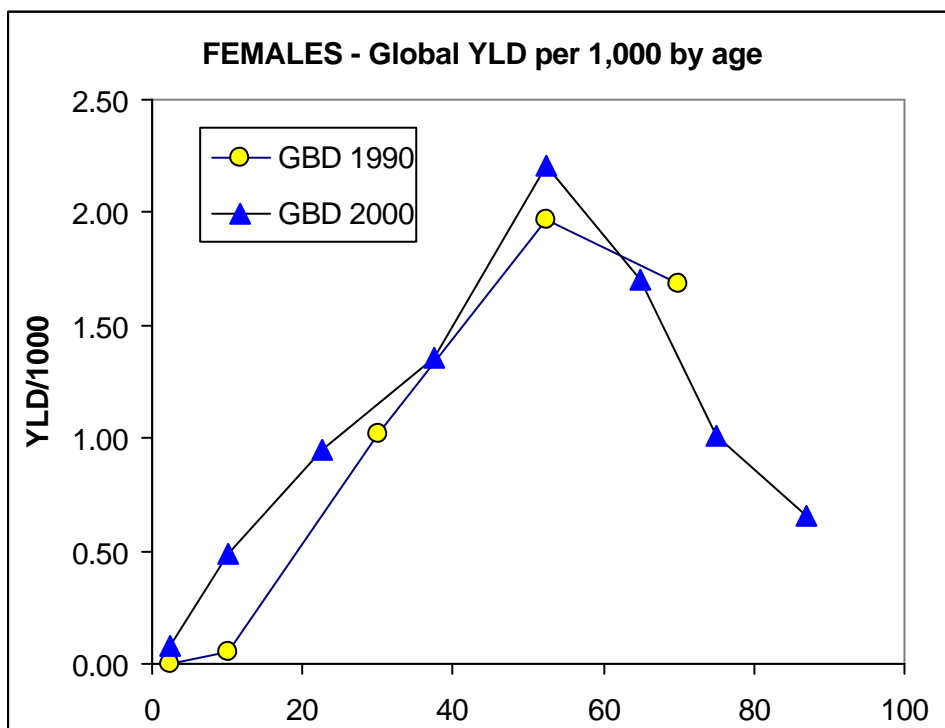
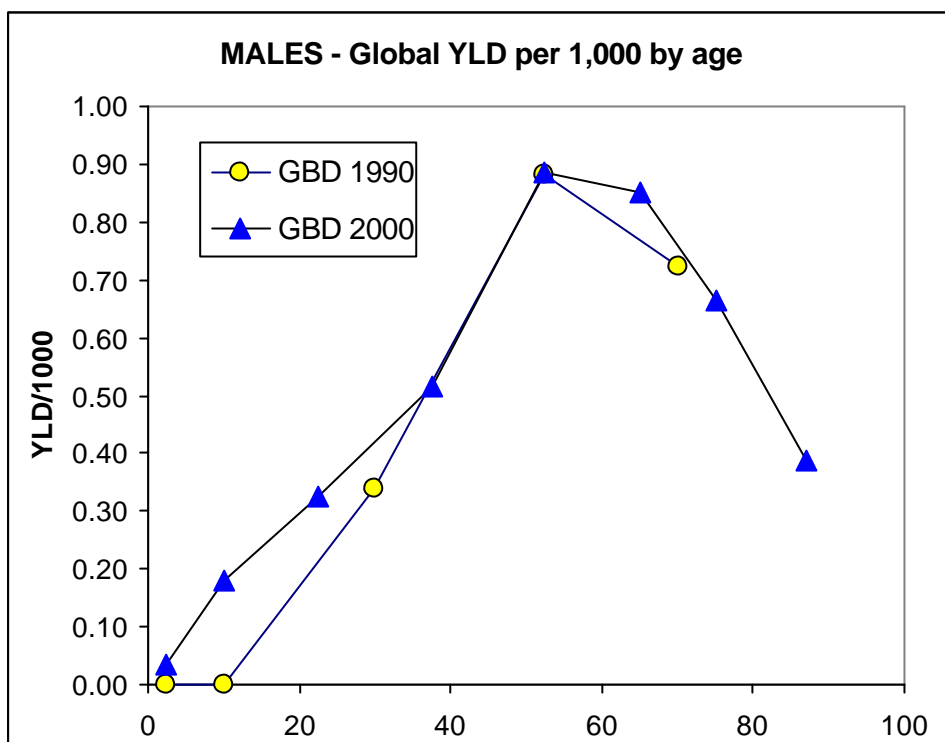
Subregion	YLD/100,000		YLL/100,000		YLD (‘000)	YLL (‘000)	DALY (‘000)
	Males	Females	Males	Females			
AFRO D	32.4	50.5	1.0	1.9	139	5	144
AFRO E	29.5	46.4	1.1	2.0	128	5	134
AMRO A	53.9	129.4	2.4	5.9	285	13	298
AMRO B	49.1	185.1	1.6	6.2	521	17	538
AMRO D	46.1	174.2	4.7	6.6	79	4	83
EMRO B	40.3	97.5	0.0	0.0	95	0	95
EMRO D	36.8	96.9	0.1	0.2	92	0	92
EURO A	53.3	139.5	2.2	6.9	400	19	419
EURO B1	70.2	204.5	1.8	5.5	229	6	235
EURO B2	36.7	97.7	1.8	2.9	34	1	36
EURO C	68.4	196.0	3.4	8.2	335	15	349
SEARO B	19.7	53.0	4.1	5.6	143	19	163
SEARO D	39.0	94.5	0.8	1.6	889	16	905
WPRO A	49.5	119.7	4.8	11.1	127	12	139
WPRO B1	42.6	97.0	0.6	1.2	937	12	949
WPRO B2	16.5	50.4	1.4	2.2	48	3	50
WPRO B3	46.1	172.8	5.0	6.5	7	0	8
World	41.9	107.1	1.5	3.4	4,488	148	4,636



**Figure 8.1. RA prevalence rates, age group and sex, broad regions, 2000.**



**Figure 9.1. RA YLD rates, by sex, broad regions, 1990 and 2000.**



**Figure 9.2. Global RA YLD rates, by age and sex, 1990 and 2000.**

## 9. Uncertainty analysis

General methods for uncertainty analysis of estimates for the Global Burden of Disease 2000 are outlined elsewhere (92). Uncertainty analysis for RA has not yet been completed.

## 10. Conclusions

The task of compiling an accurate set of estimates of the number of individuals with musculoskeletal problems will never be complete. There will always be the possibility of a more up-to-date estimate, of focusing on a smaller geographical area or on a more homogeneous population group. It is important to fill some of the major gaps – for example in Eastern Europe, South America and Africa. Single large surveys that investigate several conditions simultaneously are of more value than a series of small single condition studies. However, estimating the number of cases of a condition is only the first step in burden of disease analysis and it is possible to move forward with uncertain estimates of numbers rather delaying progress by waiting for more precise figures. Uncertainty intervals will be provided for RA burden estimates.

Large numbers of additional data sets should be explored: these may include governmental surveys, insurance company, health care and pension fund data such as HMO, managed care organizations and governmental providers. These sources of information are frequently underutilized in studies on musculoskeletal conditions because they are usually collected for different purposes. Data on different types of arthritis, such as infectious arthritis, gout and undifferentiated arthritis, which are more relevant in developing countries, should be also collected.

There are two main reasons for incompleteness of the existing data on RA incidence and prevalence. First, figures from Africa, South America and Asia are scanty and need to be improved to allow understanding of intra- and inter-regional variability of RA. Second, several data suggest that both epidemiological and clinical features of RA vary over time. Therefore, repeated studies are needed in the same area to identify changing patterns of the disease. In a priority scale, epidemiological studies of RA in developing countries should come first. In areas where data are poor, extrapolation of incidence figures from neighboring or similar countries could be used. To the extent that social, economic, genetic, and environmental determinants and correlates of RA can be identified, they can be used to improve the estimation for such regions.

These are version 2 estimates for the GBD 2000. Apart from the uncertainty analysis, updating estimates to reflect revisions of mortality estimates and any new or revised epidemiological data or evidence, it is not intended to undertake any major addition revision of these estimates.

We welcome comments and criticisms of these draft estimates, and information on additional sources of data and evidence. Please contact Colin Mathers (EBD/GPE) on email [mathersc@who.ch](mailto:mathersc@who.ch)

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