A COMPARISON OF GUJARATI ASIAN AND CAUCASIAN PATIENTS WITH RHEUMATOID ARTHRITIS

Thesis submitted for the degree of

Doctor of Medicine

at the University of Leicester

by

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2008

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Acknowledgments

I would like to thank Dr Waji Hassan and Dr. Mike Browning, my supervisors, and Dr. Peter Sheldon, Dr. Ash Samanta, Dr. Roger Oldham and Dr. Frank Nichol in the Dept of Rheumatology in Leicester for enabling me to do this research, and for much needed encouragement.

My interpreter Bhagwati Dursara was fantastic, and this research could not have taken place without her help.

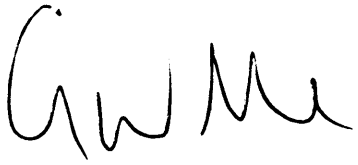
Dr David Smillie and all the staff at the National Blood Centre in Sheffield who were both helpful and patient with a novice in the lab, and kindly checked my results for errors.

Dr. Helen Doll at the Department of Public Health, University of Oxford, kindly checked my statistics.

The support, comments and endless re-reading by my father Dr. Ed Neville were invaluable, and so much appreciated.

My husband Richard, whose constant encouragement and support enabled me to finish the thing.

The contents of this thesis are solely my own work, and have not been submitted for any other degree.



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SUMMARY OF STUDY

Background

Rheumatoid arthritis is a symmetrical erosive inflammatory polyarthritis that may affect ethnically different populations in different ways. Gujarati Asians are the largest ethnically distinct group living in Leicester other than the indigenous population. This study examined the Gujarati Asian and the Caucasian patients with RA living in the Leicester region to identify differences and similarities. Socioeconomic status, disease manifestations and activity, HLA shared epitope frequency, treatment and psychological status were all examined as factors that may impact on patients.

Method

133 patients with RA, 61 Gujarati and 73 Caucasian subjects as defined by modified 1987 ACR criteria were recruited from the outpatient clinics of the Leicester hospitals. The Caucasian group was manipulated by excluding the more elderly male patients, to produce a group of 61 Caucasian patients who were equivalent to the Asian patients in terms of age (Asian 52.2 years, Caucasian 54.7 years), sex (Asian 89% female, Caucasian 79% female) and disease duration (Asian 10.03 vs. Caucasian 10.21 years). They partook in a

detailed interview, including an examination and blood testing for plasma viscosity, Hb and HLA DRB1 subtype.

Results

Gujarati and Caucasian patients had no differences in marital status, education and housing. The Gujarati patients had significantly more family at home (2.11 vs. 1.38, p=0.0005), more children at home (1.42 vs. 0.48, p=0.0002) and were more likely to have in-laws living with them (11% vs. 1%, p=0.03). They also had a larger network of helpers (3.15 vs. 1.89, p=0.0004). They were less likely to drink alcohol (85% teetotal, compared with 28% Caucasians, p<0.0001) and to smoke than the Caucasian patients (85% Asians had never smoked, compared with 56% Caucasians, p<0.0001). They were largely vegetarian, and ate an 'Indian' diet.

Gujarati patients were largely unable to work because of disability (59% vs. 31%), whereas Caucasian patients had retired (36% vs. 8%). There was a significant association between category of ability to work and ethnic group, p=0.0008. The Gujarati patients were significantly likely to have had a less skilled occupation than the Caucasians (77% vs. 38% in minimal training jobs, p<0.0001).

The Gujarati patients were significantly more likely to have some form of social services support from Leicester City Council (75% receiving support vs. 54%, p=0.01), and to have more kinds of support than the Caucasian patients (1.69 vs. 1.03, p=0.005).

Caucasian patients had a higher swollen joint count (10.39 vs. 8.07, p=0.05), higher incidence of nodulosis (46% vs. 16%, p=0.0005) and higher rate of seropositivity for RF (66% vs. 45%, p=0.02). Gujarati patients had longer EMS (1.36 hrs vs. 0.86 hrs, p=0.03), more pain on VAS (5.1 vs. 3.7, p=0.0008) and more disability on HAQ (1.9 vs. 1.2, p=0.0001). They also had a higher plasma viscosity (1.78 vs. 1.70, p=0.003) and a lower Hb (11.7g/l vs. 12.5g/l, p=0.0001). They had an earlier age of disease onset than the Caucasians (42.0 yrs vs. 46.3 years, p=0.01).

Gujarati patients were less likely than Caucasians to express the shared epitope (0.77 copies/patient vs. 1.12 copies/patient, p=0.01). If they did express the epitope, it was significantly likely to be HLA DRB1*10 (21% vs. 3%, p=0.0009), whereas the Caucasian patients expressed HLA DRB1*04 (37% vs. 12%, p=0.001) and DRB1*01 (15% vs. 1%, p=0.0007).

There were no differences in treatments given between the two groups. There were no differences in number of intra-articular injections, surgical procedures, hospital admissions, number or type of DMARDs used, steroid use or analgesic

use. Gujarati patients were more likely to be taking calcium and vitamin D supplements (16% vs. 2%, p=0.004). Patients reported equal compliance. Gujarati patients were significantly more likely to complain of a rash as a DMARD side-effect (28% vs. 7%, p=0.002), but no more likely to experience any side-effect than Caucasians. Gujarati patients rated their treatment significantly less effective than the Caucasians on a 5 point scale (3.3 vs. 3.8, p=0.0009).

79% Gujarati and 69% Caucasian patients had tried complementary therapies. Gujarati patients were more likely to have tried acupuncture (30% vs. 15%, p=0.05). Neither group rated CAM above their hospital initiated DMARD treatment.

Gujarati patients were highly significantly depressed on the SRQ (9.44 vs. 5.16, p<0.0001), despite having no difference in threatening life events measured on the list of threatening life experiences (1.28 vs. 1.00). Ethnic group was an independent predictive factor for depression (odds ratio 3.76, p= 0.006).

Ethnic group was an independent significant predictor of HAQ (p <0.0005), when other variables were adjusted for, along with pain, SJC, number of deformities, age and seropositivity for RF. In Caucasians, HAQ was predicted by SJC and pain. In Asians, it was predicted by age, deformities and EMS. SJC was predicted by number of deformities, nodules and PV in the combined group of patients.

Conclusions

There are marked differences between Gujarati and Caucasian patients with RA in Leicester. Socioeconomically, the Gujarati patients had a larger support network. Gujarati patients are more likely to have had low skilled jobs despite equivalent education. Their higher uptake of social services reflects their increased disability, but may contribute to their feelings of helplessness.

The nature of their rheumatoid disease is different. They are less likely to have factors suggesting severe rheumatoid disease, such as nodulosis or RF seropositivity, but have higher levels of pain and disability. There are no obvious differences in their treatment to explain this. Ethnicity predicts disability, so there may be cultural differences that predispose to poorer outcomes.

Despite having factors that should protect against depression, they are significantly depressed. Their higher levels of disability may be either a cause or a result of this. Depression and pain may be undertreated in this group of vulnerable patients.

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CHAPTER 1. INTRODUCTION AND BACKGROUND

1. 1. RHEUMATOID ARTHRITIS: HISTORY OF THE DISEASE

Rheumatoid arthritis (RA) is a complex, chronic multi-system autoimmune inflammatory disease, characterised by a symmetrical erosive polyarthropathy. It was first described in 1800 by Augustin-Jacob Landré-Beauvais, as part of a thesis submitted to the University in Paris, and named 'rheumatoid arthritis' by Sir Alfred Baring Garrod in 1859 (Garrod 1859), although there was confusion between RA, gout and osteoarthritis for many years. A review of all available palaeopathological and written data of arthritis in Europe in 1952 failed to find any evidence of RA existing in Europe before 1800 (Snorrason 1952). It is thought to predate this in the New World, where Native American Indian skeletons with characteristic changes have been found dating back to 3000 to 5000 years ago (Rothschild, Turner et al. 1988).

1. 2. PREVALENCE

1.2.1. Prevalence In The United Kingdom

Rheumatoid arthritis is the commonest inflammatory arthropathy. A very early study by Lawrence demonstrated that it had a prevalence in the general population of the UK ~1% (Kellgren, Lawrence et al. 1953). This study was based on radiographic change in the general population in Wensleydale, Yorkshire and Leigh, Lancashire, in what was almost certainly an entirely Caucasian population.

A study in 1994 by Symmons et al using the Norfolk Arthritis Register (NOAR) showed an incidence of 36/100 000 for women and 14/100 000 for men (Symmons, Barrett et al. 1994). NOAR showed a prevalence of 0.8% in the adult population of Norfolk (Symmons, Turner et al. 2002). This is an ethnically Anglo/Saxon/Celtic population.

The Arthritis Research Campaign's (ARC) Epidemiology Unit has been at the centre of research into the epidemiology of RA in the UK. Their work with twin studies, families and the Norfolk Arthritis Register has significantly advanced our understanding of the disease, and in particular, the contribution of genetic influence on the incidence.

1. 2. 2. Ethnicity: Differing Prevalence Of RA

Some ethnic groups seem to have a particularly low rate of RA. It is rarely seen in rural Africa, as examined in South Africa, where the prevalence was found to be 0.0026% (Mody and Meyers 1989), and Nigeria, where no definite cases of RA were found by Silman et al (Silman, Ollier et al. 1993). It is possible that the low life expectancy of the average rural dwelling African may mean that the disease has less time to develop in this population. The incidence and mortality from infectious disease is particularly high in this group. Rheumatoid factor false positivity is also common. Urban African populations show higher rates of

incidence, although still lower than a Caucasian population (Solomon, Robin et al. 1975). A survey in a more temperate area of Southern Africa, Lesotho, showed a prevalence of RA closer to European levels (Moolenburg, Moore et al. 1984). A Black-Caribbean population in Manchester, UK had an incidence of 2.9/1000, compared to a White incidence of 8/1000 (MacGregor, Riste et al. 1994). The WHO-ILAR COPCORD studies in the Philippines (Manahan, Caragay et al. 1985) and Indonesia (Darmawan, Wirman et al. 1983) also suggest low rates of RA.

1. 2. 3. Urban And Rural Differences In RA

It seems that there is a higher incidence in a Westernised urban population. Population prevalence studies from developed areas of the world suggest an average prevalence of between 0.5 and 1%. However, the Chinese of Hong Kong show a low prevalence of RA, 0.35% (Lau, Symmons et al. 1993), and an Italian study also showed a lower than expected prevalence of 0.33% (Cimmino 1998). This would count against a hypothesis that suggests there is something about the urban environment that triggers RA.

Hameed studied rural and urban Pakistani populations. He found a prevalence rate in the rural area of 0.9/1000, but in the urban affluent area of 1.98/1000 (Hameed, Gibson et al. 1995). However, the groups of patients that he examined were ethnically mixed, and derived from at least three different backgrounds.

The prevalence of RA in a rural Indian population near Delhi was reported as 0.75% by Malaviya et al (Malaviya, Kapoor et al. 1993). They had a study population of 44 551 adults in a rural area near Delhi, and found 299 with RA as defined by revised ARA criteria (see next section). It is interesting to note that 82% of these individuals were rheumatoid factor (RF) positive, and only a small fraction had hand X-rays. They comment that the North Indian population is genetically closer to Caucasians than other ethnic groups, and that this may explain the higher incidence than in other eastern ethnic groups.

1. 3. CLINICAL MANIFESTATIONS OF RHEUMATOID ARTHRITIS

1. 3. 1. Clinical Manifestations: The Classical Description

The disease characteristically affects the joints, particularly the metacarpophalangeal and proximal interphalangeal joints of the hands, the wrists, elbows, shoulders, knees, ankles and metatarsophalangeal joints, although it can affect any joint. It causes a symmetrical deforming erosive polyarthropathy.

The American College of Rheumatology (called at that time the 'American Rheumatism Association' or ARA) published internationally accepted diagnostic criteria in 1987 (Arnett, Edworthy et al. 1988). The patient must have four or more of the following manifestations for at least 6 weeks. This includes

symptoms previously recorded by a physician, to allow for disease in remission or intermittent disease. These criteria are:

1. Morning stiffness in and around joints lasting at least 1 hour before maximal improvement.
2. Soft tissue swelling (arthritis) of three or more joint areas observed by a physician.
3. Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints.
4. Symmetrical swelling (arthritis).
5. Rheumatoid nodules.
6. Presence of rheumatoid factor (RF).
7. Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

This was validated in this paper to show 91-94% sensitivity and 89% specificity for RA when compared to controls without the disease.

The disease can be associated with a wide range of extra-articular manifestations, which may affect almost any system in the body. These occur in about 40% patients, and are associated with worse disease prognosis (Turesson, O'Fallon et al. 2000). Fatigue is common, as is weight loss. Pulmonary manifestations include interstitial lung disease leading to fibrosis, pleural

effusions, bronchiectasis, rheumatoid nodules and bronchiolitis obliterans. The commonest eye manifestation is a sicca syndrome as part of secondary Sjogren's syndrome, but also may include scleromalacia, episcleritis and corneal melt. A rheumatoid vasculitis may affect almost any organ, particularly the skin, the kidneys or the gut. Carpal tunnel syndrome is the commonest neuropathy, but mononeuritis multiplex and central nervous system vasculitis have been described. Atlanto-axial subluxation, secondary to pannus eroding the odontoid peg, may result in cord compression. Conduction defects, pericarditis, pericardial effusions and myocarditis have all been well described as cardiac manifestations. Patients with long standing disease may acquire amyloidosis (Kent and Matteson 2004).

The expression of phenotype can vary greatly between individuals. Understanding of the disease has accelerated greatly but its aetiology is still unclear.

1. 3. 2. Factors Governing Severity Of RA

The NOAR has shown that rheumatoid factor seropositivity is a predictor of disease progression in terms of erosions (Bukhari, Lunt et al. 2002). Rheumatoid nodules are also associated with a poorer prognosis (Turesson, O'Fallon et al. 2000). A review by Harrison showed that RF and an articular index are the strongest predictors of joint damage (Harrison and Symmons 2000). High levels

of inflammatory markers, notably the C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) have also been correlated with progressive erosive damage (Matsuda, Yamanaka et al. 1998), but these values can fluctuate, making them less reliable.

Cigarette smoking has also shown to be a risk factor, both increasing the likelihood of developing RA (Costenbader, Feskanich et al. 2006), and worsening its severity (Manfredsdottir, Vikingsdottir et al. 2006).

RA is a disease that has already changed significantly over the years. Silman et al (Silman, Davies et al. 1983) have noted that successive groups of patients with RA in the UK were less likely to be seropositive, less likely to have nodules, and less likely to be erosive. The Mayo Clinic has noticed a fall in the annual incidence of RA in the USA (Doran, Pond et al. 2002), and the Norfolk group has demonstrated a fall in the incidence of rheumatoid vasculitis (Watts, Mooney et al. 2004).

1. 3. 3. Ethnic Differences In Disease Manifestation In RA

Different populations also experience disease in differing ways. This is a complex issue, and tied up in this are environmental and cultural differences, genetic influence and access to treatment. Genetic factors may have an impact on the severity or aggression of the disease. Cultural factors may impact on how an

individual responds to the disease state, the way they deal with disability and pain, and influence their dealings with medical services. Different ethnic groups may have differing access to medical services, depending on both their status in society and the services available in the area they live in. Cultural perceptions about pain and disease may alter how they view medicine, both Westernised, and traditional. Environment may have a role to play, both with respect to physical environment, and other factors such as diet and life style.

It has been suggested that Asian patients in the UK have less severe disease than their Caucasian counterparts (Griffiths, Situnayake et al. 2000). This was measured by presence of erosions on X-ray, presence of nodules, and lower frequency of the shared epitope in their HLA (see chapter on HLA). The Asian patients had similar levels of rheumatoid factor seropositivity, swollen joints and serological measures of inflammation. A study in North India has suggested that their patients have 'milder' disease, based on observation of less severe deformity at presentation (Malaviya, Mehra et al. 1983). The patients in this study were also less likely to suffer from extra-articular manifestations, with only 8.5% having nodules. A small group of 40 RA patients from North India were HLA typed by Mehra et al (Mehra, Vaidya et al. 1982), and found to have a significant association with HLA DR4. This group all had erosive disease, and were overwhelmingly seropositive.

Immigrant communities have cultural, physiological and socioeconomic reasons why their responses may differ in RA. The Hispanic population in America shows some of these differences in outcomes. A recent study of RA patients in New York showed that they scored significantly worse than Caucasians or African Americans with respect to HAQ, morning stiffness and psychological distress (Yazici, Kautiainen et al. 2007), yet were not different in terms of inflammatory markers or joint count.

1. 3. 4. Methodological Difficulties Comparing Ethnic Groups With RA

This highlights the difficulties in comparing two groups of people, even when living in the same geographical location. An immigrant group may lead an unrecognisable lifestyle in comparison with the indigenous population. When populations live in different climates, have different genetic backgrounds, different religions, widely varying cultural beliefs and standards of living and health care, extrapolating between them must be done with caution.

1. 4. GENETIC CONTRIBUTION TO THE INCIDENCE OF RA

1. 4. 1. Evidence From Twin And Family Studies

There is a significant genetic contribution to the incidence of RA. Twin studies in Finland and the UK have shown concordance rates in monozygotic twins from 12 to 15%, and in dizygotic twins from 3.6 to 4% (Aho, Koskenvuo et al. 1986; Silman, MacGregor et al. 1993). This indicates that genes may confer susceptibility rather than absolute risk for the disease. Other studies have shown clustering in families and a higher prevalence than in the general population for first degree relatives, perhaps as high as 10% (Wolfe, Kleinheksel et al. 1988) . There is evidence supporting genetic anticipation in familial RA, with an earlier disease onset in offspring (McDermott, Khan et al. 1996; Radstake, Barrera et al. 2001), but a recent large study suggested that these findings may be due to observational bias (Deighton, Criswell et al. 2007). There is no evidence that familial RA has a worse phenotype (Wolfe, Kleinheksel et al. 1988; Radstake, Barrera et al. 2000).

Deighton showed in a UK population that number of siblings and proportion of siblings sharing HLA haplotypes were the most important factors explaining clustering of RA in families (Deighton and Walker 1992). An increased risk of RA was also shown with greater number of siblings in Pima Indians (O'Brien, Bennett et al. 1967), suggesting that this is a factor that may be present across different

ethnic groups. This suggests that a complex interplay of genetic influences and environmental triggers may be responsible for the disease.

1. 4. 2. Human Leukocyte Antigen And Its Role in the Immune System

The discovery of the Human Leukocyte Antigen system, known as 'HLA', provided further insight into heritability of RA. The genes for these molecules are found in the major histocompatibility complex (MHC) on chromosome 6. MHC was originally identified as a major gene locus controlling tissue transplant rejection (Amos 1965), hence the name 'histocompatibility'. It was later that its role in controlling the immune response was identified (Benacerraf 1981).

The MHC contains more than 200 genes (Consortium 1999). Up to 40% have a role in the function of the immune system. There are three regions to the human MHC; the HLA class I region, the HLA class II region and the central MHC (or class III region). HLA class I comprises the three classical class I genes: HLA-A, -B and –C, and other related molecules. HLA class II contains three main loci: HLA -DR, -DQ and -DP. All these loci are subject to a large degree of polymorphism.

HLA class II molecules are glycoproteins that are expressed on leucocytes that act as antigen presenting cells. These molecules consist of alpha and beta chains, and present fragments of antigen, to specific leucocytes; the T helper

cells ('T' stands for thymus, as it is the main organ in the T cells' development). White blood cells can be subdivided depending on their functions, and the role of T helper cells seems to be to regulate the immune response to foreign protein through the release of cytokines. This enables the body to sense intrusion by foreign material, such as a virus, and then to formulate the most appropriate defence against it. The HLA class II molecule binds peptides derived both self and foreign proteins. It then binds to the CD4 receptor ('CD' stands for 'cluster of differentiation') on T helper cells. The T cell should then be able to detect the difference between self and foreign antigen, and appropriately ignore the self antigen, while marshalling an immune response to the foreign antigen (Simmonds 2005). The type of response elicited depends on the strength and character of the bond between the HLA class II molecule and the T cell receptor. There are large numbers of possible HLA alleles for both HLA class I and class II gene loci; molecules are encoded by a highly polymorphic gene family. Many of these polymorphisms lead to variability in the amino acids that are clustered around the peptide binding cleft (Gregersen 2004). This assumes that, depending on allele type, there must be significant variability between individuals with respect to the character of interactions between HLA molecules and the T cell receptors.

1. 4. 3. HLA and Its Role in RA

It is suggested that in autoimmune disorders such as rheumatoid arthritis, there is some disruption or fault in the way that the body differentiates self from non-self, leading to the immune system treating self as non-self, resulting in disease process. This theory is strengthened by the association of certain allelic variants of HLA class II molecules with different autoimmune conditions. There may be some characteristic in the way that certain polymorphisms of HLA class II molecules bind to peptides and presents these to T helper cells, that initiates or encourages disorders of immunity.

In 1978, patients with RA were shown to have an association with HLA DR4 (Stastny 1978). At this time, cellular and antibody reagents were used for HLA typing, and nomenclature was different to the current, genetically based system of nomenclature. DR4 is now described as DRB1*04, and is known to have a number of further subtypes. Other HLA subtypes associated with RA were identified, such as DRB1*01. Further studies of RA populations have identified a series of HLA DRB1 alleles that seem to be associated with RA. The strength of the association is variable, depending on the population and allele type. These alleles share a common preserved sequence of amino acids, known as the 'shared epitope'. This common short sequence of amino acids at positions 70 to 74 is found in all the HLA subtypes that are associated with RA. This was first noted by Gregerson in 1987 (Gregersen, Silver et al. 1987). It is found in the third

hypervariable region of the HLA DRB1 gene. The shared epitope has been found to be expressed with increased frequency in many different ethnic populations with RA.

The shared epitope is found in the following HLA DRB1 subtypes (Reveille 1998):

DRB1 *0101, *0102, *0104 (previously DR1)

DRB1 *0401, *0404, *0405, *0408, *0409, *0410, *0413, *0416, *0419, *0421 (previously DR4)

DRB1 *1001 (previously DR10)

DRB1 *1402, *1406 (previously DR14)

The sequence of the shared epitope has some variability, but always contains an arginine at position 72, and alanine at positions 73 and 74. Table 1 shows the HLA DRB1 subtypes and the relevant shared epitope sequences is below (du Montcel 2005).

Table 1. Table Of Amino Acids Found At Positions 70 To 74 In The HLA DRB1 Alleles That Code For The Shared Epitope

HLA DRB1 subtype	**Amino acid positions**				
	70	**71**	**72**	**73**	**74**
***0101**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0102**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0104**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0401**	Glutamine	Lysine	Arginine	Alanine	Alanine
***0404**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0405**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0408**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0409**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0410**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0413**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0416**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0419**	Glutamine	Arginine	Arginine	Alanine	Alanine
***0421**	Glutamine	Arginine	Arginine	Alanine	Alanine
***1001**	Arginine	Arginine	Arginine	Alanine	Alanine
***1402**	Glutamine	Arginine	Arginine	Alanine	Alanine
***1406**	Glutamine	Arginine	Arginine	Alanine	Alanine

1. 4. 4. HLA Class II Molecules and Antigen Presentation: the Shared Epitope And Implications For Pathogenesis

As described in section 1. 4. 2, HLA class II molecules are essential for the presentation of self and non-self antigens by antigen presenting cells to CD4+ T helper cells, and thus highly significant in immune regulation. The amino acids that make up the shared epitope are situated on the α helix of the DR β chain (Penzottia 1996), where it is in a position to affect both peptide binding, and interactions between the T cell receptor and the DRB1 molecule.

There are several theories for the role of the shared epitope in the pathogenesis of RA. It has been proposed that a specific peptide antigen, or combination of antigens may be involved in the initiation of RA, and that the DRB1 alleles containing the shared epitope may present these peptides in a specific or enhanced way to the immune system, thereby triggering or encouraging development of RA (Buckner 2002). It is important to note that although many candidate antigens have been investigated, so far robust findings have remained elusive. It has also been proposed that shared epitope alleles may select specific T cell receptors in the thymus, and thus influence the overall T cell population. There is some evidence to support this (Walser-Kuntz 1995), but it is unclear whether this then promotes an at risk environment. There is some similarity between the shared epitope and viral antigens (specifically the Epstein-Barr virus), raising the possibility of molecular mimicry (Roudier 1989). However,

these insights have not been supported by studies that show how the shared epitope is directly involved with RA susceptibility or propagation.

1. 4. 5. Dose Of Shared Epitope And Impact On Disease

It has been suggested that the dose of the allele also confers increased risk, so an individual with two copies of the shared epitope will be more likely to have RA, and perhaps more severe RA, than an individual with one copy, or no copies of an allele containing the shared epitope. Gorman et al (Gorman, Lum et al. 2004) performed a large meta-analysis of 3,240 patients to examine the impact of presence of the shared epitope and its relationship to erosive disease in RA. In European patients and Asian patients, the risk was dose dependent – the more copies of the shared epitope, the more likely to have erosive disease – while in Hispanic patients, the association only held for patients with two copies. They also noted that European and other Caucasian patients were the most likely of the different ethnic groups to have two copies of the shared epitope (25%). African Americans had a particularly low frequency of the epitope, only 7% having two copies.

They also examined the type of alleles containing the shared epitope and showed an association between DRB1*0401 and erosive disease, in a Northern European population. The patients with this allele were statistically more likely to have erosions, and one copy seemed to confer as much risk as two copies of two

other shared epitope alleles. The Norfolk Group also examined the effect of the various alleles on erosions and found that DRB1*0404 conferred the most risk (Thomson, Harrison et al. 1999). This was in a similar white Northern European population. Other than concluding that the DR4 subtypes seem to be the most important in terms of their effect on the presence and outcome of the disease, it seems that there is still much uncertainty about the significance and impact of the HLA subtypes on disease.

1. 4. 6. Ethnicity May Affect The Impact Of The Shared Epitope

Gorman et al also noted the lack of an association of the shared epitope and erosions in the Greek populations they included. They noted that the Greek population seemed to have less severe disease, in that they had less destructive arthropathy and less extra-articular manifestations such as nodules (Drosos, Lanchbury et al. 1992). It has been hypothesised that this may be due to their diverse genetic background and other environmental factors, such as the benefit of a Mediterranean diet (Linos, Kaklamanis et al. 1991). Ethnicity seems to have an impact on disease. They concluded that there was ethnic variability confusing the risk imparted by the shared epitope.

1. 4. 7. A New Specific Auto-Antibody For RA: Possible Interactions with the Shared Epitope And Impact On Pathogenesis

Antibodies to peptides that contain the modified amino acid citrullinine have been associated with RA. Anti-cyclic citrullinated peptide antibody (anti-CCP) has been identified as being highly specific for RA; 97 to 98% specific, but less sensitive; 40 to 68% (Schellekens 2000; Bizzaro 2001). Anti-CCP antibody has also been identified as a prognostic indicator, with patients positive for anti-CCP having more erosions on XR than CCP negative patients, and thus deemed to have more severe disease (Kroot 2000; Berglin 2006). Investigators have shown that patients with RA and HLA DRB1 shared epitope alleles are significantly more likely to also express anti-CCP antibodies. This has been demonstrated in ethnically diverse populations around the world; for example in Hungary (Poór 2007), Japan (Furuya 2007), Holland (van Gaalen 2004), Korea (Cha 2007) and Northern America (Irigoyen 2005).

The population based studies found that different subtypes of the shared epitope alleles were variably related to presence of anti-CCP. In Hungarian and Dutch patients, HLA DRB1*0401 and *1001 had the strongest association (van Gaalen 2004; Poór 2007). In Japanese patients, the strongest association was with HLA DRB1*0405 (Furuya 2007). In German patients, HLA DRB1*04 and *01 had the strongest associations (Kaltenhäuser 2007). This demonstrates that there is unexplained ethnic variability in the frequency of anti-CCP positivity and

presence of the shared epitope. It does not give information on whether this is relevant in terms of disease severity.

Several of these studies also sought to examine the relationship between disease severity, presence of the shared epitope and anti-CCP antibody. They showed that erosive disease can be predicted by presence of the shared epitope and presence of anti-CCP antibody (van Gaalen 2004; Cha 2007; Kaltenhäuser 2007). However, other studies showed that shared epitope was less important than anti-CCP positivity in predicting erosions (Mewar 2006), and have suggested that the shared epitope is merely a marker for anti-CCP, rather than being an independent risk factor. Researchers in Holland examined patients with undifferentiated arthritis, and monitored whether those with anti-CCP positivity with or without shared epitope presence went on to develop classical RA (van der Helm-van Mil 2006). They found that anti-CCP antibodies were strongly correlated with progression to RA, and that presence of shared epitope was correlated with CCP positivity, but not with progression to RA. The relationship between shared epitope alleles and anti-CCP antibody, and the effect on the phenotype of the disease is still unclear.

Smoking tobacco causes citrullination of proteins. It is also recognized to be a poor prognostic indicator in RA, and to increase the chance of developing disease (see section 1.3.2). Linn-Rasker et al showed that tobacco smoke exposure increased the risk of developing anti-CCP antibodies in shared epitope

positive patients (Linn-Rasker 2006). This interaction seemed to be dependent on the shared epitope allele type, with DRB1*0101, *0102 and *1001 alleles showing the strongest response (van der Helm-van Mil AH 2007). A possible pathogenic mechanism may be that tobacco exposure citrullinates peptides, which are then preferentially bound and presented by shared epitope positive HLA class II molecules. This may then cause production of anti-CCP antibodies. It is unclear if these are pathogenic in themselves or a marker for another process, which ultimately concludes with development of RA.

1. 4. 8. Ethnicity And HLA Frequencies

Different ethnic populations have different frequencies of the shared epitope alleles, and are likely to have different subtypes of alleles (table 2). It was noted that Native American Pima Indians had a greatly excess risk of RA (Del Puente, Knowler et al. 1989). Between 1983 to 1990, there was an incidence of 380/100 000, which is more than 10 times the incidence found by Symmons in Norfolk, UK in the late 1980s (Jacobsson, Hanson et al. 1994). Over 90% Pima Indians express HLA DRB1*1402 or DRB1*1406, both of which contain the shared epitope (Williams and McAuley 1991). High frequencies can also be found in the Tlingit (Nelson, Boyer et al. 1992) and Yakima Native American Indians (Willkens, Nepom et al. 1991), and the Alaskan Inupiat Eskimos (Boyer, Benevolenskaya et al. 1997), and all these groups have a higher prevalence of RA than Northern European communities. Attempts have been made to identify

other environmental factors that contribute to developing RA on this background of genetic susceptibility, particularly as there has been a sharp decline in the incidence of RA in the last 25 years. This has been seen markedly in the Pima Indians (Jacobsson, Hanson et al. 1994), and has also been noted in Britain (Silman 1988) and America (Doran, Pond et al. 2002). The huge changes in lifestyle, diet and reduction of background infective disease may be partially responsible for this. Ethnic and environmental differences may have a confounding effect on the impact of the shared epitope in RA susceptibility.

Table 2. The frequency of the shared epitope in different ethnic populations with RA

Population	HLA type	Frequency	*P* value	Reference
Pima Indians	DRB1*1402 DRB1*1406	90%	<0.01	(Williams and McAuley 1991)
Mexican Americans	DRB1*01 DRB1*04 DRB1*14	11% 29% 18%	<0.001	(Del Rincon and Escalante 1999)
British Caucasians	DR4	67%	<0.0001	(Jaraquemada, Ollier et al. 1986)
North India	DR4	70%	<0.001	(Mehra, Vaidya et al. 1982)
Indians in Varanasi (east of Delhi)	DR4	57% 4 patients only	Not significant	(Agrawal 1996)
Indians in SA (Hindus)	DR 10	32%	<0.01	(Mody and Hammond 1994)
Indians in Leicester	DR1 (not subtyped)	RR 7.0	0.0022	(Woodrow, Nichol et al. 1981)
Indians in Leeds (~ ¾ Punjabi)	DRB1*10	25%	<0.0001	(Griffiths, Situnayake et al. 2000)

1. 5. PSYCHOSOCIAL IMPACT OF RA

1. 5. 1. Psychological Factors In RA

Chronic medical illnesses and among them, rheumatic diseases, have long been associated with psychological distress, anxiety and depression. The presence of pain coupled with disability means high levels of depression are common. Chronic physical illness is associated with an increased risk of suicide, and up to 30% patients attending hospital may have depressive symptoms (Royal College of Physicians and Psychiatrists 2003). These are frequently missed, either because the reticence of the patient to report symptoms, or because of the oversight or reluctance of the health professional to investigate. A large population based study from Canada reported up to 10% of patients with arthritis having major depression (Patten, Beck et al. 2005). In this study, the prevalence of depression was higher in younger people. 42% RA patients in another study in America met criteria for depression (Frank, Beck et al. 1988).

There are well described risk factors for developing depression. They include previous history of depression, lack of social support, substance abuse and stressful life events such as loss of job or marital difficulties. Failing to treat the depression associated with chronic disease may make treating the disease itself more difficult. It may amplify physical symptoms, cause significant distress, and can predict functional outcome, independent of severity of illness.

Many chronic diseases are associated with pain and disability, both of which are independently associated with depression. A large meta-analysis by Dickens et al looked at 12 studies of patients with rheumatoid arthritis and depression levels (Dickens, McGowan et al. 2002). They found a consistent association between depression and RA, with the effect size varying in linear manner in proportion for the effect size for pain. Different methods were used to examine depression in these populations, with the Hospital Anxiety and Depression score used most commonly, but this also gave different effect sizes to that of other scales used. The gold standard, that of an hour long structured interview by a psychiatrist, is rarely used, being too unwieldy for use in large population studies.

1. 5. 2. Pain In RA

Pain is common in patients with RA, and may be a significant confounder in terms of depression. One might assume that the more active a patient's disease, the more pain, and thus the more severe the depressive symptoms. However, several studies have suggested that depression is actually independent of disease activity, yet correlates with pain. This suggests that pain does not have a direct correlation with disease activity. When disease activity is controlled, depression is still associated with pain (Callahan, Kaplan et al. 1991). This confirms the suspicion that pain is far more complex than a simple mechanical problem. It is difficult to say whether pain increases depression, or if it is depression that amplifies the experience of pain. In RA, no studies have given

answers to the causal relationships, but studies in other musculoskeletal diseases suggest that they work both ways. Pain increases depression, and depression increases pain (Magni, Moreschi et al. 1994).

1. 5. 3. Disability And RA

Disability is also a source of depression for RA patients. Decreased ability to perform normal activities may increase depressive symptoms. Depression also predicts worsening disability, with decreases in function and increases in hospital admissions (Katz and Yelin 1993). Depression and disability may interlock in terms of their causal relationship as well.

1. 5. 4. Socioeconomic Factors

While disability and pain are important factors influencing a patient's psychological state, they are not the only influences. An individual may suffer significant pain and disability, and yet not be depressed. Other factors also have a role, particularly psychosocial factors. Individuals from lower socioeconomic groups (Lorant, Deliege et al. 2003), those with more stressful life events and less schooling (Gallo, Royall et al. 1993) are more vulnerable to depression. Psychosocial problems in RA are common and distressing. 42% of newly diagnosed patients in the Netherlands are registered as work disabled within 3 years (Albers, Kuper et al. 1999). Socioeconomic deprivation was found to be

associated with a poorer disease prognosis by the Early Rheumatoid Arthritis Study (ERAS) group (Young and group 2001). Lack of social support and stressful life events have been shown to be strongly associated with depression in RA (Murphy, Creed et al. 1988). There is evidence that marriage may be protective against depression, particularly in men (Casey, Kelly et al. 2006). However, problems with relationships are common as one partner becomes increasingly dependent. Sexual intercourse becomes difficult and painful. Breakdown of a marriage, or death of a partner, are significant risk factors for depression (Paykel 2001). Suicide is also more frequent in RA sufferers (Timonen, Viilo et al. 2003). This study also noted that a depressive disorder had preceded suicide in 90% of patients, suggesting that a window of opportunity for intervention exists.

1. 5. 5. Depression And Ability To Cope With Illness

Helplessness and hopelessness have a marked impact on the way an RA suffer thinks about disease, and is associated with depression. Depressed patients feel their disease is more severe, they are more worried about it, and are less hopeful about a cure than patients without depression, even when disease severity is controlled for (Murphy, Dickens et al. 1999). They are less able to cope, especially with pain. A recent study from Australia showed that disability, passive coping and helplessness have a significant effect on the levels of pain and depression felt by RA patients (Covic, Adamson et al. 2003).

Depression has an impact on their interaction with their health professionals. They are more likely to seek help, to report physical symptoms, and less likely to be reassured by their doctors. Counter intuitively, they are less likely to be compliant and take their medication (DiMatteo, Lepper et al. 2000).

Depression creates a huge additional burden for these patients. It is well recognized that it is likely to be overlooked and left untreated in patients with chronic disease. Some of this may be because of a misconception that their depression is reactive – understandable in the face of their disease, and therefore inappropriate to treat. It also may reflect a health professional's bias towards physical ailments – something more tangible and perhaps amenable to treatment.

1. 5. 6. Difficulty Diagnosing Depression In RA

There is also difficulty in diagnosing depression in RA patients. Many of the physical symptoms of depression are found in RA – fatigue, nausea, weight loss and so on. Many questionnaires designed to detect depression in populations contain questions that focus on somatic symptoms, which would act as confounders in a rheumatoid population, instantly giving them falsely high readings (Pincus, Callahan et al. 1986). This is reflected in the lack of

concordance between different tools for measuring depression in RA populations (Dickens, McGowan et al. 2002).

There is research to suggest that use of anti-depressants may give rapid results and also have an analgesic benefit, such as amitriptyline. Dickens and Creed (Dickens and Creed 2001) suggest that up to 2/3 of patients with depression and RA would benefit from use of an anti-depressant, and that those with most severe disease would benefit the most. They suggested that depression is a far more widespread and serious problem than had been previously recognized.

1. 5. 7. Ethnic Variation In Psychology

Ethnic groups may have different physiological and psychological responses to disease. There are well documented ethnic differences in pain perception. It is not known if this is physiological or psychological, or a combination of factors. Certainly different cultures approach dealing with pain and illness very differently. This is bound to have an impact on the patient's experience of the disease. It may also influence care, as the physician is likely to make judgments based on history, experience, and their own cultural understanding of pain.

Immigrant communities may also have higher levels of depression and anxiety as they struggle to cope with an alien environment. This is very pronounced in

refugee communities, particularly if fleeing war or persecution, as they try to cope with the challenges of the new as they deal with the scars of the old.

Most of the Indian communities in the UK are economic migrants. They may not have the stress of dealing with war or famine, but nonetheless they face daunting circumstances in England. New immigrants must learn a new language, accustom themselves to dealing with new social structures and rules, and deal with a damp, cold climate. This may have to be done far away from family and friends. Some never fully integrate with the indigenous population, and there are many, particularly older women, who never learn English.

CHAPTER 2. THE ASIAN COMMUNITY IN LEICESTER: SOCIOECONOMIC AND HEALTH STATUS

2.1. ORIGINS

The Asian community in Leicester, UK, like in so many other parts of the country, is not a homogenous one. The largest immigrant group is originally from the state of Gujarat in north-west India (fig. 1). The people currently living in Gujarat are descended from Caucasian groups who swept down into India many centuries ago, displacing the Dravidians who moved to the south of the country.

The immigrant group is not just immigrants from Gujarat itself, but also a large number of East African Indians of Gujarati extraction. Immigrants moved from Gujarat in the 1950s to the coast of East Africa, particularly Uganda and Kenya. Both had thriving communities of an Indian merchant middle class. When Idi Amin came to power in Uganda in the 1960s, he expelled the Indian population. Many of these people took advantage of the offer of British passports made by the British government.

Why did they move to Leicester? The Leicestershire Regiment were traditionally stationed in Gujarat in the days of the British Empire, so many immigrants from India had links to the area, and chose to move somewhere with some measure of familiarity. As more people moved to the area, their families and friends followed,

creating new lives, setting up businesses and working in Leicester's traditional industries, particularly hosiery and embroidery.

Fig. 1 Map of India showing Gujarat state on the North West border

2. 2. POPULATION SIZE

The census from 1991 showed a population of 60 000 individuals of Indian extraction living in Leicester City, while the White population numbered 193 000 (OPCS 1991). By 2001, with the Indian population had increased to 72 000, making up 25% of the city's population (Statistics 2005).

2. 3. CULTURAL EMBEDDING OF THE GUJARATI POPULATION

It is difficult to assess how culturally embedded the Gujaratis in Leicester are. They are recent immigrants, largely moving to the UK in the late 1960s and early 1970s. They are first generation immigrants, all speaking Gujarati as a first language, and largely wearing traditional clothing, and eating traditional foods. They are mostly Hindu, and live in large, often fairly self-sufficient communities. If they do not work for themselves, they often work for businesses within their community. Their family links are extensive and strong, they often have a wide network of friends and family to help them. Their children wear Western clothing and are usually fluent in English and Gujarati. Many of their traditions are still important parts of their culture. This would suggest that they are very much still embedded in the Indian culture. However, it is extremely difficult to know how much Westernisation has crept into their beliefs and practices. Hameed, looking at Pakistani groups, suggested that there was little difference between populations living in London and in Karachi (Hameed and Gibson 1997). It may

be that comparing successive generations is the only way to truly assess the impact of culture on disease.

2. 4. IMMIGRATING COMMUNITIES AND DISEASE

It is clear that immigrant populations do not always suffer from the same problems as their parent communities. Immigrants may face a change in climate, culture, food, and also the stress associated with being a minority group in a new country. As a simplistic example, the incidence of skin cancer is phenomenally high in Australia thanks to the large immigrant British and Irish population whose pale skins are unprepared, even after 4 or 5 generations, to resist the higher ultraviolet levels (Registries 2004). Although an immigrant group may have a more affluent lifestyle than those in the community they left behind, alienation may negate the apparent benefits. A Western diet may not always suit. The reason for immigration may also influence health. If they are fleeing conflict, there may be huge psychological scars that adversely affect their mental health. Without the necessary language skills and education, they may find themselves struggling to survive, perhaps with the added pressure of sending money back to relatives in their own country. A study in Norway showed significantly higher levels of psychological distress in low and middle income immigrants compared with native Norwegians and high income immigrants (Dalgard, Thapa et al. 2006).

2. 5. DISEASE IN THE BRITISH ASIAN COMMUNITY

It is well recognised that the immigrant Indian communities have an excess of certain diseases. The South Asian population in the UK has an excess of cardiovascular disease, although it seems to be more pronounced in those in a lower socioeconomic group (Nazroo 2001). There is also a markedly increased risk of type two diabetes mellitus in this group (King and Rewers 1993), triggering much debate as to the possible causes. Patients in Leicestershire who had strokes tended to be younger if they were of South Asian descent (Hsu, Ardron et al. 1999). There is also a rising incidence of ulcerative colitis in the Asian population of Leicester (Carr and Mayberry 1999). A higher prevalence of systemic lupus erythematosus has also been documented (Samanta 1992), as has a high rate of renal disease (Lightstone, Rees et al. 1995).

A high prevalence of iron deficiency anaemia has been noted in South Asian women (Chapple 1998). It is unclear what underlies this, but factors including menorrhagia and cultural nutritional beliefs are thought to be important.

Osteomalacia is also extremely common in the British Asian community, and it seems particularly common in the patients attending rheumatology clinics (Serhan, Newton et al. 1999). It is also well documented in the healthy Gujarati population of Leicester (Hamson, Goh et al. 2003). This can contribute to pain and disability. It is multi-factorial. It may be partly due to darker skin, and so less

efficient use of the sunlight available in Northern Europe. The Asian community also tends to expose less skin in the sun than the white British community. The flour that is used to make chapattis (a traditional Indian unleavened bread), also contains phytate (inositol hexaphosphate) which inhibits the absorption of dietary calcium, and some small trials have shown improvement on excluding chapattis from the diet (Ford, Colhoun et al. 1972). This means that vitamin D deficiency is rife among the South Asian immigrant community, and often unrecognized. It is an important confounding factor in pain and disability in this group.

Chronic pain is common and widespread amongst the immigrant Asian community in the UK. The Manchester ARC Unit has shown that widespread pain in found more often in Asian communities in the Midlands, even when acculturation is controlled by using a scoring system to assess its extent (Palmer, Macfarlane et al. 2007).

2. 6. TRADITIONAL HEALING: AYURVEDA

This has been practiced in the Indian subcontinent for centuries. It involves herbal preparations, dietary advice and can also involve massage prescribed by a trained practitioner. In India, there are professional bodies regulating its practice, and it is taught in some states on the medical curriculum. It is widely practiced in India, with dedicated hospitals, and indeed all over the world.

2. 7. PSYCHOSOCIAL PROBLEMS IN ASIAN COMMUNITIES IN BRITAIN

Work done by the ARC unit in Manchester has established that there are high levels of chronic pain experienced by South Asians in the community (Allison, Symmons et al. 2002). This may be a contributing factor to their distress. A paper comparing depression levels in migrants in the UK and their siblings in India showed that there was no significant difference in depression between them, despite the UK Indians having had significantly less stressful life events than their Indian siblings (Creed, Winterbottom et al. 1999). Clearly the increase in affluence does not make up for the stresses of a new country. There is a well documented excess of suicide in Asian women in the UK, particularly those from East Africa. These women are likely to be Gujarati (Soni Raleigh and Balarajan 1992).

Asian patients may not get the best out of their medical care. They may have limited access to health care facilities. There is evidence that those with cardiovascular disease are less likely to be referred to specialist care (Stewart and Rao 2002), despite the fact that Asians in the UK are more likely to attend their GPs (Gillam, Jarman et al. 1989).

They may be suspicious of Western medicine. This may lead them to have less trust in their doctors, and thus be less likely to take conventional treatment and more likely to try alternative remedies. A study done by Helliwell and Ibrahim in

Bradford (Helliwell and Ibrahim 2003), showed that patients of a South Asian origin were more likely to stop their DMARDs earlier than white Northern European patients, and were likely to stop the drugs because of rashes, perceived inefficacy, and concern about side effects.

Asian patients may also fail to access all the social services benefits that they are entitled to. This may be because of a lack of understanding of their rights, either because of communication difficulties, or because of ignorance of the systems.

2. 8. AIMS OF THE THESIS

1. To compare socioeconomic factors between Gujarati Asian and British Caucasian patients with RA.
2. To compare disease severity in Gujarati Asian and British Caucasian patients in Leicester with RA.
3. To compare HLA sub typing with respect to presence of the shared epitope in Gujarati Asian and British Caucasian patients with RA.
4. To compare treatment factors that may influence disease course in Gujarati Asian and British Caucasian patients with RA.
5. To compare complementary medicine use in Gujarati Asian and Caucasian patient with RA.
6. To compare depression in Gujarati Asian and British Caucasian patients with RA.

CHAPTER 3. DESCRIPTION AND EVALUATION OF METHODOLOGY

3. 1. DESIGN OF THE STUDY AND THE INTERVIEW QUESTIONNAIRE

This was a descriptive, cross-sectional study.

Ethical approval was sought from and granted by the local ethics committee.

The interview questionnaire was carefully designed to deliver the information required for the aims of the thesis. Demographics were important, as were basic socioeconomic values. Background is an essential component of any comparative study, as differences in environment may be responsible for perceived differences in outcome. A copy of the questionnaire is in appendix 3.

3. 2. DEMOGRAPHICS

3. 2. 1. Age

Age is an important factor both with respect to disability, disease impact and depression. Older patients may have impaired function as a result of degenerative disease. Younger patients with RA have been shown to be more depressed (Wright, Parker et al. 1998). As a result, it was important to ensure that age was controlled for.

3. 2. 2. Gender

The sex ratio in RA has been established at around 3:1 female: male in British Caucasians (Symmons, Barrett et al. 1994). It was important to ensure that the sex ratio was controlled for, so a fair comparison could be made.

3. 2. 3. Marital Status

There is evidence that being married may protect individuals with RA from depression (Katz and Yelin 1993; Abdel-Nasser 1998). This advantage disappears especially if a partner dies, and indeed is a risk factor for depression. If one population had a higher rate of single or widowed individuals, this may predispose that group to depression.

3. 2. 4. Ethnic Background Of Patients

This was extremely important. As outlined in the introduction, populations have similar genetic backgrounds, provided they originate from certain geographical locations. Research has shown that Northern Europeans have recognizably similar genetic material, distinct from other areas in Europe (Seldin, Shigeta et al. 2006). This is thought to be due to the waves of invasion and immigration across Northern Europe, particularly from the Scandinavian countries to West Europe. Indian populations have also been shown to have similar genetic backgrounds,

depending on their geographical location. The Aryan invasion from North Asia down into India pushed the Dravidian population before it to the south of the country. As a result, the Northern Indians have a broadly similar genetic background, and could in fact be said to be Caucasian (Palanichamy, Sun et al. 2004). The southern Indian population is Dravidian.

For the purposes of this study, we used the terms the patients themselves used to define themselves. The patients of Gujarati extraction referred to themselves as 'British Asian' or 'Gujarati', so in this study they are referred to as 'Asian' or 'Gujarati'. The ethnically British White patients are referred to as 'Caucasian', although, as shown, both groups could be said to be 'Caucasian'.

It was important to establish precise backgrounds, particularly if the patient was an East African Indian. This allowed us to ensure we were selecting only patients from specific ethnic groups, rather than from many different areas on the Indian sub-continent. Patients were asked where they came from, and where their parents and grandparents came from, to ensure that only ethnically Gujarati and ethnically white British individuals were included.

3. 2. 5. Year Of Immigration

When an individual moves to a new country, it is very variable how rapidly they assimilate the habits, beliefs and attitudes of their new homeland, if at all. A patient who has recently emigrated might be more embedded culturally in the culture of their homeland than a person who has been living in the UK for many years. Duration of time in a new country is not the only factor governing the assimilation of a new culture. Some immigrants live for decades in their new home without ever learning the local language, mixing only with other immigrants in self-contained communities. Cultural embedding is extremely complex and variable and takes into account such factors as religion, diet, entertainment, family ties and community links. This study was not designed to study this in detail. Year of immigration to the UK may help to understand in a crude way how much a patient may have been exposed to a Western culture.

3. 2. 6. Acculturation

Acculturation is the length to which an individual adopts the beliefs, lifestyle, values and culture of a host country on immigration (Mavreas, Bebbington et al. 1989). It is very difficult to assess how much the culture of a group affects their response to stresses and pressures. Nonetheless, it is clear that any response may be influenced by the expectations and behavioural patterns of the cultural environment of an individual. When people have two cultures to assimilate, as in

an immigrant population, these may have varying impacts. How to assess and judge the weight of cultural influence with respect to an individual's responses was beyond the scope of this study. Basic questions such as language spoken at home and religion were asked. Religion may act as a surrogate marker, both for how much an immigrant has acquired the values and beliefs of their new country, and as another source of social support outside the immediate family.

3. 3. SOCIOECONOMIC STATUS

Socioeconomic status has been shown to make a significant impact on health, with deprivation also strongly associated with depression (Lorant, Deliege et al. 2003). Social deprivation has been shown to be associated with increased musculoskeletal pain (Urwin, Symmons et al. 1998). Several different factors were examined, including education, occupation, housing and social services support.

3. 3. 1. Number Of Family Members At Home And Social Network

The extent of a social network may act as an unexpected protective factor in many diseases. Socially isolated women have an excess of mortality after diagnosis of breast cancer (Kroenke, Kubzansky et al. 2006), while social support is correlated with survival (Funch and Marshall 1983). A protective factor against depression in RA has been recognised to be the extent of the social

network of the patient. Lack of social support was highly correlated with depression and anxiety in Irish rheumatoid patients (Zyrianova, Kelly et al. 2006). Asian patients are thought to live in larger family groups than Caucasians, and in closer knit wider communities, and thus may be protected from depression.

3. 3. 2. Education

A large prospective study of healthy adults in America showed that future depression was related to years of schooling (Gallo, Royall et al. 1993). Low education level has also shown to be correlated with increased psychological distress and low mood in RA (Evers, Kraaimaat et al. 2002). RA patients in Israel with low levels of education had more severe disease manifestations (Amit, Guedj et al. 1996). It was important to examine it as a possible confounder as our patient groups may have had widely differing access to education.

3. 3. 3. Smoking

Exposure to cigarette smoke may increase incidence of RA, and cigarette smoke is recognized to be a risk factor in the severity of RA, as described in the previous chapter. Smoke exposure is linked to socioeconomic deprivation.

3. 3. 4. Alcohol Intake

There is a well documented link between alcohol and depression. Significant intake of alcohol may contribute to depression, or be a symptom of it. It has also been shown that there are less alcohol related deaths than expected in RA patients, suggesting that alcohol protects from RA (Myllykangas-Luosujarvi, Aho et al. 2000).

3. 3. 5. Diet

The Indian patients may have a very different diet to the Caucasians. This may have an impact on disease. The Norfolk Arthritis Register (NOAR) group showed that those consuming moderate and high amounts of vitamin C had a third of the risk of developing RA of those who consumed a low amount of vitamin C (Pattison, Silman et al. 2004). They also showed that those with a diet rich in red meat and meat products had a higher risk of developing RA. A vegetarian population may therefore be protected from developing RA by their diet. However, a vegetarian diet may predispose to dietary insufficiencies, and contribute to anaemia (Alexander, Ball et al. 1994).

3. 3. 6. Employment, Occupation And Housing

Employment is an indicator of function and of socioeconomic status. The ERAS group showed that 1/3 patients with RA are out of work by the end of the fifth year of diagnosis (Young, Dixey et al. 2002). They showed that those in manual occupations were more at risk. Occupation is also a surrogate marker for socioeconomic class, which is strongly associated with depression, with those in lower socioeconomic classes more vulnerable to depression (Lorant, Deliege et al. 2003). Albers et al showed that ¼ patients newly diagnosed with RA had income reduction by 3 years (Albers, Kuper et al. 1999).

Housing may also represent socioeconomic status. In the UK, council housing is provided for those who fall into lower socioeconomic categories. Owning a home may be a marker of affluence.

3. 3. 7. Social Services Support And Benefit

It is anecdotally claimed that various groups receive more or less support from social services. There is a perception that immigrant and indigenous communities receive differing levels of support from government agencies. This often leads to deep divisions locally and much anger and bitterness, for example that seen in the Oldham riots (Ritchie, Ahmad et al. 2001). It is also the case that people who do not speak the local language and do not understand their rights in

a country may not be able to take advantage of the support that is rightfully theirs. This is a very sensitive issue.

We simply asked patients what benefits they received. The list included income support, carers' allowance, disability living allowance, mobility allowance, incapacity benefit, disabled car sticker.

3. 3. 8. Past Medical History

Patients with other medical problems may have confounding factors influencing their pain and disability. Ischaemic heart disease is very prevalent in the Asian community as noted in the previous chapter, and may have a significant impact on exercise tolerance above and beyond that of painful joints, due to angina or breathlessness.

3. 4. ASSESSMENT OF RHEUMATOID DISEASE

3. 4. 1. Date Of Onset And Disease Duration

This is import to establish disease duration. Longer disease duration is related to more disability as the disease progresses and greater levels of depression (Newman, Fitzpatrick et al. 1989). Patients must be matched for disease duration, or it is impossible to draw conclusions about their condition.

3. 4. 2. Age Of Onset

Younger patients have been shown to be more depressed than older patients at onset (Ramjeet, Koutantji et al. 2005). Age of disease onset does not have an impact on severity of disease (Pease, Bhakta et al. 1999).

3. 4. 3. Date Diagnosis Made

This allows for diagnostic delay to be calculated. This may be an indicator of initially mild disease, or a measure of access to specialist medical attention.

3. 4. 4. Family History Of RA

There is conflicting data about familial impact on the onset and expression of RA as previously discussed. Impact may be different in different populations.

3. 4. 5. Early Morning Stiffness

Early morning stiffness (EMS) is an indicator of active inflammatory disease, and part of the diagnostic criteria. It may show differences in inflammation between the two groups. It was measured here in hours.

3. 4. 6. Pain

Pain is a very important aspect of RA. It is closely related to depression and coping ability. There are a number of ways of measuring pain. A very reliable way is to use a visual analogue scale carefully explained to the patient. This is both reproducible and easy to use. Its use has been validated extensively in RA and other rheumatic diseases (Bellamy 1993).

3. 4. 7. Disability Measured On The Stanford Health Assessment Questionnaire

Disability can be difficult to assess between patients. One may feel disabled by relatively mild impairment; another may manage well with significant impairment. The Stanford Health Assessment Questionnaire (HAQ) was developed as a way to compare levels of abilities to perform simple day to day tasks of normal living (Fries, Spitz et al. 1980). It consists of 8 separate categories each scored from 0 to 3, which are averaged and rounded up to a score from 0 to 3, where 3 is most

disabled. It has been validated in British patients with rheumatoid arthritis (Kirwan and Reeback 1986) and in India (Kumar, Malaviya et al. 2002). The British version rather than the Indian version was used. This was because the Indian version included such questions as 'Are you able to squat in the toilet?' While this may be relevant to patients in India, it would not be relevant to our patients living in British houses with Western facilities. The HAQ is a well validated outcome measure of RA, and has been shown to predict mortality (Wolfe 2003) and disease progression (Wolfe and Sharpe 1998). A copy is in appendix 4.

3. 4. 8. Extra-articular Involvement

RA is a multi-system disorder and many patients experience symptoms in systems other than their joints. Every system can be affected, to a greater or lesser extent. Specific questions were asked designed to screen for some of the commoner manifestations. These included rash and nodules. They were also asked about sicca symptoms, Raynaud's and digital gangrene or vasculitis. They were asked about breathlessness and known lung or cardiac involvement. They were asked about renal or gastrointestinal tract involvement, and about neuropathies including carpal tunnel. Notes were checked to verify.

3. 5. EXAMINATION:

This was done by the same investigator each time, to avoid inter-observer bias.

3. 5. 1. Swollen Joint Count

A swollen joint count is a measure of how many joints have active synovitis at a particular point in time. The more active the arthritis, the more joints are likely to be swollen. Tools to assess activity have been developed, largely to assist in determining outcome measures in large drug trials. These are usually composite measures. The DAS (Disease Activity Score, (van der Heijde, van't Hof et al. 1993) is an example of one such score, widely used in trials. It involves both swollen joint counts and tender joint counts as part of a composite measure.

In this study, the separate components of a composite score (pain on VAS, inflammatory markers, joint count) were collected, but not amalgamated into a single score. The tender joint count was deliberately excluded. This was because tender joint counts may be subjective, assuming that all patients feel tenderness in a similar way, which also implies that they have similar pain perception. It was important to control for the differing perception of pain in this study, as it may have been a confounder. It has been shown that the composite DAS fluctuates depending on patient perception, due to the VAS component (Kievit, Welsing et al. 2006).

Some of the composite scores also exclude certain joints. The DAS 28 excludes any joint involvement below the knee (Prevoo, van 't Hof et al. 1995). It was possible that ethnically diverse patients may have a differing pattern of joint involvement, which could be missed by using such a tool.

All joints were examined in a 56 joint count. Any swelling present was counted as a swollen joint: no attempt was made to assess the activity or aggressiveness of the synovitis. This was to avoid the assessment only counting 'hot' joints, which would be more open to bias, as disease activity may fluctuate considerably over time.

3. 5. 2. Nodules

Note was made of nodulosis.

3. 5. 3. General Examination

A standard examination of cardiovascular, respiratory and gastrointestinal systems was made.

3. 6. TREATMENT: DRUGS AND INTERVENTIONS

3. 6. 1. Delay In Starting Disease Modifying Anti-Rheumatic Drugs

A delay in starting a disease modifying anti-rheumatic drug (DMARD) may indicate access to secondary care, and severity of initial symptoms. For patients with longer disease duration, it may represent clinical thinking at the time they were diagnosed. Notes were examined for confirmation of reported regimens and tolerances.

3. 6. 2. DMARDs Tried, Reasons For Stopping And Side Effects Experienced

There may be differences between the tolerances of the patients for medications. Helliwell and Ibrahim showed that South Asian patients in Bradford were more likely to stop their DMARDs, particularly because of concerns about side effects of treatment (Helliwell and Ibrahim 2003). There may be differences in certain types of medication effective in different ethnic groups.

3. 6. 3. Use Of Prednisolone, Frequency And Dose

Some patients may have had prolonged courses of prednisolone during their treatment, despite not currently taking it. This may be an indicator of past disease severity, or difficulty with other DMARDs.

3. 6. 4. Analgesics And Non-Steroidal Anti-inflammatory Drugs

Patients' pain is a significant factor both with respect to disease severity and depression. Analgesic and non-steroidal anti-inflammatory drug (NSAID) use may give an insight into this.

3. 6. 5. Calcium and Vitamin D

In the UK, there is widespread osteomalacia in the Asian community. There are several explanations as outlined in the previous chapter. Osteomalacia can contribute to arthralgia and myalgia (Reilly 1999), which may confound measures of pain. Treatment for this may reduce symptoms.

3. 6. 6. Perceived Efficacy Of Medication

Patients were asked how they felt their medication regimen was working. This was simply divided into 5 responses; excellent, good, ok, not so good and no use at all. This was an attempt to estimate how confident the patients felt in their treatment, and if they actually felt it was working regardless of whether the drugs were genuinely controlling disease.

3. 6. 7. Interventions: Hospital Admissions For Flares Or Treatment

A marker of disease severity may be the number of times a patient needs to be admitted to hospital. Increasingly patients are being managed as outpatients, even during flares, but some severe cases may still require admission.

3. 6. 8. Interventions: Intra-articular Injections

Intra-articular injections are used when a patient has significant inflammation in one or several joints. Many active joints would usually require more generalised treatment – perhaps a change in dose of their DMARD, or an intra-muscular steroid injection to calm all joints down. The need for an injection represents a troublesome joint that is not settling on current treatment and may represent disease severity. It may also represent access to medical care and willingness of the patient to be injected. This may be different in different ethnic groups.

3. 6. 9. Interventions: Surgery

Joint ankylosis is the end result of an untreated, or inadequately treated rheumatoid joint. Many patients with severe disease will have joint replacements for pain. There are many other surgical procedures that are carried out to preserve function and reduce pain. Surgical procedures are usually only carried out on badly deformed joints, and so may represent a measure of disease

severity. Number of procedures may also represent access to surgical services, which may be different to different communities.

3. 6. 10. Compliance

It is well recognised that people are poor at complying with medical regimens. Up to 70% of patients did not take their medication in a study examining bisphosphonates (Gold, Safi et al. 2006). Compliance in RA is often better than other conditions, with only ¼ consistently non-compliant (Viller, Guillemin et al. 1999). Patients were asked if they missed their tablets, and if so, how often, and why, to gain an idea of how compliant they were.

3. 7. COMPLEMENTARY THERAPIES: USE AND PERCEIVED EFFICACY

Use of complementary and alternative therapies (CAM) is extremely common in RA and other rheumatic diseases (Rao, Mihaliak et al. 1999). Studies have shown that many patients try a variety of different treatments. The London School of Homeopathy showed in a randomised controlled trial that homeopathy was ineffective in RA (Fisher and Scott 2001). There is conflicting evidence surrounding acupuncture, the trials showing benefits have been small and of poor quality (Cherkin, Sherman et al. 2003). Copper bracelets and magnets have no good evidence, but are popular in the general community. Herbal remedies, such as green-lipped mussels have been tried. The Indian population often turns

to Ayurvedic treatments. This is the commonly accepted local medicine in India, where Western treatment may be too expensive for ordinary people. Patients were asked if they had tried various popular alternative treatments, and to rate their perceived efficacy on the same 5 point scale used to rate their conventional treatment.

3. 8. PSYCHOLOGICAL STATUS

3. 8. 1. Depression

The scale used to assess depression was the 'Self Reporting Questionnaire' (see appendix 6). It was devised by the World Heath Organisation as a screening tool to use in the community, particularly in developing communities. It has been validated in the third as well as the first world, and also in Indian communities (Beusenberg and Orley 1994). The cut off score for a probable psychiatric disorder is > or = 8, with a sensitivity of 79% and a specificity of 75%. This questionnaire has been validated in India (Sen and Williams 1987), and in immigrant Asians in the UK (Upadhyaya, Creed et al. 1009). The gold standard for assessing depression has traditionally been an hour long interview with a fully trained psychiatrist. This is obviously a tool that is hard to use in a community setting, or as a screening tool. Those scoring 8 or above should be referred for formal assessment by a psychiatrist.

There are a large number of screening tools designed for use in a variety of settings. This one was chosen as it has been validated in the relevant communities, and for use outside a hospital setting, as all recruited were outpatients.

The actual questionnaire itself contains a variety of questions about different aspects of wellbeing. It was chosen to leave out the questions which dealt with somatic symptoms:

7. Is your digestion poor?
19. Do you have uncomfortable feelings in your stomach?

Many patients are treated for their rheumatoid arthritis with drugs that can cause gastrointestinal upset. Non-steroidal anti-inflammatory drugs (NSAIDs) frequently cause dyspepsia or abdominal discomfort. Methotrexate and other DMARDs can cause nausea, and this is a commonly reported side-effect. It was felt that the patients may have symptoms which would be expected in the context of their treatment which would be misleading in terms of their psychiatric status. While there is clearly a strong relationship between physical well being and depression, other measures were being used to assess disease status and side effects. It was felt that this might bias the study.

It was also chosen to omit the question

13. Is your daily work suffering?

This was because many of the patients had given up work as a consequence of their disease, and were confused by the question, as they no longer were able to work. It became clear during the study that this was a difficult one for patients to answer, particularly the Gujarati patients, and may not have necessarily reflected their mood.

Leaving out these questions will have made the tool less sensitive, but less likely to be confounded by somatic symptoms, or lack of understanding.

3. 8. 2. Serious Life Events

The context of an individual's life can have significant implications on their psychological distress. It is well recognized that serious life events, such as losing a job, moving house, divorce and bereavement can have a substantial impact on depression and anxiety levels. It is possible that immigrant groups may have a higher number of serious life events to contend with as they deal with an unfamiliar environment. The life event list used to assess this was used by the Manchester ARC research group in their studies into back pain in the local South Asian communities, and the questions asked were those they had particularly

identified as being relevant to those groups (Appendix 7, (Brugha, Bebbington et al. 1985).

3. 9. BLOOD TESTS

Blood was taken by the investigator. The laboratories at the Leicester Royal Infirmary tested for rheumatoid factor, full blood count, inflammatory markers and biochemistry. A separate EDTA sample was taken for HLA testing, which was done by the investigator as outlined in the chapter on HLA.

3. 9. 1. Inflammatory Markers

Erythrocyte sedimentation rate (ESR) and plasma viscosity (PV) are both used as markers of inflammation in the blood. High levels reflect disease activity in rheumatoid arthritis. ESR is more widely used, but is not available in the Leicester hospitals, where the laboratory measures plasma viscosity instead. These two measures are not directly comparable. The blood was run on a Benson machine according to standard protocols. Normal values for PV are from 1.5 to 1.72.

3. 9. 2. Full Blood Count

The full blood count (FBC) can be affected by RA. Anaemia can be caused by chronic disease, or by iron deficiency. This may be as a result of dietary insufficiency or secondary to gastric irritation due to use of NSAIDs. The white cell count can be lowered both by the DMARDs used to treat RA, and by the disease itself. The platelet count can be elevated as a marker of active inflammation, and lowered as an autoimmune response.

Full blood counts in the Leicester laboratory were run on a SE 9500 machine, according to standard protocols.

3. 9. 3. Rheumatoid Factor

Rheumatoid factor (RF) is an autoantibody which is directed at the Fc fragment of IgG molecule. It may be of IgM, IgA, IgG or IgE class. IgM RF has been most clearly characterised as related to the severity of RA, and IgA is also thought to be associated, but the role of other classes are less clear (Wener 2004). Agglutination testing is usually specific for IgM RF, but can also cross react with IgA RF. IgM RF was found to be 69% specific and 85% sensitive for RA in a large meta-analysis (Nishimura 2007). Seropositivity can impact on disease severity (as described in section 1.3.2). RF may be found in other conditions (see table 3), and in low titre in the healthy population, particularly in the elderly.

Table 3. Table Showing Range of Conditions That May Be Associated With a Positive Rheumatoid Factor (Wener 2004)

Autoimmune diseases	Sjogren's
	Mixed connective tissue disease
	Systemic lupus erythematosus
	Juvenile RA
	Scleroderma
	Polymyositis
	Hypersensitivity vasculitis
	Mixed cryoglobulinaemia
Infections	Tuberculosis
	Leprosy
	Syphilis
	Subacute bacterial endocarditis
	Salmonellosis
	Acute rheumatic fever
	Acute viral infections (rubella, mumps, infectious mononucleosis, influenza)
	Hepatitis C
	Parasitic infections (schistosomiasis, malaria, trypanosomiasis)
Other	Sarcoidosis
	Chronic liver disease
	Primary biliary cirrhosis
	Interstitial lung disease
	Smoking

Blood taken for rheumatoid factor (RF) was analysed by a nephelometry process in a BN2 analyser from Dade Behring. This uses the latex method, where RF in the blood binds to preparations of human IgG coated onto latex particles. Light scattered through the then aggregated latex particles gives a value proportionate to the binding titre of the RF.

3. 9. 4. Biochemistry

Albumin may be a surrogate marker of disease activity, and also of nutritional status. Blood for biochemistry was run on an Aeroset machine according to standard protocols.

3. 10. PATIENT SELECTION

Subjects were identified largely through out patient clinics, both at peripheral hospitals and the teaching hospitals in Leicester; Leicester Royal Infirmary, Glenfield General Hospital, and Leicester General Hospital. They were also identified through the patient database collected in the department, which identifies any patient ever started on a DMARD.

3. 10. 1. Patient Recruitment

Patient recruitment was particularly important. Many studies comparing different ethnic groups do not specify a single group, but recruit patients from many different backgrounds, assuming that they are similar. The population of Leicester is very ethnically mixed. People from India, Pakistan and other geographically related areas may be mistakenly grouped together under the umbrella term 'Asian'. People from these regions may be widely different in terms of geography, culture and genetic background. It would be inappropriate to collect them together and assume that they would behave in the same way. The largest ethnic immigrant group in Leicester is from Gujarat, as described previously. It was therefore important to only recruit Gujarati patients.

Patient recruitment to the study occurred between August 2001 and November 2002. Patients were approached when they attended for their clinic appointment. They were approached either by the investigator, or if they spoke no English, by a Gujarati Nursing Auxiliary, who had worked in the Rheumatology Outpatients Department for many years. Study patients were of Gujarati origin. By this, they had either been born in Gujarat State in India themselves, or their parents or three of four grandparents had been born there. All these patients spoke Gujarati as a first or second language, and referred to themselves as Gujarati. The Caucasian British patients were also approached in clinic, and recruited if they were of Anglo-Celtic origin.

The patients responded fantastically, with only a tiny handful of Asian or Caucasian patients refusing to take part, over the eighteen month recruitment period.

3.10. 2. Selecting Two Comparable Groups

Patients were recruited randomly. More Caucasians were recruited than Asians, due to population proportions. After recruitment and once the results were anonymous, initial analysis showed that the mean age of the Caucasian patients was significantly greater than that of the Asians. There was also an excess of male Caucasian patients. The older male Caucasian patients were excluded in order to provide two groups that had comparable age and sex ratios. This may have introduced some potential bias, in that the younger Caucasian patients may have been selected for rather than being random representatives. However, the older male Caucasian patients were likely to be less comparable to younger female Asian patients, and this may have made the results less reliable, particularly when looking at disability, and socioeconomic factors. The revised groups had no significant difference in age or sex ratio, as described in chapter 4.2.1. Disease duration was also not significantly different between the two groups. The original complete data group was used when a mathematical model could be used to adjust for age and sex. When appropriate, for the purposes of

comparing two groups, the revised age and sex adjusted data set was used. This is noted in the text.

3. 10. 2. Patient Information And Informed Consent

Patients were informed about the nature and aims of the study, and all received an information leaflet designed by the author, outlining the aims of the study and their role in participating (see appendix 1). In particular, it carefully explained the nature of the HLA testing. Patients were given time to read this document before signing a form indicating informed consent (appendix 2).

3. 10. 3. Bias

It is difficult to control for bias when recruiting from a hospital based population. One has to consider if there is a significant number of patients who are not referred to secondary care, either because of their inability to access medical facilities, or their mistrust of medicine, as may happen in an immigrant community. There may also be numbers of patients with relatively mild disease who are not referred because either they don't complain, or their GPs do not feel they warrant further treatments, or do not recognise that they might benefit from further treatments.

A pilot telephone survey of a small sample of GPs was performed. GPs were selected who practiced in an area with a geographically largely Asian population, or a largely Caucasian population. They were asked how many patients with RA they had in their practices that they did *not* refer on to specialist care. None of the GPs felt they had anyone in their care with RA that they did not refer for secondary care. It was therefore felt that there were unlikely to be large numbers of patients with RA unknown to the Rheumatology Department, which would allow the conclusion that the patients seen in clinic were an accurate representation of those with the disease in the community at large.

3. 11. PATIENT INTERVIEW

The interview was conducted by the same examiner each time to eliminate inter-observer differences. If the patient did not speak English, the same interpreter was used each time. This was a Gujarati Nursing Auxiliary who had worked in the Rheumatology Outpatients at Leicester Royal Infirmary for many years, and was not only familiar with the relevant terms, but also knew most of the patients well.

The possibility of translating the interview questionnaire into Gujarati was considered. However, after taking advice from our Gujarati staff, it transpired that those who cannot read English are often illiterate in their own language. Thus all patients, Caucasian and Gujarati, were taken through the questionnaire by the

examiner, rather than asking them to complete it alone. This also allowed concepts to be explained so there was less misunderstanding in both groups.

3. 12. ANALYSIS

The SPSS package version 12.0 was used by the author to analyse all data. Extensive consultation with carried with regard to the analysis, and advice taken from two different statisticians, Helen Doll at the Dept of Public Health, University of Oxford, and Gabrielle Durrant, an independent statistics tutor.

Parametric and nonparametric testing was used, depending on the data, and the appropriate test is noted in the text. Initially, as a trial, both tests were used but as the sample sizes were relatively small, and in some cases skewed, nonparametric tests were more appropriate. In these situations the non-parametric test was the more rigorous, with parametric testing having greater significance values (for example: comparing pain scores between the two ethnic groups with an independent t-test has a significant difference of $p < 0.0005$, while a Mann-Whitney U test gives a significance of $p = 0.001$). This is because nonparametric tests do not assume normality. The chi-squared test was used for categorical data and the Mann-Whitney U test was used for continuous data. The test used is noted next to the relevant p value in the results, with explanation where necessary. The level of meaningful significance was taken to be <0.05.

CHAPTER 4. SOCIOECONOMIC DIFFERENCES IN GUJARATI AND CAUCASIAN PATIENTS WITH RA

4. 1. BACKGROUND

122 patients, 61 Asian and 61 Caucasian subjects (the revised data set, see section 3.10.2) were recruited, as outlined in the previous chapter. They all underwent the interview detailed in appendix 3 with the author, and a translator if necessary, as discussed previously. The socioeconomic similarities and differences were then assessed. Parametric testing was used where the data was normally distributed. As the sample sizes were small, and much of the data skewed, and therefore not normally distributed, much of the analysis was performed using nonparametric tests. These are more appropriate in this situation. The tests used are documented in the text.

4. 2. RESULTS

4. 2. 1. Demographics of Revised Data Set

For descriptive statistics of the complete data set, see appendix 7.

The mean age of the Asian patients was 52.1 (standard deviation (sd) = 11.2) years with a range of 30 to 74. The mean age of the Caucasian patients was 54.7 (sd = 10.7) years, with a range of 27 to 74. The two groups were not

statistically significantly different (p = 0.16, independent samples t-test, see table 4).

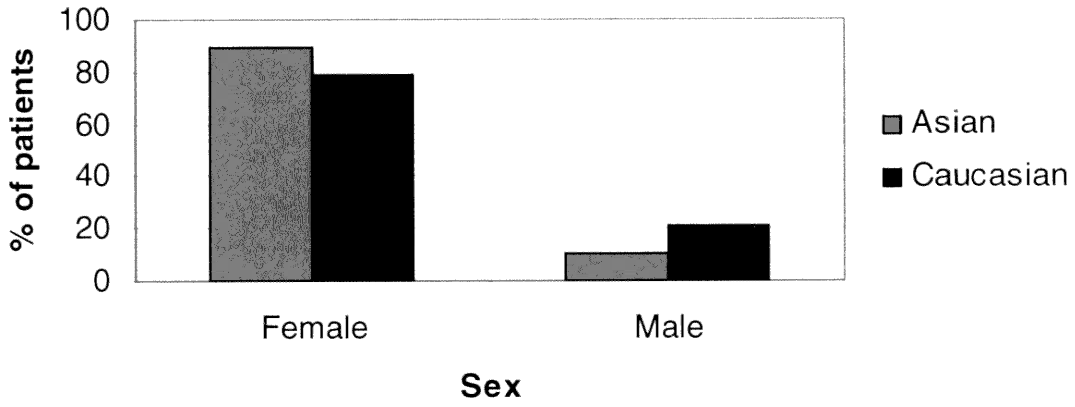
The mean disease duration of the Asian patients was 10.03 (sd = 6.4) years with a range of 1 to 27, and the mean disease duration of the Caucasian patients was 10.9 (sd = 9.4) years with a range of 0.75 to 28. This was not statistically significant (p = 0.6, independent samples t-test).

Table 4. Mean Age And Disease Duration Of Caucasian And Gujarati Patients

Variable	**Gujarati Mean**	**Standard deviation**	**Caucasian Mean**	**Standard deviation**	***P* value (independent t-test)**
Age / years	52.10	11.2	54.70	10.7	0.16
Disease duration/ yrs	10.03	6.4	10.90	9.4	0.6

The ratio of men to women in the Asian group was 7 to 54, so 11% were male. In the Caucasian group there were 12 men to 49 women, so 21% were male. (Fig 2). On chi-squared analysis, the difference between the groups was not significantly different in a sample size of 122 (p = 0.09). Fisher's exact test showed p = 0.15.

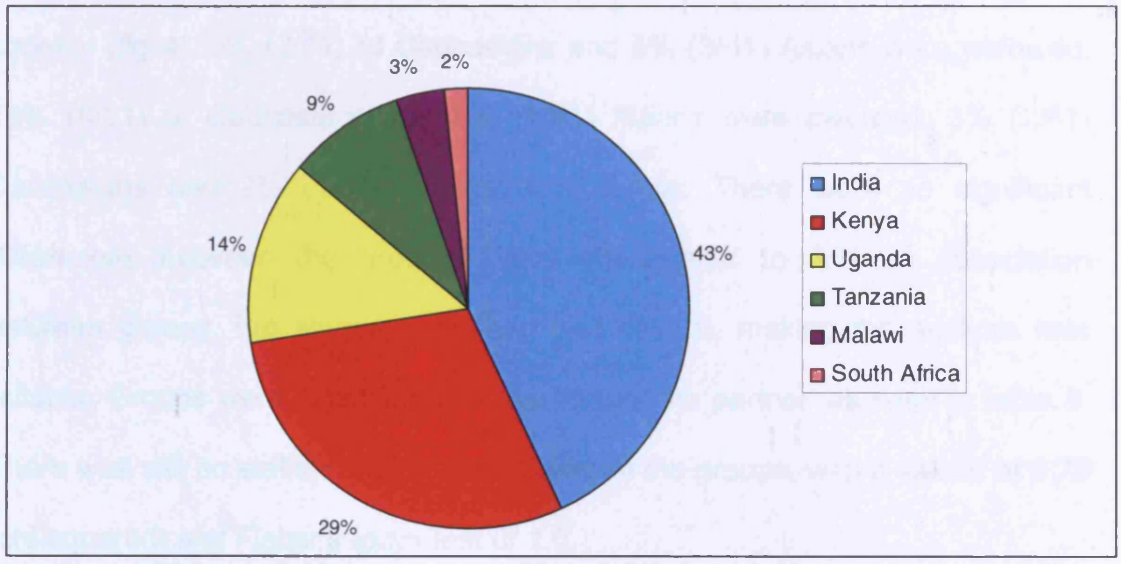
Fig. 2: Graph showing sex ratios of the Caucasian and Gujarati Asian patients



4. 2. 2. Ethnic Background: Asian Patients

All the Asian patients referred to themselves as 'Gujarati'. None were born in England, all being immigrants. In only one case were all four grandparents NOT born in Gujarat area of India. In this case, the patient had been born in India after her grandparents had moved back to India after having been born themselves in Africa to immigrant 'Gujarati' parents. Only 25/61 patients were actually born in India in the Gujarat region (fig. 3). Two were born in other areas of India. The rest were born in Africa. Eight were from Uganda, 17 from Kenya, 5 from Tanzania, 2 from Malawi and 1 from South Africa. Eleven of the patients who were themselves born in India immigrated first to Africa before coming to the UK to settle. Thus 44/61 – 72% of all patients – had come to Leicester by way of Africa. The mean year of immigration was 1974 (SD 116), with a range of 1957 to 1998.

Fig 3. Asian Patients' Country of Origin



4. 2. 3. Ethnic Background: Caucasian Patients

A control group of Caucasian patients were also recruited. They were all British, with grandparents born in the UK, and spoke English as a first language. The White patients all thought of themselves as 'British', and of these, only one was born in Ireland, the rest in England. One had Irish and one had Welsh parents. 5 had one parent from another country. These countries included Scotland, Wales, Ireland and Canada, although the Canadian parent had had English parents. One patient had 2 grandparents from America of non specific 'Anglo-Saxon' background. Out of 61 patients, 33 (54%) were actually born in Leicestershire.

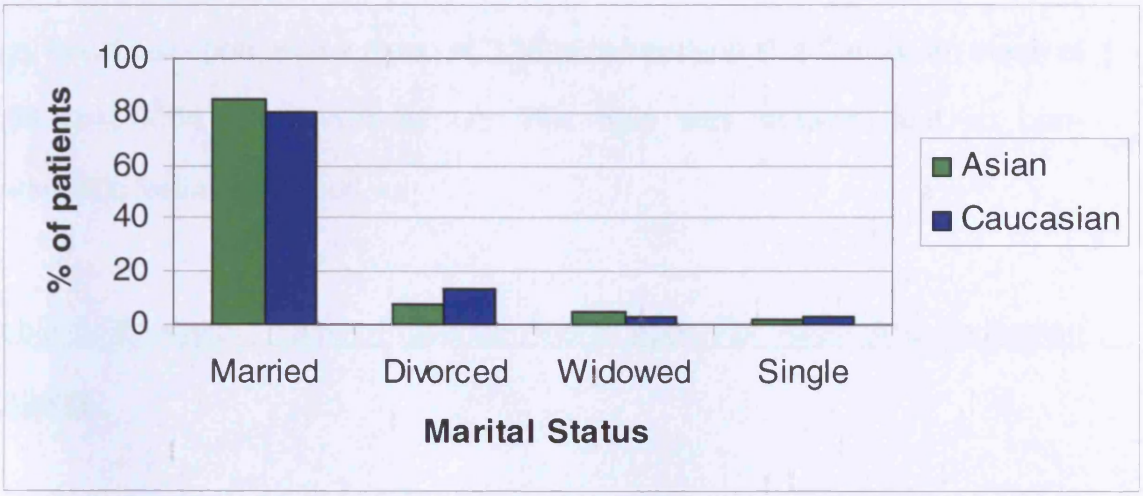
4. 2. 4. Social Factors

80% (49/61) Caucasian patients were married, compared with 85% (52/61) Asian patients (fig 4). 3% (2/61) of Caucasians and 5% (3/61) Asians were widowed, 13% (8/61) of Caucasians and 8% (5/61) Asians were divorced. 3% (2/61) Caucasians and 2% (1/61) Asians were single. There were no significant differences between the groups, using chi-squared to find an association between groups, but several cells had less than 5, making the analysis less reliable. Groups were simplified into 'partner' or 'no partner' as seen in table 5. There was still no statistical difference between the groups, with *p* values of 0.79 (chi-squared) and Fisher's exact test of 1.0.

Table 5. Marital Status of Asian and Caucasian Patients

Marital Status	**Gujarati patients (%)**		**Caucasian patients (%)**		***p* value (chi-squared)**
	No.	**%**	**No.**	**%**	
Married	52	85	49	80	
Divorced	5	8	8	13	0.56
Widowed	3	5	2	3	
Single	1	2	2	3	
Partner	52	85	53	87	0.79
No Partner	9	15	8	13	

Fig 4. Chart Showing Marital Status In Gujarati And Caucasians With RA



4. 2. 5. Education And Support Network

Although there was a tendency for Asians to have fewer years of education, and to have left education at a younger age than the Caucasian patients, this did not reach significance (table 6). This data was not normally distributed, with the vast majority of Caucasian patients leaving at school at 16 years, and the Asian patients leaving school at 14 years, 16 years, and some leaving when much younger. Non-parametric analyses were used (Mann-Whitney U test).

There was no difference between the groups in terms of having a partner at home, as described in section 4.2.4, but there were highly significant differences between the groups in terms of numbers of family members at home. There were also significant differences in the number of people the patient could call upon to help. The Asian patients were far more likely to have more people at home with

them, with a mean of 2.1 compared to a Caucasian mean of 1.38 (p=0.0005, Mann-Whitney U). They also had a bigger supportive network of people whom they could call upon, with a mean of 3.15 in comparison to a Caucasian mean of 1.89 (p=0.0004, Mann-Whitney U). This data was skewed, and so non-parametric testing was used.

Table 6. Education, Family Presence And Support For Asian And Caucasian Patients

Variable	**Gujarati mean**	**Standard deviation**	**Caucasian mean**	**Standard deviation**	***P* value (Mann-Whitney U)**
Years of education	9.90	3.77	11.89	3.15	0.08
Age of leaving education	15.47	3.70	16.4	3.14	0.73
Number of family members at home	2.11	1.31	1.38	1.00	**0.0005**
Number of friends and family who help	3.15	2.24	1.89	1.38	**0.0004**
Children at home	1.02	0.98	0.48	0.91	**0.0002**
In-laws living at home	7 patients (11%)	N/A	1 patient (1%)	N/A	**0.028 (chi-squared)**

Asian patients had more children at home, with a mean of 1.02, while Caucasians had a mean of 0.48 (p=0.0002, Mann-Whitney U). Asian patients were also significantly more likely to have their in-laws living with them (p=0.028, chi-squared), although these groups contained very small numbers, so the results must be interpreted with caution. Overall, the results fit with the expectation that the Asian families are more likely to be living both in larger family units, and with more extended family in the vicinity.

4. 2. 6. Religion

The Indians were either Hindu or Muslim, with 10/61 (16%) being Muslim and 51/61 (84%) being Hindu. The Caucasians described themselves as either Christian, 44/61 (72%) or 'not religious', 17/61 (28%) denying being part of any religious group.

4. 2. 7. Language

Only 7 (11%) Gujarati patients spoke no English. All Gujarati patients spoke at least two languages. They spoke significantly more languages than the Caucasian patients with a mean of 2.67 (sd 0.89) languages spoken to a Caucasian mean of 1.10 (sd 0.30). Languages spoken by the Gujarati patients as well as Gujarati and English included Hindi, Swahili, Urdu, Punjabi, Portuguese

and Kurchi. Mean difference was 1.57; 95% confidence interval 1.34 to 1.81, $p<0.0001$, Mann-Whitney U. Six Caucasians could speak languages other than English. Three spoke French, two German, and one spoke Japanese. None could speak any Asian language.

4. 2. 8. Alcohol

The majority (54/61, 85%) Asian patients were teetotal. Of the 7 who drank alcohol, only 2 drank regularly, and the other 5 restricted themselves to less than one drink a week. 17 (28%) of the Caucasian patients were teetotal, and 19 (31%) had less than one drink a week. 15 (25%) drank moderately, 1 to 5 units a week, 5 (8%) drank 5 to 10 units a week, and 5 (8%) drank over 10 units a week (table 5). The Caucasians patients intake was significantly more than the Gujarati patients (p <0.0001, Z=-5.6, Mann-Whitney U). The data was not normally distributed, as so few Asian patients drank. This also made statistical testing inaccurate if subdivided into groups, as there would be too few numbers in several cells. Direct non parametric testing was used; using the data for actual number of units drank per week by each individual, rather than the subdivisions shown in table 7, which are shown for ease of displaying the data.

Table 7. Alcohol Intake of Caucasian And Gujarati Patients

Alcohol Units/week	Gujarati		Caucasian		*P* value for overall alcohol intake (Mann-Whitney U)
	No.	%	No.	%	
0	54	85	17	28	
<1	5	8	19	31	
1 to 5	2	3	15	25	0.00000002
5 to 10	0	0	5	8	
>10	1	2	5	8	

4. 2. 9. Smoking

6/61 (10%) of the Asian patients smoked, and one was an ex-smoker. 85% Asian patients had never smoked (table 8).

9 (15%) of the Caucasian patients were current smokers. 18 (30%) were ex-smokers, so only 56% of the Caucasians had never smoked. The Gujarati patients had significantly less smoking history than the Caucasian patients, when divided into groups of 'ever smoked' or 'never smoked' (difference 29%; 95% confidence interval 22% to 70%, $p<0.0001$, chi-squared).

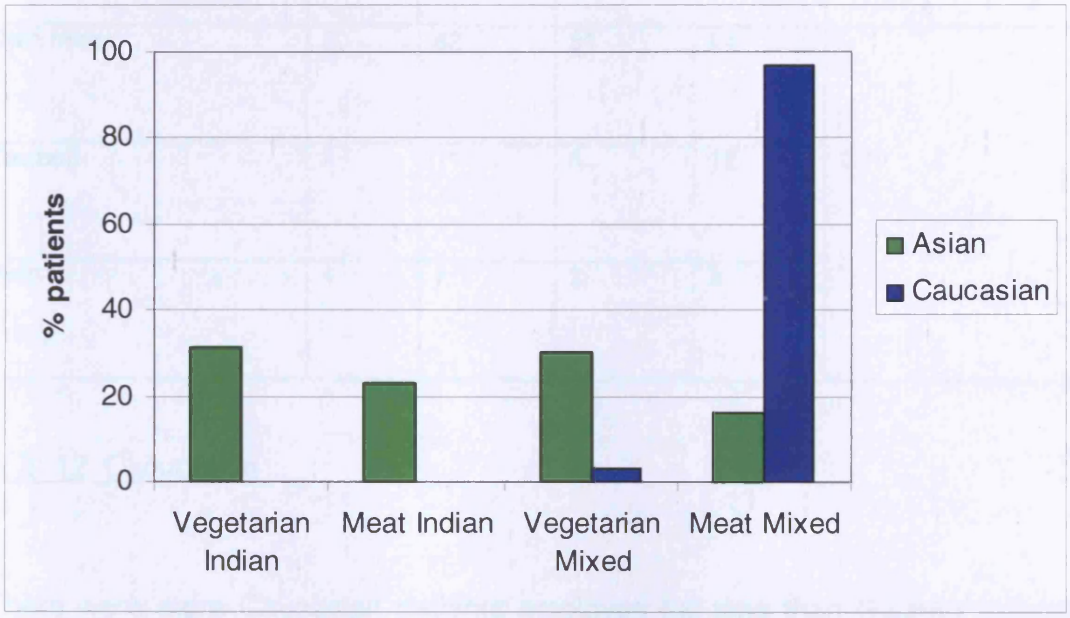
Table 8. Smoking habit of Caucasian and Gujarati Patients

Smoking habit	Gujarati		Caucasian		*P* value for smoking history (chi-squared)
	No.	%	No.	%	
Current smokers	6	10	9	15	
Ex-smokers	1	2	18	30	**0.00002**
Non smokers	54	85	34	56	

4. 2. 10. Diet

Diets were very different between the two groups of patients. 27/61 (44%) Gujarati patients were vegetarian, with 33/61 (54%) Gujarati patients eating an exclusively 'Indian' diet, with no European style food. Only 2/61 (3%) Caucasian patients were vegetarian (fig 5).

Fig 5. Bar chart showing spread of dietary type in Gujarati and Caucasian patients



4. 2. 11. Housing

There were some general expectations about housing that were not confirmed by the study. One was that the Gujarati population would be more likely to own their own homes, because of a perceived desire within the community to achieve this. However, the housing for both groups was remarkably similar (table 9), suggesting that our patients in fact came from similar socioeconomic groups.

Table 9. Housing Types For Caucasian And Gujarati Patients

Housing	Gujarati		Caucasian		*P* value (chi-squared)
	No.	%	No.	%	
Own home	50	82	51	84	
Council	7	11	8	13	0.70
Rent	4	7	2	3	

4. 2. 12. Occupation

There were more Caucasian patients employed full time than Gujarati patients (20% vs. 13%). The Asian patients were more likely to class themselves as 'not working because of ill-health or disability' (59% vs. 31%) or to be doing domestic work in the home full time (16% vs. 3%). Caucasians were more likely to class themselves as 'retired' (36% vs. 5%) (table 10). Overall, there was a significant association between category of work and group (chi-squared, p=0.0008).

Table 10. Occupational Status of Caucasian And Gujarati Patients

Category of work	Gujarati		Caucasian		*P* value (chi-squared)
	No.	%	No.	%	
Full-time	8	13	12	20	
Part-time	2	3	6	10	
Unemployed but seeking work	0	0	0	0	
Domestic work in the home	10	16	2	3	**0.0008**
Not working because of ill health or disability	36	59	19	31	
Student	0	0	0	0	
Retired	5	8	22	36	
Patients in work	10	16	18	30	0.09

The spread of occupations undertaken by the patients were divided into jobs that required minimal, moderate or extensive training. Minimal training included working in factories, as a porter, shop assistant, health care assistant or carer. Moderate training included clerical work, administration, and jobs such as plumber, electrician or carpenter, hairdresser, beautician. Extensive training included teacher, manager, lawyer, and nurse. The Asian patients were far more likely to be working in jobs with minimal training than the Caucasians, who were more likely to be in skilled worker roles requiring moderate or extensive training (table 11). There was a significant association between type of occupation and

ethnic group (chi-squared, $p<0.0001$). There was no significant difference in patients in work between the two groups (chi-squared, $p=0.09$).

Table 11. Spread Of Occupations In The Caucasian And Asian Patients, Categorised By Amount Of Training Required

Occupation	Gujarati		Caucasian		*P* value (chi-squared)
	No.	%	No.	%	
None	7	11	0	0	
Minimal training	47	77	23	38	**<0.0001**
Moderate training	5	8	23	38	
Extensive training	2	3	15	25	

4. 2. 13. Social Services Support

There was a general perception amongst the Gujarati patients that they did badly in terms of support received. This is not supported by the results (fig 6, table 12), which show that across the board, the Gujarati patients were just as likely to be receiving some kind of social support as were the Caucasians. In fact, Caucasian patients were significantly likely to be receiving *no* form of social services support

(46% vs. 25%, difference 21%; 95% confidence interval 4% to 38%), while the Gujarati patients received significantly more forms of social services support than the Caucasian patients did (mean 1.69 vs. 1.03, difference 0.66; 95% confidence interval 0.21 to 1.10, p=0.005, Mann-Whitney U). This shows that despite any cultural or language barriers, the Leicester council is still managing to allocate support to those needing it.

Fig 6. Bar Chart Showing The Percentage Of Gujarati And Caucasian Patients Who Received Different Types Of Social Services Support

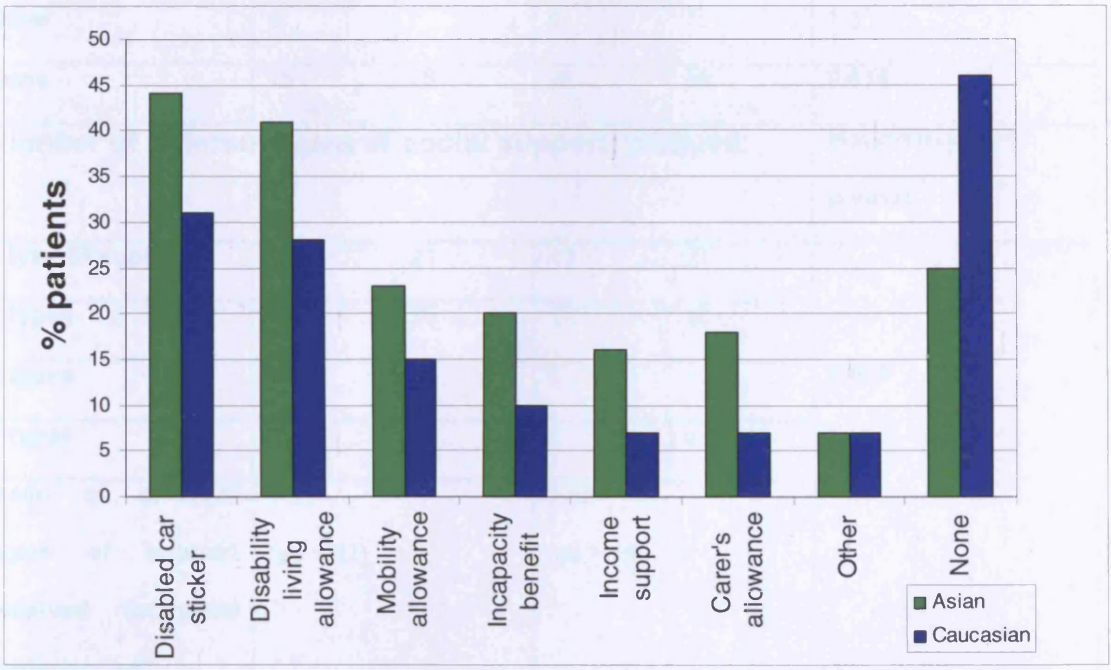


Table 12 Table Showing The Range Of Social Services Support Received By Gujarati Asian And Caucasian Patients In Leicester With RA

Social services support	**Gujarati patients**		**Caucasian patients**		***P* value (chi-squared)**
	No.	**%**	**No.**	**%**	
Disabled car sticker	27	44	19	31	0.14
Disability living allowance	25	41	17	28	0.13
Mobility allowance	14	23	9	15	0.25
Incapacity benefit	12	20	6	10	0.13
Income support	10	16	4	7	0.09
Carer's allowance	11	18	4	7	**0.05**
Other	4	7	4	7	1.0
None	15	25	28	46	**0.014**
Number of different types of social support received:					**Mann-Whitney U *p* value**
1 type of support	13	21	13	21	**0.005**
2 types	16	26	11	18	
3 types	10	16	8	13	
4 types	7	11	1	2	
Mean of different types of support received (standard deviation sd)	1.69 (sd 1.32)		1.03 (sd 1.15)		

4. 3. SUMMARY OF SOCIOECONOMIC DIFFERENCES

Overall, there are striking differences between the two ethnic groups with RA.

The Gujarati patients live in larger extended families, with a large network of friends and family who help them, often in their own houses. They are non-smokers who don't drink, and likely to be eating exclusively ethnic food. They follow their religion, be it Hindu or Muslim. They are less likely to be working, having given up because of their illness, but if they are working, it is likely to be as an unskilled worker.

The Caucasian patients live in small family units, often with just a partner, and have few friends and family to call on for help. They are likely to own their own home. They are more likely to have had a smoking history, and to drink alcohol. They eat a mixed diet. They are less likely to follow a religion. They are more likely to be retired, but if they are working, it will be as a skilled worker.

4. 4. SOCIOECONOMIC DIFFERENCES: DISCUSSION

There were considerable differences socioeconomically between the Gujarati and Caucasian patients with RA. There were some similarities: they had equivalent marital status. There was no difference in their education, or in housing. There were obvious differences that might be expected, such as religion and language. Gujarati patients were practicing the religions of India, and speaking a range of languages, with English as a second language. In these aspects, they remain as they would, were they still living in India.

4. 4. 1. Acculturation

This suggests a lack of 'acculturation', the act of adopting the culture, values, beliefs and life style of an immigrant's new country (Mavreas, Bebbington et al. 1989). It has been suggested that the more an individual adopts the culture of his or her new country, the less environmental factors can explain differences in health outcomes between immigrants and the indigenous population (Deyo, Diehl et al. 1985). Hameed et al (Hameed and Gibson 1997), when studying the differences between Pakistani patients in Pakistan and in immigrant Pakistani patients in England, noted that the domestic clothes, household furnishings and diet of the two groups were notably similar. This suggests a lack of acculturation of immigrant Pakistanis in the UK. This study suggests that there is a similar lack of acculturation in first generation immigrant Gujarati patients in Leicester,

although it was not designed to show this. Family structure, dietary habits and alcohol use were all similar to that which one might expect to find in a Gujarati population in India. This lack of adaptation may impact on the way that these patients experience their disease.

4. 4. 2. Social Support And The Extended Family

There are clear cultural differences between Asian and Caucasian populations in terms of their family structure and social network. This study confirmed the hypothesis that the Asian patients live in extended families, with more children at home, and many more relatives and friends around to help them than the Caucasians. The indigenous population tend to live in small contained family groups, with few friends or family around to help. Gujarati patients are also more likely to be a member of a religion than the Caucasian patients, which implies the social gathering and support associated with organised religion. This wealth of human contact and extensive support network would be expected to be a significant help to these vulnerable disabled patients. There is evidence that a larger social network protects individuals with RA from depression, and low levels of social support predicted disease activity at 3 year follow up in the Netherlands (Evers, Kraaimaat et al. 2003). It therefore might be expected that the Gujarati patients would be less likely to be depressed. The study shows quite the opposite.

This may be because there is no indication of the quality of the social support. The mere presence of other people does not necessarily relate to meaningful physical and psychological help. It is the quality of that support that acts as a buffer against depressive symptoms, and this has been shown in patients with RA (Goodenow, Reisine et al. 1990). Additional people living at home may be a burden rather than a help. Most RA patients are female, and many Gujarati patients had children at home. Struggling to care for small children at home may be an additional source of psychological distress, rather than a help. This may be because the children are too young, or that the spouse is away at work for long periods. There may be difficulties within the family, so that family members are disinclined to lend aid. There may be a cultural expectation that a woman will perform all household chores and look after her husband, family and possibly her in-laws. This would be the traditional structure of a Gujarati home. This traditional model may poorly adjust to a disabled mother. Creed et al showed that social difficulties independent of RA were correlated with depression in RA patients in Stockport (Dickens, Jackson et al. 2003). This study showed that Gujarati patients were significantly more likely to have in-laws at home with them, suggesting that many families were indeed modelled on this traditional structure.

Male patients may also fail to conform to this cultural model. There may also be an expectation that a male patient should be able to provide for his family, and aid his relatives, which may be impossible with disability. It is easy to see how, even with the most supportive family, failure to fill a traditional role would be a

significant stressor for an individual. There is also evidence from Leicester that in spite of large extended social networks, these do not necessarily function as expected to give support. Katbamna et al demonstrated that carers of South Asian background had limited support, regardless of extended families (Katbamna, Ahmad et al. 2004). They also showed that cultural attitudes to disability and fear of obligation prevented many from seeking help from the wider community.

The Gujarati patients in this study failed to be protected from depression by their extended families and large social support network.

4. 4. 3. Diet: Is It Significant?

The Gujarati and Caucasian patient groups have very different diets, and this is one of many important factors that may influence the disease process. Over 50% of the Gujarati patients ate exclusively 'Indian' food, another sign of their lack of acculturation. 44% of Gujarati patients were vegetarian, while only 3% of Caucasian patients were vegetarian.

Studies in the Mediterranean have claimed to show diminished disease activity in RA with a 'Mediterranean diet'; rich in olive oil, fresh fruit and vegetables (Linos, Kaklamani et al. 1999). There may be other benefits to a vegetarian diet, with the Norfolk Arthritis Register (NOAR) showing lower risk of RA with diets rich in

vitamin C and low in red meat (Pattison, Silman et al. 2004). A recent study in Glasgow used weekly education sessions with cooking classes to promote a Mediterranean diet (McKellar 2007). The intervention group had significantly lower pain, disability and EMS after 6 months. Scandinavian health farms which supply a vegetarian diet have been shown in small studies to have some benefit in a subgroup of 'responders' with RA (Kjeldsen-Kragh J. 1991). A more rigorous study with a larger patient group used a vegan and gluten free diet, and found modest improvements in a subgroup of patients, whom were classified as responders, but with no change in disease progression as measured by erosions (Hafstrom I. 2001). They noted that a large number of patients were unable to comply, with only 22 completing 9 months of the study diet. Of these 22, 9 achieved ACR20 (20% improvement in ACR activity criteria), compared with 1 patient in the control group. This was not reported as being statistically significant. A study in Norway showed a clinical response to fasting and a vegetarian diet in 53 RA patients (Kjeldsen-Kragh 1994). They assessed the psychological profile of their patients, and concluded that patients self selected for the trial, with those that responded clinically having a significantly lower belief in their conventional treatment, and stronger belief in the efficacy of alternative treatments.

Exclusion and elimination diets have been trialled with some success. A study in Leicester compared a 2 week elimination diet to 2 weeks of 15mg prednisolone daily, and found similar clinical improvements in pain, EMS and articular index

(Podas 2007). While this is encouraging, these trial diets are often impractical for long term use. It is also very difficult to blind the intervention group in these studies, introducing a potential bias.

A meta-analysis of omega-3 fatty acid supplementation showed that treated patients with inflammatory joint disease had significantly less pain, EMS and tender joints (Goldberg 2007), suggesting that this dietary supplement is a useful additional treatment.

Turmeric has garnered interest recently as a potential anti-inflammatory. It has been used for many years in Ayurvedic preparations, and an Indian study of curcumin, which is a constituent of the rhizome of turmeric, demonstrated improvement in morning stiffness, walking time and joint swelling in patients with RA (Deodar, Sethi et al. 1980). This outcome suggests an anti-inflammatory effect of turmeric. This finding has been tested in Lewis rats, an experimental model of RA, and turmeric extracts showed potent inhibition of joint inflammation in this model (Funk, Frye et al. 2006). As our Gujarati patients ate traditional Indian diets, likely to be rich in turmeric, it is possible that they may have reaped some additional anti-inflammatory benefit from this. However, their longer morning stiffness and greater disability does not support this hypothesis. It is also possible that without turmeric, the Asian patients would have had even longer EMS and greater disability.

From this evidence, it might be thought that the diet of the Asian patients would be protective. They overwhelmingly follow a strict vegetarian diet, which is rich in turmeric, although it is not traditionally gluten free. Despite the potential advantages seen in other patient groups with vegetarian diets, they did not seem to be protected. A traditional Asian diet may contain substances that exacerbate pain, or it may be that the advantages are too slight to have a significant impact on disease.

4. 4. 4. Alcohol And Smoking: Do The Bad Habits Of The Caucasians Help Them?

There were other important differences between the Asian patients and the Caucasians. The Asians are teetotal, and unlikely to smoke. The explanation offered by many smokers is that it relieves their stress, although there is little evidence to support this. There is no evidence that smoking relieves the pain and distress of disease, and so this cannot be seen as an explanation for the differences between the two groups.

The NOAR group showed that people who had ever smoked had an increased risk of developing polyarthritis (Symmons, Bankhead et al. 1997). There is also good evidence that smoking is related to disease severity, with those exposed to cigarette smoke having more severe disease (Albano, Santana-Sahagun et al. 2001). As our Caucasian patients had highly significantly more smoke exposure

than the Asian patients, it would be expected that this would predispose them both to developing the disease, and to a more severe phenotype. They did show many characteristics of severe disease, such as seropositivity, nodulosis and high joint counts, which may imply that they did indeed have more severe disease. However, their pain and disability scores were significantly lower than the Asians, so their functional outcomes were better than expected from their smoke exposure.

Alcohol is frequently used by those in distress to offer a short lived escape from their pain. This is only a temporary response, and alcohol abuse is clearly linked to depression (Lukassen J 2005). This study does not confirm that those with more pain drink more alcohol. This may be because the Asian patients have cultural reasons why the majority of them do not drink, despite their increased pain. Again, their lack of adoption of the drinking habits of the UK is another indication of their lack of acculturation. Voight et al found higher alcohol consumption was associated with a reduced risk of RA (Voight, Koepsell et al. 1994), and there are less alcohol related deaths than expected in RA sufferers (Myllykangas-Luosujarvi, Aho et al. 2000), so it may be that the bad habits of the Caucasians did offer some protection from their disease, at least in the case of alcohol.

4. 4. 5. Housing And Occupation: Clues To Economic Prosperity

The Gujarati and Caucasian rheumatoid patients live in the same kind of housing. On face value, it appears that the Gujarati population were doing as well economically. However, this can be challenged by examining the occupational history. Gujarati patients were likely to be factory workers, while Caucasians were more likely to be working in skilled worker jobs that require training, and thus command a larger pay packet. The ERAS group has shown that those in manual jobs are particularly vulnerable to loss of work once RA is diagnosed (Young, Dixey et al. 2002), and the Gujarati patients were more likely to class themselves as unable to work because of disability or illness. The ERAS group has also shown that socioeconomic deprivation is associated with a poorer clinical outcome in rheumatoid disease (Young, Dixey et al. 2000), which may be relevant in this group of patients, particularly if they are in low income jobs.

It might be expected that an immigrant community may not have the English language skills to work in jobs involving more training and communication. The lack of skilled jobs undertaken by the Asians may indicate a lack of availability of training, either in their own country, or in the UK, after immigration. There was no difference in education, so it may represent a lack of willingness of employers to employ the Asian patients. There were also more managers and professionals in the Caucasian group. This shows up a socioeconomic divide not evident in housing status, as more of the Asians than expected own their own houses,

taking occupation into account. This lends weight to the hypothesis that the Asian community places value on owning one's own house.

So the apparent affluence in the large number of Asian patients who own their own house may be more a reflection on the aspirations of the Asian immigrant population, than representing an equal ability to earn. This desire to purchase housing may give a misleading impression of affluence. It is important to also remember that most of the patients in the study were women, and in the vast majority of households, theirs may be the second salary. Information about the affluence and occupation of partners was not gathered.

The apparent difference in patients classing themselves as 'retired', and 'unable to work because of illness or disability', may not just be due to the higher prevalence of manual work in the Asian group. The Caucasian patients classed themselves as 'retired', which might imply that they were more accepting of their disability, and had taken early retirement. The Asian patients classified themselves as unable to work because of disability or illness. As the patients were age equivalent, it may be that the Asian patients were feeling a greater pressure to contribute financially at home and thus more frustrated. This, in turn, may contribute to their feelings of helplessness, which may predispose to depression. However, it may be that the Caucasians were 'giving up' by retiring early, which could imply a similarly negative mindset.

4. 4. 6. Utilisation Of Social Services

This study showed that the Asian patients received more support from the Leicestershire social services than the Caucasian patients. Qualification for various forms of social services support in the UK depends notably on assessment of disability. The Asian patients had significantly higher disability scores, so it might be expected that they would therefore qualify for more social services support. Other studies have suggested that Asian patients in the UK underutilise social services (Sin 2006). A study of elderly Gujaratis living in Leicester showed that they had poor knowledge of social services, and were unlikely to be successful in applying for services (Lindesay, Jagger et al. 1997). This finding was not replicated in this study. It may be that the impact of one adult member of the family out of work is highly significant in this younger group of patients. It has already been established that they are likely to own their own home, and yet are likely to have low income jobs. A mortgage to support may mean that they are more likely to seek financial help from social services.

This reliance on social services, while necessary, may contribute to feelings of worthlessness and helplessness, compounding their frustration at not being able to work. These negative cognitions may predispose towards depressive mood.

CHAPTER 5. RHEUMATOID DISEASE ACTIVITY AND SEVERITY

5. 1. BACKGROUND

122 patients, 61 Gujarati and 61 Caucasian subjects with RA who were age, sex and disease duration equivalent (revised data set as described in section 3.10.2) were recruited, interviewed and examined by the author as described in chapter 3. Blood was drawn and analysed for markers of inflammation as described in the relevant chapter. The results were gathered and analysed as reported. Non parametric testing was more suitable, as the sample sizes were small, and much of the data was skewed (e.g. EMS had a skewedness value of 1.92 for the Gujarati group), rather than normally distributed. Non parametric testing does not assume normality, and is therefore a more appropriate test for the data. The means and standard deviations are reported in the text, as they proved to be useful measures despite the lack of normal distribution. The median and interquartile values, though appropriate for skewed data, did not prove as helpful in analysing the data.

5. 2. DISEASE STATUS AND SEVERITY

5. 2. 1. Age Of Onset And Diagnostic Delay

The mean age of disease onset was 42.0 (sd: 10.9) years in the Asian patients, with a range of 23 to 65 years, and 46.3 (sd: 13.5) years in the Caucasians, with a range of 9 to 69 years (table 13).

The Asian patients were significantly more likely to have an earlier age of disease onset than the Caucasian patients (mean difference 4.34; 95% confidence interval -0.05 to 8.74, p=0.014, Mann-Whitney U). This significantly earlier age of disease onset in the Asian patients is interesting, as it occurred despite correcting for age in the revised group.

The Asian patients tended to have a longer delay from onset of symptoms to when the diagnosis was made than the Caucasian patients (mean difference 11.78 months; 95% confidence interval -0.30 to 14.65), but this was not statistically significant. This shows that the reason for the older age of onset in the Caucasian group was not because of a delay in referral or diagnosis.

Table 13. Age Of Disease Onset And Diagnostic Delay In Caucasian And Gujarati Patients

Variable	Gujarati mean	Standard deviation	Caucasian mean	Standard deviation	*P* value (Mann-Whitney U)
Age of disease onset / years	41.97	10.91	46.3	13.47	**0.014**
Diagnostic delay / months	18.95	25.47	11.78	14.86	0.094

5. 2. 2. Markers Of Disease Severity

The Caucasian patients had a significantly greater swollen joint count than the Asian patients, (p=0.05, Mann-Whitney U, table 14). They were significantly more likely to have nodules, with 46% Caucasians having nodules compared with 16% of Gujarati patients (difference 29.5%; 95% confidence interval 14% to 45%, p=0.0005, chi-squared, fig 7). Caucasians were also significantly likely to be seropositive for Rheumatoid Factor, with 66% Caucasians being seropositive compared with only 45% Asians (difference 21%; 95% confidence interval 4% to 39%, p=0.02, chi-squared). There was no appreciable difference in deformities between the two groups, with each group likely to have a mean of 6 deformities. The Asian patients were more likely to have longer early morning stiffness, with a mean of 1.36 hours compared to a Caucasian mean of 0.86 hours. This was significantly different (difference 0.50; 95% confidence interval 0.04 to 0.96,

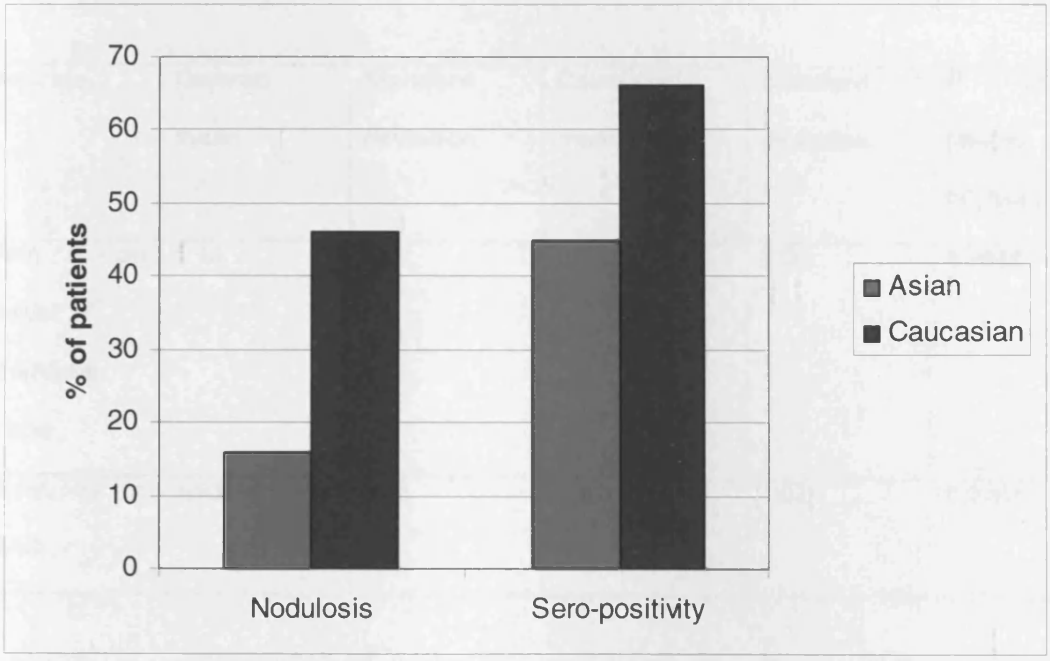
p=0.03, Mann-Whitney U). The Asian patients also had a higher plasma viscosity, with 1.77 mean compared to a Caucasian mean of 1.7 (difference 0.07; 95% confidence interval 0.02 to 0.13). This also was significant p=0.003, Mann-Whitney U test. Non-parametric testing was used as with smaller groups, there is greater risk of the data being skewed, and so it is a more suitable test as it does not assume normality.

Thirty-six percent of both groups (22/61) had a family history of RA.

Table 14. Disease Severity Characteristics In Caucasian And Gujarati Patients

Variable	Gujarati mean	Standard deviation	Caucasian mean	Standard deviation	*P* value (Mann-Whitney U)
Early morning stiffness / hours	1.36	1.40	0.86	1.14	**0.032**
Swollen joint count	8.07	4.86	10.39	6.69	**0.050**
Number of deformities	6.05	6.08	6.21	5.65	0.70
Plasma viscosity	1.78	0.16	1.70	0.13	**0.003**
Categorical variables	**Gujarati No.**	**%**	**Caucasian No.**	**%**	***P* value (χ^2)**
Presence of nodules	10	16	28	46	**0.0005**
Rheumatoid factor seropositivity	27	45	40	66	**0.018**
Presence of family history	22	36	22	36	1.00

Fig 7. Bar Chart Showing Percentage Of Patients With Nodules Present, And With Positive Rheumatoid Factor In Gujarati And Caucasian Patients



5. 2. 3. Pain And Disability

There were also highly significant differences in pain, measured on a visual analogue scale, and disability, as measured by the HAQ (table 15). Asian patients with RA had a significantly higher pain scores (mean 5.1) with respect to Caucasians (mean 3.7), p=0.0008, Mann-Whitney U (mean difference 1.40; 95% confidence interval 0.64 to 2.15). They also had a significantly higher HAQ with a mean of 1.9 to a Caucasian mean of 1.2 (p=0.0001, Mann-Whitney U, mean difference 0.72; 95% confidence interval 0.37 to 1.08) indicating worse disability.

This is despite having a lower swollen joint count, and a comparable number of deformities.

Table 15. Pain And Disability In Gujarati And Caucasian Patients

Variable	Gujarati mean	Standard deviation	Caucasian mean	Standard deviation	*P* value (Mann-Whitney U)
Pain on visual analogue scale	5.14	1.87	3.75	2.34	**0.0008**
Disability on HAQ	1.93	0.96	1.21	1.02	**0.0001**

5. 2. 4. Extra-Articular Manifestations

There was no significant difference between the two groups in terms of the number of extra-articular manifestations (p=0.49, Mann-Whitney U). However there were some differences in the kinds of manifestations (table 16). Gujarati patients were significantly more likely to have carpal tunnel syndrome, 25% vs. 10% (p=0.03, chi-squared), and overall, they were significantly more likely to have a 'mild' type of extra-articular manifestation (mean 0.97 vs. 0.64; difference 0.33; 95% confidence interval 0.20 to 0.46). As these symptoms, particularly sicca symptoms and peripheral neuropathy were largely self reported rather than

confirmed with specific testing; this may reflect their overall malaise, rather than specific problems.

Table 16. Range Of Extra-Articular Manifestations Suffered By The Two Groups, Excluding Nodulosis

Extra-articular manifestation	**Gujarati**		**Caucasian**		***P* value (chi-squared)**
	No.	**%**	**No.**	**%**	
Pulmonary fibrosis	2	3	1	2	0.56
Pleural effusion	0	0	2	3	0.15
Pericardial effusion	0	0	2	3	0.15
Corneal melt	1	2	0	0	0.32
Vasculitic rash	2	3	3	5	0.65
Total 'severe' manifestations	5	N/A	8	N/A	0.38
Carpal tunnel syndrome	15	25	6	10	**0.032**
Sensory peripheral neuropathy	11	18	10	16	0.81
Raynaud's phenomenon	7	11	6	10	0.77
Sicca symptoms	26	43	17	28	0.09
Total 'mild' manifestations	59	N/A	39	N/A	**0.000005**

5. 2. 5. Other Surrogate Markers

Haemoglobin (Hb), platelet and albumin are also surrogate markers for disease activity (table 17). They may be less useful in these communities, where the diets are so different between the two groups. This is because diet may also have a significant impact on Hb and albumin. It is interesting to see that although the Hb is significantly lower in the Asian patients; the platelets are not significantly different, suggesting that the low Hb is less likely to be due only to disease activity.

Table 17. Haemoglobin, Platelet, Albumin As Surrogate Markers Of Disease Activity In The Gujarati And Caucasian Patients

Blood markers	**Gujarati**	**Caucasian**	***P* value (Mann-Whitney U)**
Haemoglobin (g/dl)	11.7	12.5	**0.00012**
Platelets (x10 9/l)	332	300	0.18
Albumin (g/l)	40.9	40.9	0.86

5. 3. DISEASE SEVERITY: DISCUSSION

5. 3. 1. Traditional Disease Severity Markers: Are They Found In A Gujarati Population?

Disease severity is related to several indicators in a population. Seropositivity for rheumatoid factor, presence of nodules and high inflammatory markers have all been shown to indicate more severe disease, as discussed previously in chapter 1.3.2. This study showed that RA in a white ethnically British group is different in comparison to RA in an ethnically Gujarati group of patients, living in the same geographical location. The Gujarati patients seem to have a distinct phenotype of the illness. They have less seropositivity, less nodulosis, and less swollen joints. In a white Northern European population, or a white British population, this would be expected to correlate with milder disease. These findings echo research done in a similar immigrant population in another city in the UK, Leeds (Griffiths, Situnayake et al. 2000). This only partially correlates with research in Northern India, where Malaviya found that patients have less nodules, less vasculitis, and 'a milder form of joint disease' (Malaviya, Mehra et al. 1983), but equivalent seropositivity. He also found less extra-articular features in his North Indian population, in comparison to a British population. The Gujarati patients in this study had less severe extra-articular features than the Caucasian cohort, supporting Malaviya's findings.

The Asian patients had a significantly earlier disease onset than the Caucasian patients. Studies have shown that late onset RA may be just as damaging as early RA (Pease, Bhakta et al. 1999), so this is not an advantage for the Caucasians. The longer early morning stiffness of the Asians may also be misleading. It may be a marker of function, and therefore explicable by their HAQ scores, rather than as a marker of inflammation (Yazici, Pincus et al. 2004).

5. 3. 2. Are Surrogate Markers Helpful In Assessing Severity In This Group Of Patients?

The Asian patients did have a significantly higher plasma viscosity. Inflammatory markers are used as surrogate markers for disease activity. Plasma viscosity is a relatively non-specific tool to measure inflammation, and can be altered by immunoglobulin levels in the blood, which were not measured. There are age related differences in inflammatory markers, but these populations were age matched. It is possible that the normal range in the Asian population may not be that of an ethnically Northern European population. ESR is high in healthy African populations, both in Africa (Bester, Weich et al. 1993) and America (Gillum 1993).

The same holds true for the relevance of the significantly lower haemoglobin count in the Gujarati patients. While it may represent an increased disease activity, there is evidence that Gujarati women, in particular, are likely to be

anaemic, independent of disease (Chapple 1998). It is unclear what factors influence anaemia in this community, but is thought to be partially related to cultural beliefs around nutrition, including a vegetarian diet. As such, it seems that low haemoglobin levels cannot be used as a surrogate marker for disease activity in Gujarati patients with RA, unless compared directly to healthy members of the same community, rather than with Caucasian norms. So both low haemoglobin and a high plasma viscosity may be difficult to interpret as markers for disease activity in this population. It is notable that platelet count, another surrogate marker for inflammation, was not significantly elevated.

5. 3. 3. Pain, Disability And Potential Confounders

The data seems somewhat conflicting – there are both factors arguing a 'milder' phenotype, and factors suggesting a more severe phenotype. It would be expected that if the Asian patients have a 'milder' phenotype of the disease, that they would have less pain, and less disability associated with their disease, and thus would be better at coping with the illness.

However, the evidence of this study does not bear this out. The Gujarati patients have significantly more pain, and significantly more disability, and as such, their experience of disease has significantly more impact on their lives than on the lives of the Caucasian patients. There is evidence that there is ethnic variability in pain responses that may be due to polymorphism of pain receptor subtypes (Kim,

Neubert et al. 2004). Watson et al in Leicester showed that healthy South Asians had a lower heat pain threshold, and demonstrated higher pain reports than matched White British subjects (Watson, Latif et al. 2005). An excess of pain response was also found in South Indian males when injected intra-dermally with capsaicin, in comparison to Caucasian controls (Gazerani and Arendt-Nielsen 2005). This suggests that South Asians may have greater sensitivity to pain than Caucasians. This may partially explain their greater pain scores, despite their lower swollen joint counts. This may also partially explain the high frequency of generalised musculoskeletal pain found in South Asian communities in the UK (Allison, Symmons et al. 2002).

Pain and disability are complex issues, and may be influenced by more than just disease activity, and there are many confounding factors. They may predict depression, and a 2 year longitudinal study showed that pain and disability may account for ~25% of the variance in depression (Smedstad, Vaglum et al. 1997). Gujarati patients are significantly more disabled, and their higher pain levels may contribute to their disability. HAQ scores have been shown to be a sensitive indicator of disease activity, pain and psychological factors (Wolfe 2000), but there is disagreement as to how each interlinking factor affects the others, and to what degree. One study found that 33% disability was explained by disease severity, and 20% by psychological factors (Escalante and del Rincon 1999). What is clear is that disability is not merely a function dependent on joint damage, but a complex mesh of physical and psychological factors. In the

Gujarati patients, disability may not just reflect their joint disease, but also their pain, ability to cope and helplessness. Coping is a concept that refers to an individual's strategies in dealing with disease, and helplessness is their perceived lack of control. Covic et al showed that disability, helplessness and passive coping had a significant impact on levels of pain and depression in RA (Covic, Adamson et al. 2003).

A more detailed analysis of the factors that may influence disability in this group of patients can be found in chapter 10.

CHAPTER 6. HLA TYPING IN THE GUJARATI AND CAUCASIAN RA PATIENTS

6. 1. BACKGROUND

98 RA patients with RA, 39 Asian and 59 Caucasian subjects were recruited as described in chapter 3.10. These patients had blood taken to be tested for HLA (see section 1.4.3 to 1.4.7). Local Ethics Committee approval was sought and granted specifically for HLA testing.

Patients were specifically consented for HLA testing and blood was taken into an ethylenediaminetetraacetic acid (EDTA) tube to anti-coagulate. HLA testing was done by the investigator at the National Blood Centre at Sheffield. This was done in collaboration with the staff there, after training by Dr David Smillie, the Deputy Director. HLA typing was carried out by polymerase chain reaction amplification with sequence specific primers (PCR-SSP) (Olerup 1992; Bunce 1995).

6. 2. PROCESSING THE BLOOD SAMPLES

6. 2. 1. DNA Extraction

Deoxyribonucleic acid (DNA) was extracted by using the QIAGEN®, or QIAamp® DNA Mini Kit. This is a commercial kit available from Qiagen Ltd (Crawley, West

Sussex). Because this is a commercial kit, the exact components of the various reagents are unknown, and are thus referred to by their commercial names.

200ul anticoagulated blood from an EDTA sample was placed in a 1.5 ml microcentrifuge tube, and 200 µl lysis buffer (called 'AL' in the kit) and 20 µl 'Proteinase K' from the QIAGEN® kit was added. This was mixed by vortexing for 15 seconds, and then the tubes were incubated at 56°C for 10 to 15 minutes. 200 µl of Ethanol (Absolute) was then added to each tube, and mixed thoroughly by vortexing.

The labelled QIAGEN column was placed in a clean 2 ml collecting tube and the lysed sample was carefully added, keeping the rim of the column clean. This was spun for 1 minute at 6000rpm, and the collecting tube and its contents were then discarded. The column was placed in a clean 2 ml collecting tube, and 500 µl binding buffer was added (also from the Quigen kit, called 'AW1'). This was spun at 6000 rpm for 1 minute, and again the collecting tube and its contents were discarded. The column was again placed in a clean collecting tube, and 500 µl of a second binding buffer, called 'AW2' was added. This time it was spun for 3 minutes at 13000 rpm. The collecting tube and contents were again discarded. The column was then placed in a labelled 1.5 ml microcentrifuge tube, and 200 µl of sterile filtered distilled water was added to elute the DNA. After 5 minutes at room temperature, it was spun at 6000 rpm for 1 minute, and the eluted DNA was collected in the microcentrifuge tube.

6. 2. 2. HLA Analysis

Polymerase chain reactions included 10 picomoles of each sequence specific primer, 75 milimoles 2-Amino-2-(hydroxymethyl)-1,3-propanediol, hydrochloride (Tris-HCl) pH 8.8, 20 milimoles ammonium sulphate, 0.01% polyoxyethylene (20) sorbitan monolaurate (Tween® 20), 2% Ficoll® (a hydrophilic polysaccharide made by GE Healthcare), Cresol Red (a triarylmethane dye), 1.75 milimoles magnesium chloride, 200 micromoles deoxynucleoside triphosphates (manufacturers: ABgene), 0.5 units of DNA polymerase (ABgene) and 4 microlitres of genomic DNA (extracted as described), in a total volume of 10 microlitres.

Each well in a 96 well prepared dried thermal cycler plate contained 10 microlitres, as described above. SSP mixes for allele groups are shown in table 18 and sequences for individual primers are shown in table 19. HLA DQ was tested by default, as it was part of the plate, but the results were not relevant to this study. The total volume in each well was then 10µl. The plates were spun briefly, at 2000 rpm for 30 seconds, and then sealed with the correct rubber lid. These plates were then put into the thermal cycler (GeneAmp® PCR 9700) and subjected to polymerase chain reaction (PCR).

The thermal cycling parameters were as shown in table 20.

Table 18. PCR-SSP Primer Set for DRB1 and DQB1

PCR-SSP Primer Set: DRB1 and DQB1 (Low Resolution)				
Reaction	**HLA Alleles**	**Product size**	**Primer F**	**Primer R**
1	DRB1*01	255	5' 01	3' 047/3' 048
2	DRB1*15	197	5' 02	3' 01
3	DRB1*0103, 16	213/196(103)	5' 01/5' 02	3' 02/3' 10
4	DRB1*0301, 0302, 0303	151	5' 03	3' 03
5	DRB1*0301, 0304	217	5' 06	3' 048
6	DRB1*04	260	5' 04	3' 047/3' 048
7	DRB1*11	179	5' 05	3' 06M
8	DRB1*12	248	5' 08	3' 08
9	DRB1*1301, 1302	130	5'03	3' 10
10	DRB1*1303, 1304	171	5' 05	3' 045
11	DRB1*14	224	5' 05/5' 08	3'11
12	DRB1*07	232	5'07	3'079
13	DRB1*08	214	5'08	3'05
14	DRB1*09	236	5'09	3'079
15	DRB1*10	204	5' 10	3' 047
16	DRB1*0302, 1302, 1305, 1402, 1403	189	5' 03	3' 047
17	DQB1*0201, 0202	205	Q5' 07	Q3' 07
18	DQB1*0301	122	Q5' 09	Q3' 09
19	DQB1*0302, 0305	119	8A	Q3' 08
20	DQB1*0301, 0302, (0303)	141	DQBAMPA	Q3' 09
21	DQB1*0401, 0402	201	4A	4B
22	DQB1*0501, 0502, 0503	143	5A	5B
23	DQB1*06011, 06012, 0602, 0603	248/139	6.1 + 6.2/3	6B
24	DQB1*0603, 0604, 06051, 06052, 0607, 0608, 0609	175	6.3-8A	6.3-8B

Table 19. HLA-DRB1 Primer Sequences

HLA-DRB1 Sense Primers			
Primer	**5'Exon 2**		**3' Exon 2**
5' 01	109	TTG TGG CAG CTT AAG TTT GAA T	130
5' 02	107	TCC TGT GGC AGC CTA AGA G	125
5 ' 03	175	TAC TTC CAT AAC CAG GAG GAG A	196
5' 04	104	GTT TCT TGG AGC AGG TTA AAC A	125
5' 05	104	GTT TCT TGG AGT ACT CTA CGT C	125
5' 06	147	GAC GGA GCG GGT GCG GTA	164
5' 07	108	CCT GTG GCA GGG TAA GTA TA	127
5' 08	113	AGT ACT CTA CGG GTG AGT GTT	133
5' 09	104	GTT TCT TGA AGC AGG ATA AGT TT	126
5' 10	160	CGG TTG CTG GAA AGA CGC G	178
HLA-DRB1 Anti-Sense Primers			
3' 01	303	CCG CGC CTG CTC CAG GAT	286
3' 02	319	AGG TGT CCA CCG CGG CG	303
3' 03	325	TGC AGT AGT TGT CCA CCC G	307
3' 045	274	TGT TCC AGT ACT CGG CGC T	256
3' 047	363	CTG CAC TGT GAA GCT CTC AC	344
3' 048	363	CTG CAC TGT GAA GCT CTC CA	344
3' 05	326	CTG CAG TAG GTG TCC ACC AG	307
3' 06M	276	GCT GTT CCA GTA CTC CTC AT	257
3' 079	339	CCC GTA GTT GTG TCT GCA CAC	319
3' 08	360	CAC TGT GAA GCT CTC CAC AG	341
3' 10	304	CCC GCT CGT CTT CCA GGA T	286
3' 11	327	TCT GCA ATA GGT GTC CAC CT	308

Table 20. Thermal Cycling Parameters For PCR Programme On Thermal Cycler

Temperature	Duration	Number of cycles
96°	60 seconds	1
96° 70° 72°	25 seconds 45 seconds 30 seconds	5
96° 65° 72°	25 seconds 45 seconds 30 seconds	21
96° 55° 72°	25 seconds 60 seconds 120 seconds	4
72°	10 mins	1
4°	∞	

Following PCR, 10µl of PCR product from each well were transferred to wells in a 1.5% agarose gel (standard grade from CLP; www.clpdirect.com) and electrophoresed for 20 minutes at 150 volts to ascertain which HLA types were present. Photos of the finished gels were taken using an ultraviolet transilluminator and gel documentation system (Alphaimager 1200, Alpha Innotech). The photo was attached to the appropriate protocol to be studied for typing (see fig 8). HLA type was determined by the presence (or absence) of PCR amplicons of appropriate size in allele specific PCR.

6. 2. 3. HLA typing: Specificity And Limitations of Low Resolution Testing

Low resolution HLA typing was used. This means that typing was not able to differentiate between the subtypes of each DRB1 allele, for example, although HLA DRB1*04 could be identified, the difference between *0401 and *0404 could not (see section 1.4.3 for list of alleles containing shared epitope). If the frequency of HLA DRB1 alleles that did not contain the shared epitope was higher than the frequency of those that did contain the shared epitope, it is possible that false conclusions about the frequency of the shared epitope in the population studied would be reached. The frequency of shared epitope alleles with respect to alleles that do not contain the shared epitope can be examined by looking at results of allele frequencies in the general population.

The frequency of the alleles which contain the shared epitope in the general population is far higher than the frequency of the alleles that do not. In the British Caucasian population, the phenotype frequency of *0101 is 19.8%, while the allele frequency is 0.102 (Doherty, Vaughan et al. 1992). The phenotype frequency of *0102 in the same study was 1.1% (allele frequency 0.006). The only other *01 allele found was *0103, which had a phenotype frequency of 5.1% (allele frequency 0.025). *0103 is one of the few alleles which can be identified on the low resolution kit, so is less likely to cause false positives. Other *01 allele subtypes were not found at all in the British population.

A similar picture is found in the *04 subtypes. The same study found a phenotype frequency of 25.1% for *0401 (allele frequency 0.124), 7.6% for *0404 and 4% for *0405. *04 alleles which do not contain the shared epitope had frequencies of 0.8% (*0402) and 3.9% (*0403). Other *04 alleles were <1% or not found. Again, the frequency of shared epitope alleles in the general population means that an *04 is significantly more likely to be a shared epitope containing *04 than one that does not. There was no data for background frequencies of *10 or *14 subtypes.

There is little data for background frequencies of HLA DRB1 subtypes in immigrant Asian communities in Britain. It tends to be in small biased groups, such as renal failure patients. There is some population data from India. This is not from Gujarat. The closest area that had been studied was Northern Hindu populations around Lucknow (Rajalingam, Krausa et al. 2002). The allele frequencies recorded in these populations may not be able to be extrapolated to the immigrant Gujarati population. This study showed an allele frequency for HLA DRB1*0101 of 0.028, but no recorded frequencies for any other *01 subtype. There was no evidence of any *10 or *14 subtypes, but there was some evidence for *04 subtypes. *0404 had an allele frequency of 0.026, and *0401 of 0.009, with *0405 of 0.005. These frequencies are substantially lower than the background Caucasian frequencies. Non shared epitope *04 allele subtypes all had frequencies less than 0.01, other than *0403, which had an allele frequency of 0.037. These background frequencies may not be relevant to the Leicester Gujarati immigrants, so it is harder to draw conclusions about the frequency of

shared epitope alleles in the study population. An assumption has been made that the alleles found are likely to be those containing the shared epitope, but without further testing and more knowledge of the background allele frequencies in this very specific population it is difficult to be certain. The results should therefore be interpreted with some caution.

FRM/SHE/DI/115/03

HISTOCOMPATIBILTY LABORATORY NBS SHEFFIELD

BKB115 (L)

HLA-DRB1* AND DQB1* ALLELES BY PCR-SSP

NAME 39

LAB NO 14.02

HLA-DRB1* 02,03

HLA-DQB1*

		MW
1	DRB1*0101-0108	254
2	DRB1*1501-1511	196/258
3	DRB1*0103, DRB1*1601/02/03/05/07/08, DRB1*1510	195/212
4	DRB1*0301- 0320 (NOT DRB1*0304/09/11/14/15/17)	150
5	DRB1*0301-29 (NOT 0302/03/05/07/09/14/17), DRB1*1327	216
6	DRB1*0401-42 (NOT 0423/34), *DRB1*1122*, DRB1*1410	259
7	DRB1*1101-42 (NOT 1105/22/30/31/33/35/36/38), DRB1*0308	172
8	DRB1*1201-1208 (NOT 1203), DRB1*0812/22, DRB1*1428	247
9	DRB1*1301/02/06/10/15/16/27/28/31/32/34/36/39-41, DRB1*1116/20	129
10	DRB1*1303/04/12/13/21/30/32/33/38/48/49, DRB1*0312, DRB1*1413	170
11	DRB1*1401/04/05/07/08/11/14/16/23/26/28/33/35/36, DRB1*1117	223
12	DRB1*07011/03/05	231
13	DRB1*0801-0823 (NOT 0805/14/18/20/21), DRB1*1415	213
14	DRB1*09012	235
15	DRB1*1001	203
16	DRB1*0302/05/14,DRB1*1109/20,DRB1*1302/05/26/29/31/34/36/39/41, DRB1*1402/03/09/13/19/24/27/30, DRB1*010	186
17	DQB1*0201-03	204
18	DQB1*0301/06/10	121
19	DQB1*0302/07/08	118
20	DQB1*0301/03-06/09/10 (& DQB1*0302)	140
21	DQB1*0401/02	207
22	DQB1*0501-04, DQB1*0305	143
23	DQB1*0601/012/013/02/03/08/10/11/13/14/16	246/139
24	DQB1*0603/041/042/051/052/07-09/ 06112/12/14/17	175

DATE

DNA PREPARATION

PCR SET UP

GEL BATCH NO

GEL RUN

PHOTO/IMAGE

INTERPRETATION

HITS TEST REQUEST NUMBER

PCR-SSP BATCH LABEL

ALLELE ASSIGNMENT UPDATED 07/2001. REFER TO SEQUENCE ALIGNMENTS FOR CURRENT INFORMATION

ALLELES IN ITALICS HAVE INCOMPLETE SEQUENCES WHERE PRIMERS ARE LOCATED

Fig 8. Example Of Photograph Of Finished Gel Strip Attached To Protocol For Typing

6. 3. RESULTS OF HLA TYPING

6. 3. 1 Statistical Analysis

The data was analysed using SPSS version 12.0. Non-parametric testing was used as the groups were small, and so unlikely to be normally distributed. The test used to analyse the data was chi-squared, unless specifically mentioned in the text. A p value of <0.05 was taken as representing a statistically significant difference between the parameters under analysis.

6.3.2 Results of HLA Typing For Individual Patients

Full results of all the HLA typing are listed in table 21, with the associated dose of shared epitope. Presence of nodules and seropositivity for RF is also listed.

Table 21. Results of HLA DRB1 Loci Typing In Patients With RA, Associated With Clinical Findings

Ethnic Group	HLA DRB1 Allele Types		Shared epitope	Seropositivity	Nodules
Gujarati	*15	*10	1	N	N
Gujarati	*15	*15	0	Y	N
Gujarati	*15	*0301	0	Y	N
Gujarati	*10	*07	1	N	N
Gujarati	*04	*11	1	Y	N
Gujarati	*16	*04	1	N	N
Gujarati	*07	*07	0	N	N
Gujarati	*15	*10	1	Y	N
Gujarati	*15	*07	0	N	N
Gujarati	*15	*15	0	N	N
Gujarati	*08	*10	1	N	N
Gujarati	*11	*04	1	Y	N
Gujarati	*15	*10	1	Y	Y
Gujarati	*0301	*10	1	N	N
Gujarati	*04	*11	1	Y	Y
Gujarati	*10	*10	2	N	N
Gujarati	*0301	*10	1	Y	N
Gujarati	*0301	*11	0	N	N
Gujarati	*15	*12	0	Y	Y
Gujarati	*14	*13	1	Y	N
Gujarati	*04	*07	1	Y	N
Gujarati	*15	*13	0	N	N
Gujarati	*15	*13	0	Y	N
Gujarati	*04	*11	1	Y	N
Gujarati	*15	*15	0	N	N
Gujarati	*11	*14	1	N	Y
Gujarati	*11	*13	0	Y	Y
Gujarati	*15	*11	0	N	N
Gujarati	*11	*10	1	N	N
Gujarati	*04	*10	2	Y	N
Gujarati	*15	*11	0	N	N
Gujarati	*07	*10	1	Y	N
Gujarati	*04	*04	2	N	N
Gujarati	*14	*10	2	Y	N
Gujarati	*10	*11	1	N	Y
Gujarati	*10	*01	2	N	N
Gujarati	*14	*07	1	N	N
Gujarati	*15	*10	1	Y	N
Gujarati	*15	*1302	0	Y	N
Caucasian	*0301	*09	0	Y	Y
Caucasian	*15	*11	0	Y	Y
Caucasian	*04	*07	1	N	N
Caucasian	*04	*04	2	N	Y
Caucasian	*04	*12	1	Y	Y
Caucasian	*07	*09	0	Y	N

Continuation of table 22

Ethnic Group	HLA DRB1 Allele Types		Shared epitope	Seropositivity	Nodules
Caucasian	*01	*0301	1	N	N
Caucasian	*0301	*11	0	Y	Y
Caucasian	*15	*04	1	Y	Y
Caucasian	*01	*0103	1	Y	Y
Caucasian	*01	*04	2	Y	N
Caucasian	*04	*0301	1	Y	Y
Caucasian	*04	*07	1	Y	N
Caucasian	*01	*07	1	Y	Y
Caucasian	*15	*04	1	N	Y
Caucasian	*07	*07	0	Y	N
Caucasian	*0301	*04	1	Y	Y
Caucasian	*15	*04	1	Y	Y
Caucasian	*01	*15	1	Y	N
Caucasian	*03	*09	0	Y	N
Caucasian	*04	*04	2	Y	Y
Caucasian	*01	*15	1	Y	N
Caucasian	*0301	*08	0	Y	N
Caucasian	*04	*1301	1	Y	N
Caucasian	*0103	*0301	0	Y	Y
Caucasian	*04	*11	1	Y	Y
Caucasian	*04	*04	2	Y	N
Caucasian	*04	*07	1	N	N
Caucasian	*15	*04	1	Y	Y
Caucasian	*01	*15	1	Y	N
Caucasian	*04	*07	1	N	N
Caucasian	*01	*0301	1	N	N
Caucasian	*01	*04	2	Y	N
Caucasian	*04	*04	2	N	N
Caucasian	*15	*07	0	N	N
Caucasian	*04	*09	1	Y	N
Caucasian	*01	*10	2	Y	Y
Caucasian	*04	*04	2		Y
Caucasian	*04	*04	2	Y	Y
Caucasian	*01	*15	1	N	N
Caucasian	*04	*1301	1	N	N
Caucasian	*0301	*14	0	N	Y
Caucasian	*0301	*04	1	Y	N
Caucasian	*15	*04	1	Y	Y
Caucasian	*04	*04	2	N	N
Caucasian	*01	*04	2	N	N
Caucasian	*04	*04	2	N	N
Caucasian	*0301	*10	1	Y	Y
Caucasian	*0103	*12	0	N	N
Caucasian	*01	*04	2	N	N
Caucasian	*15	*04	1	Y	Y
Caucasian	*01	*15	1	N	N
Caucasian	*15	*04	1	N	N
Caucasian	*11	*12	0	Y	Y
Caucasian	*0301	*04	1	N	N
Caucasian	*01	*10	2	Y	Y
Caucasian	*15	*04	1	N	N
Caucasian	*15	*04	1	N	N
Caucasian	*01	*15	1	Y	N

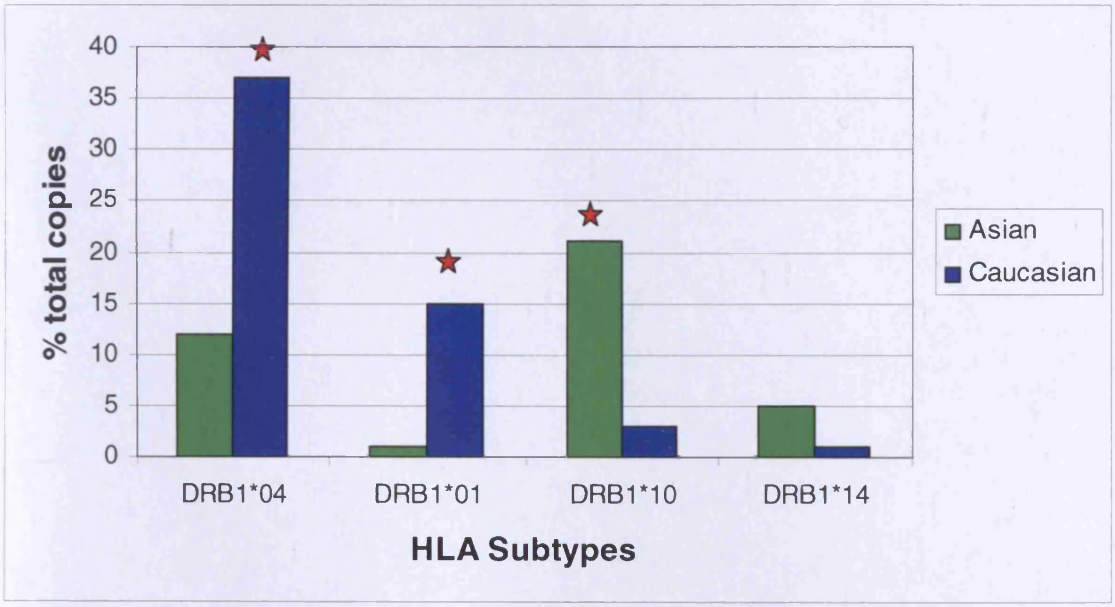
6.3.3 Differences In The Frequency Of The Shared Epitope And HLA Type

There were significant differences in both the frequency of the shared epitope, and the types of HLA DRB1 subtype found in Gujarati Asian and Caucasian patients with RA (table 22, fig. 9). Gujarati Asians were significantly more likely to express HLA DRB1*10 (χ^2, p=0.0009), and Caucasian were significantly more likely to express HLA DRB1*04 (χ^2, p=0.001) and HLA DRB1*01 (χ^2, p=0.0007). The Asian patients also had a significantly lower frequency of the shared epitope than the Caucasian patients, with a mean of 0.77 copies of the epitope per patient, in comparison to a Caucasian mean of 1.12 copies (mean difference 0.35; 95% confidence interval 0.08 to 0.63, p=0.01, Mann-Whitney U). There was no significant difference in the frequency of patients who had two copies of the shared epitope, with 13% Gujaratis compared with 22% Caucasians having 2 copies (p=0.11, χ^2).

Table 22. HLA DRB1 Subtypes In The Gujarati And Caucasian Patient Groups, And Overall Mean Frequency Of The Shared Epitope

HLA DRB1 Subtype	**Gujarati patients (n=39)**		**Caucasian patients (n=59)**		***P* value (chi-squared)**
	No. of copies	**% frequency**	**No. of copies**	**% frequency**	
DRB1*04	9	12	36	31	**0.001**
DRB1*01	1	1	15	13	**0.0007**
DRB1*10	16	21	3	3	**0.0009**
DRB1*14	4	5	1	1	0.10
Two copies of shared epitope	**No.**	**%**	**No.**	**%**	0.11
	5	13	13	22	
Mean copies of shared epitope	0.77 (sd 0.67)		1.12 (sd 0.63)		**0.013 (Mann-Whitney U)**

Fig 9. Bar chart showing percentage of specific HLA DRB1 subtypes in the Gujarati Asian and Caucasian patients



★ Represents a statistically significant difference between the two ethnic groups of $p<0.05$, see text above for exact values.

6.3.4 Do Correlations Exist Between The Presence Of Shared Epitope And Clinical Manifestations?

There was no correlation between sero-positivity for RF and presence of the shared epitope overall ($p=0.48$, chi-squared). There was also no overall correlation between presence of nodules and presence of shared epitope ($p=0.93$, chi-squared). Similarly, when just the Gujarati patients, or just the

Caucasian patients were examined, there was still no correlation between presence of shared epitope and either sero-positivity (p=0.4 or p=0.55, respectively; χ^2) or presence of nodules (p=0.73 or p=0.27 respectively; χ^2).

One way analysis of variance (ANOVA) was used to examine whether there was a relationship between dose of the shared epitope and SJC (swollen joint count) or disability as measured by the HAQ. Patients were divided in to groups according to their possession of one, two or no copies of the shared epitope. There were no statistically significant differences in SJC (F (2, 97) = 0.04, p = 0.96) or in HAQ (F (2, 97) = 0.54, p = 0.58) for the groups.

6. 4. HLA TYPING: DISCUSSION

In this study, I have used an HLA genotyping method to identify the presence of HLA DRB1 alleles associated with the shared epitope in Gujarati Asian and Caucasian patients with RA.

This study showed that Gujarati Asian patients do express HLA DRB1 alleles associated with the shared epitope, but the profile of DRB1 alleles was different to the Caucasian patients. The Gujarati RA patients had an association with HLA DRB1*10, while the Caucasian patients in our study had higher frequencies of HLA DRB1*04 and DRB1*01. This increased frequency of HLA DRB1*10 has been shown in other studies in similar populations in the UK. Griffiths et al

demonstrated a higher frequency of HLA DRB1*10 in a predominantly Punjabi population in Leeds (Griffiths, Situnayake et al. 2000). A small study in London, examining immigrants from Gujarati, the Punjab and Kashmir reported similar findings (Ollier, Stephens et al. 1991). Mody et al also showed a significant association with DRB1*10 in RA in the immigrant Hindi population living in Durban (Mody and Hammond 1994). These migrants live on the east coast of Africa, an area where there are many Gujarati immigrants, although the authors only commented on religious background rather than specific ethnicity. Studies in India itself have been largely conducted around Delhi, drawing from a range of backgrounds. Here, it is HLA DRB1*04 that has been found to be associated with RA, rather than HLA DRB1*10 (Mehra, Vaidya et al. 1982; Malaviya, Mehra et al. 1983). It is possible that the higher frequency of the HLA DRB1*10 in immigrant populations is a selection phenomenon, or that extensive testing in this particular group has yet to be performed in India.

The only other ethnic group that expresses an excess of HLA DRB1*10 in rheumatoid patients are Greek (Boki, Drosos et al. 1993; Stavropoulos, Spyopoulou et al. 1997), but the frequencies of HLA DRB1*04 or DRB1*01 are still higher than that of HLA DRB1*10 in this group, unlike the Asian patients. These patients have been shown to have milder disease than British Caucasians with RA, in that they have less inflammatory disease with less erosions (Drosos, Lanchbury et al. 1992). If allele subtypes are an important predictor or influence on clinical phenotype, it may be extrapolated that Asian patients may also have a

milder clinical picture. However, most studies have found links between frequency of shared epitope and erosions (section 1.4.5), so it is more likely that the lower frequency of the shared epitope is a more important finding than the subtype found.

HLA DRB1*04 subtypes, particularly HLA DRB1*0404 (Thomson, Harrison et al. 1999) and DRB1*0401(Gorman, Lum et al. 2004) have been implicated with increased risk of erosive disease. Erosive disease is associated with poorer clinical outcomes, such as disability (Kirwan 2001). The Caucasian patients in this study had a much higher frequency of the HLA DRB1*04 alleles, and therefore might be expected to demonstrate more disability than the Asians. The HLA typing would fit with an expectation that the Caucasian patients might have more severe disease. This expectation of more severe disease is confirmed by their higher joint counts, frequency of seropositivity and nodulosis (section 5.2.2). The Gujarati patients have a lower frequency of shared epitope positivity, and less nodules, less seropositivity for RF and less swollen joints. They have a lower incidence of the markers that usually indicate severe disease. They might therefore have been expected to have lower disability scores. This was not the case. This suggests that either other factors are influencing the disability scores of the Asian patients, or that the factors that herald severe disease in Caucasians are less relevant in a Gujarati Asian community.

The Gujarati patients had a lower frequency of alleles associated with the shared epitope than the Caucasian patients. There has been conflicting data about the contribution of the shared epitope to disease, but Gorman et al, in their large meta-analysis (Gorman, Lum et al. 2004), showed that presence of the shared epitope was related to erosive disease. They also showed that dose of shared epitope was related to erosive disease in patients from Southern Europe and South East Asia (Japan, Taiwan, Korea and Pacific Islanders), but not in Northern Europeans. In Hispanics, only patients with two copies of the shared epitope had an association with erosive disease. Gorman et al did not have any Indian studies in their meta-analysis, but this variability in impact of the shared epitope shows that a simplistic linear relationship between dose and severity of disease is the exception, rather than the rule, and is dependent on ethnicity.

In my study presence of the shared epitope was not associated with presence of RF. Other studies have failed to demonstrate a correlation between shared epitope and RF (van der Helm-van Mil 2006), but have noted a correlation with anti-CCP antibody and the shared epitope. Unfortunately, testing for anti-CCP was not available at the time of the study. Anti-CCP is found in Indian populations with RA, and predicts erosive disease (Shankar 2006). Testing anti-CCP may have allowed prediction of erosions, and may have been related to shared epitope presence, and should be considered for future studies.

In conclusion, Gujarati Asian patients with RA in Leicester had a lower frequency of alleles associated with the shared epitope than Caucasians with RA, and had expressed different allelic subtypes. Considering evidence in other ethnic groups, this might be expected to work in their favour to predispose to a milder disease phenotype. However, evidence examined in chapter 5 (sections 5.2.2 and 5.2.3) and chapter 10 seems to show that outcomes, particularly disability, are worse for the Asian patients. Shared epitope presence may be less important in Gujarati patients than in Caucasian patients in its impact on disease, with other factors being more influential in terms of disability (see chapter 10).

CHAPTER 7. TREATMENT: INTERVENTIONS AND MEDICATIONS IN GUJARATI AND CAUCASIAN PATIENTS WITH RA

7.1. BACKGROUND

122 patients, 61 Gujarati and 61 Caucasian subjects with RA (revised group, see section 3.10.2) were recruited. They were age, sex and disease duration equivalent as described in previous chapters. They had a detailed interview and review of medical notes to confirm interventions and drug treatments, particularly with reference to stopping medication. Results were analysed. Non parametric testing was more suitable, as the sample sizes were small, particularly when looking at subgroups who had taken various drugs, so much of the data was skewed, rather than normally distributed. Non parametric testing does not assume normality, and is therefore a more appropriate test for the data. The means and standard deviations are reported in the text, as they proved to be useful measures despite the lack of normal distribution.

7. 2. RESULTS: INTERVENTIONS

There was no appreciable difference between the Asian and the Caucasian patients in terms of the interventions they underwent (table 23). There was no significant difference in intra-articular injections, with the Asian having a mean of 3.9 to a Caucasian mean of 4.8 (mean difference 0.92; 95% confidence interval -

1.07 to 2.91), and no difference in the number of hospital admissions, with an Asian mean of 1.1 admissions to a Caucasian mean of 0.9 admissions (mean difference 0.23; 95% confidence interval -0.55 to 1.01). The Caucasians tended to have had more surgical procedures with a mean of 0.89 compared to an Asian mean of 0.36, but this did not reach significance (mean difference 0.53; 95% confidence interval 0.3 to1.02, p=0.07, Mann-Whitney U).

Table 23. Treatment Interventions In Gujarati And Caucasian Patients With RA

Treatment intervention	**Gujarati mean**	**Standard deviation**	**Caucasian mean**	**Standard deviation**	***P* value (Mann-Whitney U)**
Intra-articular injections	3.87	5.34	4.79	5.77	0.31
Hospital admissions	1.11	2.37	0.89	1.94	0.77
Surgical procedures	0.36	0.88	0.89	1.74	0.07

7. 3. MEDICATION

7. 3. 1. Delay In Starting A DMARD

There was no difference in the delay between diagnosis and starting DMARDs between the two groups, with most patients starting on a drug at diagnosis. There was a mean delay of 1.62 months for Caucasian patients starting

DMARDs, and of 0.59 months for Asian patients starting their first DMARD, but this was not statistically significant (mean difference 0.97 months; 95% confidence interval -0.29 to 2.23, p=0.9, Mann-Whitney U). Most of the few patients who did have a delay were diagnosed in the 1970s or 1980s, when treatment was approached differently to the late 1990s and onwards.

7. 3. 2. Range Of DMARDs Taken

Fig. 10 shows the numbers of patients who had taken each DMARD, and Table 24 shows the range of DMARDs taken by patients, the percentage who stopped because of side effects, and those who stopped because the drug was ineffective. There was only one patient who had never taken a DMARD, an Asian patient. There were no significant differences other than that significantly more patients had tried D-penicillamine, but the numbers were very small making it probable that this was a type one error. Likewise, the numbers were very small for ineffectiveness probabilities for Azathioprine and Gold, so it was difficult to draw any firm conclusions from this.

Fig 10. Graph Showing Percentage Of Patients Who Had Tried Each Different DMARD

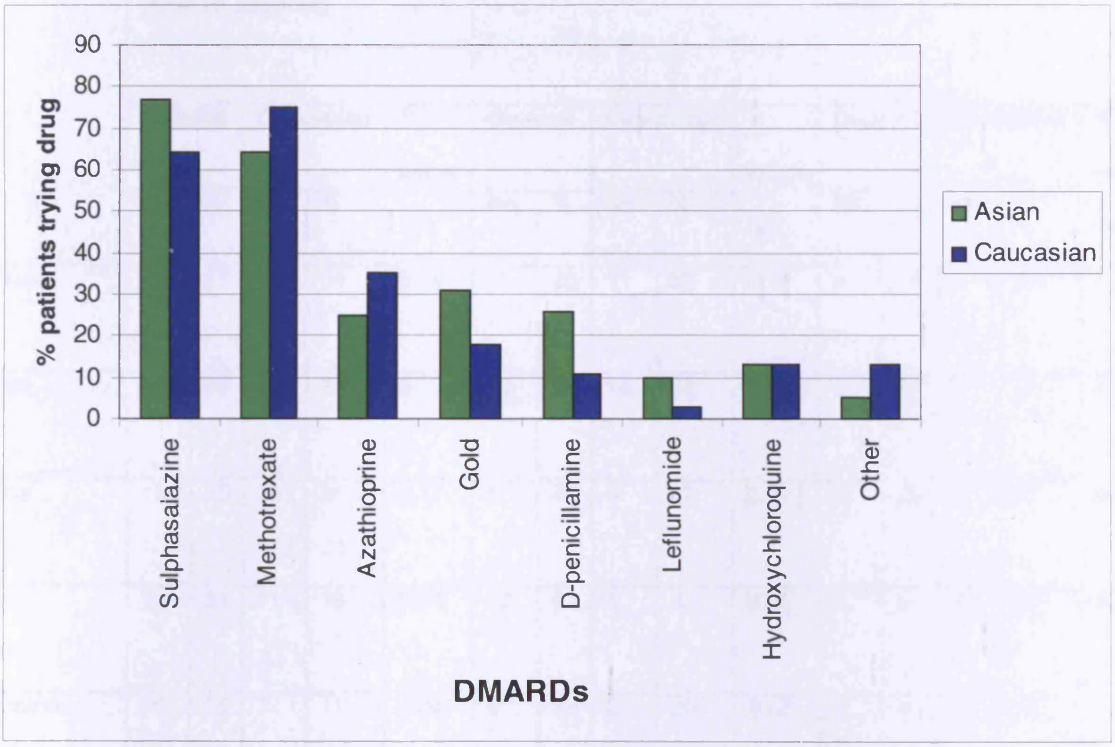


Table 24. Range of DMARDs Taken By Gujarati And Caucasian Patients

DMARDs	Patients who had ever taken drug (% of all patients)					Stopped for side effects (% of those ever taking drug)					Drug ineffective (% of those ever initiated on drug)				
	Gujarati		Caucasian		*P* value (χ^2)	Gujarati		Caucasian		*P* value (χ^2)	Gujarati		Caucasian		*P* value (χ^2)
	No.	%	No.	%		No.	%	No.	%		No.	%	No.	%	
Sulphasalazine (SSZ)	47	77	39	64	0.24	12	26	11	28	0.78	9	19	7	18	0.89
Methotrexate (MTX)	39	64	46	75	0.17	12	31	16	44	0.70	2	5	1	2	0.46
Azathioprine (AZA)	15	25	22	35	0.17	6	40	6	27	0.42	3	20	0	0	**0.03**
Gold (myocrisin)	19	31	11	18	0.09	12	63	5	45	0.35	0	0	3	27	**0.02**
D-penicillamine (D-PEN)	16	26	7	11	**0.04**	6	38	2	29	0.68	7	44	4	57	0.55
Leflunomide (LEFL)	6	10	2	3	0.14	2	33	2	100	0.10	0	0	0	0	N/A
Hydroxychloroquine (HCQ)	8	13	8	13	1.00	1	13	2	25	0.52	5	63	3	38	0.32
Other*	3	5	8	13	0.11	1	33	4	50	0.62	2	67	1	13	0.07

*The 'other' category for the Asian patients contained one patient who had had cyclosporin, which was stopped because of inefficacy, one patient who had had

cyclophosphamide, stopped because of nausea, and a patient who had had a course of an interleukin one antagonist as part of a trial.

The 'other' category for the Caucasian patients contained three patients who had had chloroquine, one who had stopped because it was ineffective, one because of blurred vision, three patients who had had cyclophosphamide, one of whom had stopped because of alopecia, one because of neutropenia, and three patients who were on anti-TNF treatment.

There was also no significant difference in the number of DMARDs that the Asian or Caucasian patients were likely to have tried (p=0.78, Mann-Whitney U, table 25).

Table 25. Number of DMARDs Gujarati Asian And Caucasian Patients Had Tried

Number of DMARDs used	Gujarati		Caucasian		*P* value comparing number of DMARDs taken (Mann-Whitney U)
	No.	%	No.	%	
None	1	2	0	0	0.78
1	16	26	15	25	
2	20	33	25	41	
3	11	18	10	16	
4	4	7	6	10	
5	6	10	5	8	
>5	3	5	0	0	

7. 3. 3. Side Effects Of DMARDs

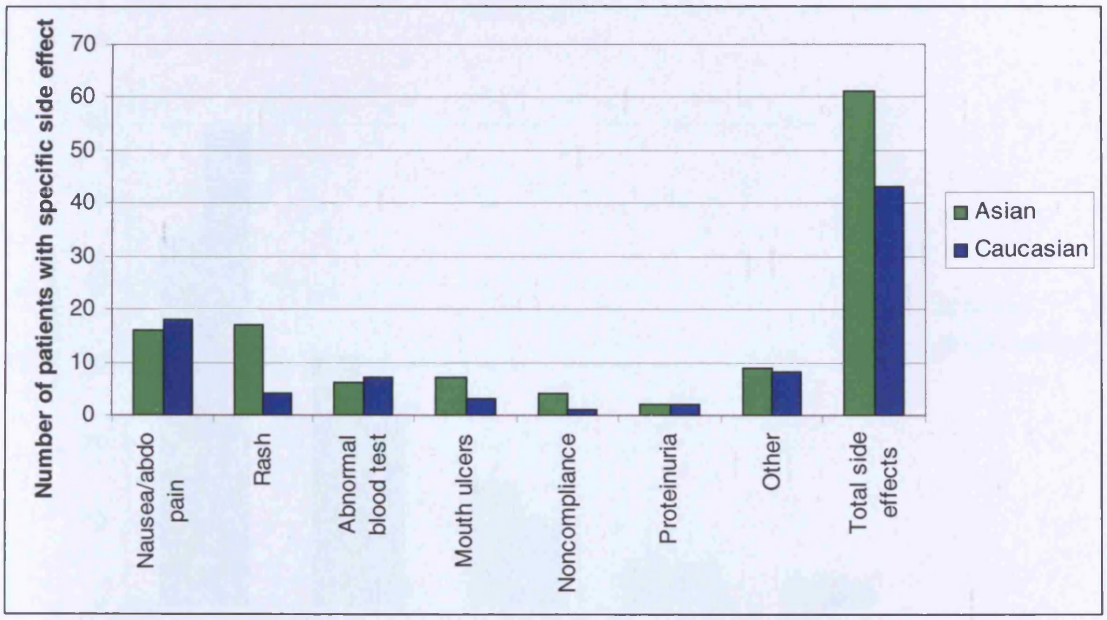
Many of the patients suffered side effects as a consequence of taking the drugs to modify their illness. Table 26 shows the number and percentage of side effects suffered by the patients.

Fig 11 represents the spread of side effects suffered by the two groups of patients. Asian patients were significantly more likely to complain of rash (28% vs. 7%, p=0.0002, chi-squared).

Table 26. Side Effects Suffered By Gujarati Patients And Caucasian Patients When Using Dmards

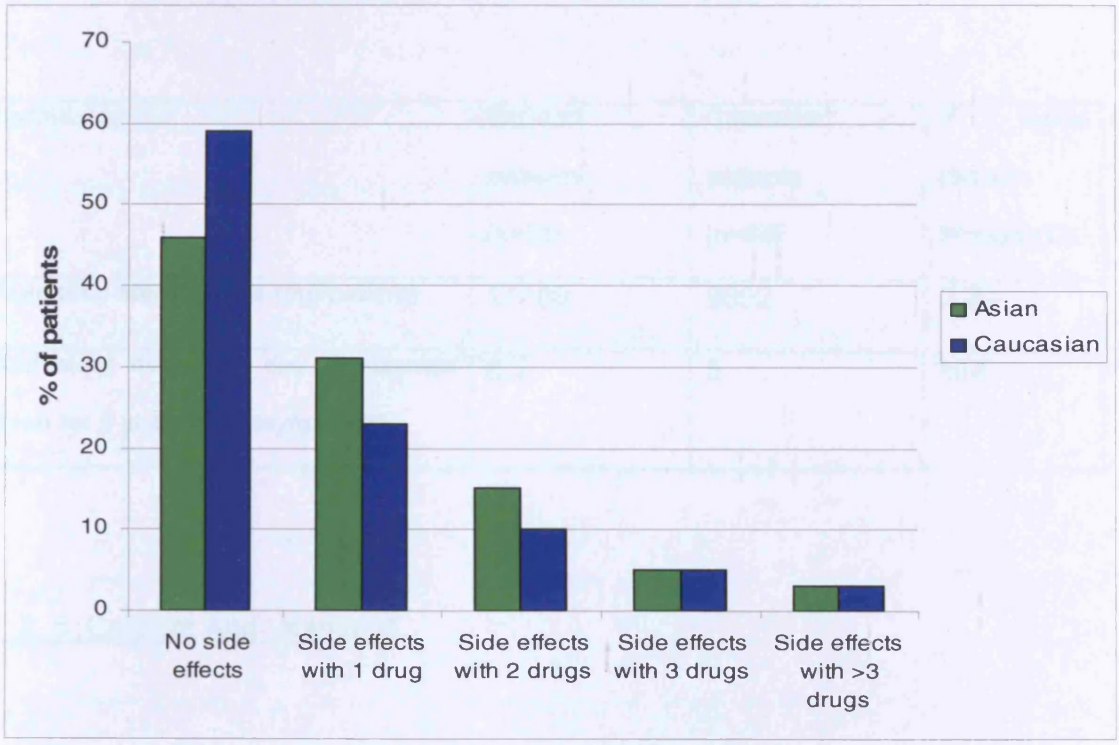
Side Effect	Gujarati		Caucasian		*P* value (chi-squared)
	No.	%	No.	%	
Nausea/ abdominal pain	16	27	18	30	0.73
Rash	17	28	4	7	**0.002**
Abnormal blood test	6	10	7	11	0.79
Mouth ulcers	7	12	3	5	0.18
Proteinuria	2	3	2	3	1.0
Non-compliance	4	7	1	2	0.17
Other	9	15	8	13	0.77

Fig 11. Spread Of Side Effects Suffered By Gujarati Asian And Caucasian Patients



Otherwise, there was little difference between the two groups. It is possible that the side effects were all down to a small minority of patients in one or other of the groups, who always experienced side effects, so fig. 12 shows the number of drugs that gave side effects for each patient. There was no significant difference between the two ethnic groups in terms of number of DMARDs that produced side effects for the patients (p= 0.20, Mann-Whitney U).

Fig 12. Percentage Of Asian And Caucasian Patients Who Had Side Effects With One Or More DMARD (*P*=0.20)



7. 3. 4. Steroid Use

In order to ascertain steroid use between the two groups, a total dose of prednisolone that each patient had taken orally was calculated (table 27). 34 Caucasian patients and 33 Asian patients had taken steroids at some point. Steroid other than prednisolone was converted to equivalent prednisolone dose. The mean dose that the Gujarati patients had taken was 11790 mg, which is equivalent to 6.5 mg od for 5 years. The mean dose that Caucasian patients had taken was 9602 mg, which is equivalent to 5mg od for 5 years. This was not

significantly different (mean difference 2188 mg; 95% confidence interval -4240 mg to 8616 mg, p=0.80, Mann-Whitney U).

Table 27. Comparison Of Gujarati And Caucasian Mean Steroid Use

Steroid dose	**Gujarati patients (n=33)**	**Caucasian patients (n=34)**	***P* value (Mann-Whitney U)**
Mean total steroid dose (mg/patient)	11789	9602	0.80
Equivalent dose per day if steroids given for 5 years (mg/day/patient)	6.5	5	N/A

7. 3. 5. Calcium And Vitamin D

10 (16%) Asian and 1 (2%) Caucasian patient were taking Calcium and vitamin D supplements. There were significantly more Asian patients taking the supplements (p=0.004, chi-squared).

7. 3. 6. Analgesic Use

Analgesia use in the two groups was also compared. This was particularly important as pain is closely linked to depression. However, there was no significant difference between the Asian and the Caucasian patients in their use

of analgesics (see table 28), despite the significantly higher pain scores of the Asian patients. 48% of the Gujarati patients and 56% of the Caucasian patients were regularly using a non-steroidal anti-inflammatory drug (NSAID), and 18% of the Asian and 15% of the Caucasian patients were using a cyclic oxygenase 2 inhibitor drug (COX-2). Some of the COX-2 drugs have since been withdrawn from sale due to their increased cardiovascular risk (Jenkins, Seligman et al. 2005). Interestingly, 25% of each group was taking no analgesics at all.

Table 28. Analgesic Use Of The Gujarati And Caucasian Patients

Analgesic use	**Gujarati patients**		**Caucasian patients**		***P* value (chi-squared)**
	No.	**%**	**No.**	**%**	
NSAID	29	48	34	56	0.37
COX-2	11	18	9	15	0.63
Neither	21	34	18	30	0.56
Paracetamol	7	11	3	5	0.19
Cocodamol	6	10	2	3	0.14
Amitriptyline	5	8	4	7	0.73
2 analgesics	6	10	2	3	0.14
No analgesics	15	25	15	25	1.0
Mean number of analgesics used	0.85 (sd 0.57)		0.79 (sd 0.49)		0.56 (Mann Whitney U)

7. 3. 7. Anti-Depressant Use

Only 2 (3%) Gujarati and 2 (3%) Caucasian patients were taking an anti-depressant as part of their medication regimen.

7. 4. COMPLIANCE

There was no significant difference in the compliance rate between the Gujarati and the Caucasian patients, with both groups self reporting excellent compliance with their medications (table 29).

Table 29. Self Reported Compliance Of Caucasian And Gujarati Patients With RA

Number of times medication is missed	**Gujarati patients**		**Caucasian patients**		***P* value comparing number of times medication missed (Mann-Whitney U)**
	No.	**%**	**No.**	**%**	
Never	38	62	38	62	
<Once a month	6	10	12	20	
Once a month	7	11	6	10	0.60
Once a week	2	3	3	5	
>Once a week	8	13	2	3	

7. 5. PERCEIVED EFFICACY OF TREATMENT

It has already been shown that there is no significant difference between the two ethnic groups in terms of their drug treatment. The greatest difference between the two groups comes not in the treatment itself, but in the perceived efficacy of that treatment. The Asian patients were significantly more likely than the Caucasian patients to score their treatment as less effective, on a simple 5 point scale of 0 to 5, where 5 was 'excellent' and 0 was 'no use at all'. The Asian mean was 3.3, which was significantly less than the Caucasian mean of 3.8 (p=0.0009, Mann-Whitney U, mean difference 0.51; 95% confidence interval 0.23 to 0.79).

7. 6. DISCUSSION OF TREATMENT:

7. 6. 1. Delays And Differences

A significant difficulty for any immigrant community is inability to access and lack of knowledge of the resources available to them in their new environment. Communication difficulties due to language and cultural barriers may compound this problem. It has been shown that in cardiovascular disease, Asian patients have inexplicable delays for specialist treatment (Feder, Crook et al. 2002). It might be expected that the Asian patients would similarly be referred later then the Caucasian patients, and have delayed treatment as a result. There is no evidence that they see their GP less than Caucasians; a large community based study in London, UK, showed that Asian men were more than twice as likely to

consult their general practitioner in the previous two weeks, independent of the presence of illness, disability, and their own health assessment (Balarajan, Yuen et al. 1989). A group general practice, also in London, found a notable increase in the standardised consultation ratio for Asians (Gillam, Jarman et al. 1989). It is unclear whether this represents excess disease, or differing illness behaviour. Attending the GP may not translate directly into increased use of hospital facilities. Cooper et al found that out-patient services are used significantly less by Asian patients (Cooper, Smaje et al. 1998).

Our study did not confirm any significant delays in treatment, also showing that there were no differences in any intervention, with Asian patients as likely to have had joint injections, admissions or surgery. This in itself brings up another question about the difference in disease severity. Are the Asian patients receiving inappropriately aggressive treatment because of their higher pain reporting and consultation seeking, or are the Caucasian patients receiving inadequate treatment because they are more stoical?

7. 6. 2. DMARDs And Side Effects

A similar profile was seen with the DMARDs, with no difference between numbers of DMARDs used in either group. Methotrexate was the most commonly prescribed, as would be expected in RA (Combe 2007). There was also no difference in steroid usage between the two groups, and both reported an

excellent compliance. Three of the Caucasian group were on anti-tumour necrosis factor drugs, suggesting aggressive disease.

It is interesting to note the differences with side effects. The Asian patients were significantly more likely to complain of rashes, which bears out the research done by Helliwell and Ibrahim in Bradford (Helliwell and Ibrahim 2003). However, this study did not replicate their findings that Asian patients are more likely to stop taking their drugs because of concern about side effects.

The main difference in treatment seemed to be with the patient's perception of their treatment, rather than the actual treatment itself. It is noticeable that the Gujarati patients were more doubting about their treatment, perceiving it as less effective. This would back up Helliwell and Ibrahim's work that suggested that lack of efficacy was one of the important reasons why Asians discontinued their treatment, although direct questioning showed that DMARDs were not more likely to be stopped for actual lack of efficacy in Gujaratis. It also suggests a level of pessimism in these patients that may reflect a learned helplessness, or a lack of trust in Western medicine.

Positive attitude may be important in showing a response to therapy. If a patient group has little faith in the treatment they are receiving, it might not be surprising that they respond poorly. They will lose the placebo effect of receiving medication, which is significant in itself, beside any activity of the drug. It is also

worth remembering that these patients scored highly on depressive symptoms, and may have had negative cognitions as a result of depression, lowering their scoring. Neame and Hammond showed that in RA patients, greater helplessness correlated with more concern about medications (Neame and Hammond 2005).

It is also possible that the Asian patients were all being under treated, and therefore correct to give a low score to the effectiveness of their treatment. This might be relevant if a health professional has solely used a joint count as a guide to treatment, rather than a more holistic approach. This seems to be unlikely considering the range of different doctors and specialist nurses who see these patients, with few seeing the same individual each time in a clinical setting. However, it is notable that despite the Gujarati patients' significantly higher pain scores, they were receiving exactly the same number and strength of analgesics as the Caucasian patients. They were also no more likely to be taking anti-depressants, despite their clinically significant depression scores.

One explanation might be difficulties in communication between the Gujarati patients and the health professionals treating them. It is highly relevant that a study in Sweden showed that satisfaction with treatment was associated with the quality of communication between the patient and the staff, with the patients assuming this was a prerequisite for the treatment to work (Ahlmen, Nordenskiold et al. 2005). Our Gujarati patients may feel less confident in the Western medical system, in its unfamiliar structure and practice. They may feel

that health professionals who do not share their background may not empathise with their particular problems. This may not just be simply due to a language difficulty, but a more fundamental problem with verbalising distress.

7. 6. 3. Osteomalacia: A Possible Confounder?

It is well recognised that Asians living in the UK have a disproportionate incidence of osteomalacia, and that this is marked in rheumatology outpatients (Serhan, Newton et al. 1999). Osteomalacia may manifest as generalised pain and disability (Reilly 1999). Macfarlane et al found that patients of South Asian origin who had widespread pain were more likely to have low vitamin D levels (Macfarlane, Palmer et al. 2005). A significant number of Gujarati patients in our study were taking vitamin D and calcium supplements, but it is still probable that the condition was under diagnosed. The Asians living in Leicester are at high risk of osteomalacia, as are all Asians living in the UK, and it is a strong possibility that a majority of our patients had some degree of this. This may have contributed to their higher pain and disability scores.

However, it is over simplistic to assume that this was the only confounding factor affecting pain and disability in our study. Helliwell et al showed in Asian rheumatology patients in Leeds that even after appropriate treatment with calcium and vitamin D supplementation, there was no improvement in the patients' pain or disability (Helliwell, Ibrahim et al. 2006). This suggests that even

if all our patients were vitamin D replete, there might still be an excess of pain and disability that osteomalacia alone cannot account for.

CHAPTER 8. COMPLEMENTARY MEDICINE: DIFFERENCES AND SIMILARITIES BETWEEN ASIAN AND CAUCASIAN PATIENTS

8. 1. BACKGROUND

122 patients with RA, 61 Gujarati and 61 Caucasian subjects (the revised data set, see section 3.10.2) were recruited. They were age, sex and disease duration equivalent. They underwent an interview, as previously discussed (chapter 3), which included questions about the use and perceived efficacy of complementary and alternative medicines (CAM). Results were collected and analyzed. Non-parametric statistical testing was used as the group sizes were too small to be sure of normal distribution, particularly as the subgroups for different medications were very small. Nonparametric testing was therefore more appropriate.

8. 2. RESULTS: USE OF CAM AND PERCEIVED EFFECTIVENESS

74% of all patients had tried complementary medications (CAM). 48 (79%) Gujarati and 42 (69%) Caucasian patients had tried CAM. This was not significantly different (p=0.22, chi-squared, mean difference 10%, 95% confidence interval -6 to 26%). Asian patients tried a mean of 1.72 CAM in comparison to Caucasians, who had tried a mean of 1.33 types of CAM. This was not significantly different (mean difference 0.39; 95% confidence interval -0.10 to 0.88, p=0.13, Mann Whitney U test)

32 (52%) Gujarati patients and 24 (39%) Caucasian patients had tried copper bracelets (table 30). This was not significantly different (mean difference 13%, 95% confidence interval -4% to 31%; p=0.15, chi-squared). However, the Asian patients tended to rate the bracelets as more effective (on a scale where 5=excellent, and 1= no use at all), with a mean of 1.19 in comparison to a Caucasian mean of 1.00, although this did not reach significance (p=0.08, Mann-Whitney U, mean difference 0.19; 95% confidence interval -0.06 to 0.44).

21 (34%) Gujerati patients had tried magnets compared with 13 (21%) Caucasian patients. This was not significantly different (mean difference 12%; 95% confidence interval -4% to 27%, p=0.15, chi-squared). The Caucasians rated this as 1.54, as Asians as 1.30, which was not significantly different (p=0.31, Mann-Whitney U, mean difference 0.24; 95% confidence interval -0.87 to 0.39).

25 (41%) Asian patients and 19 (31%) Caucasian patients had tried herbal remedies. There was no significant difference (mean difference 12%; 95% confidence interval -6% to 29%; p=0.19, chi-squared). The range of preparations that were tried was extensive, and included green-lipped mussels, feverfew, Devil's Claw, homeopathy, honey and cider vinegar and many others. In the cases of the Asian patients, they most often tried Ayurvedic treatment. Interestingly, the Asian patients were significantly more likely to rate their herbal

treatments effective compared with the Caucasian patients, with a mean of 1.96 to a Caucasian mean of 1.37 (mean difference 0.59; 95% confidence interval -0.09 to 1.27, p=0.025, Mann-Whitney U).

18 (30%) Asian patients and 9 (15%) Caucasian patients had tried acupuncture. This was significantly different (mean difference 14.8%; 95% confidence interval 0.0% to 29.5%, p=0.05, chi-squared). Both groups rated it best of the entire CAM, with a Caucasian mean of 2.56, and an Asian mean of 2.28. This was not significantly different (mean difference 0.28; 95% confidence interval -0.98 to 1.53, p=0.70, Mann-Whitney U).

Despite the higher rating that both groups gave to the effectiveness of acupuncture, they still rated it lower than their DMARD therapy. The mean rated effectiveness for DMARDs in the 18 Gujarati patients who had tried acupuncture was 3.39 (mean difference from acupuncture 1.11, SD 1.28, 95% confidence interval 0.48 to 1.75, p=0.002, Mann-Whitney U). As only 9 Caucasian patients had tried acupuncture, the numbers were too small to draw firm conclusions about the differences, but the trend was to rate DMARDs higher (mean DMARD effectiveness 3.78, mean difference from acupuncture 1.22, SD 1.79, 95% confidence interval -0.15 to 2.60, p=0.07, Mann-Whitney U).

Table 30. Table Of Complementary Medicine Use In Gujarati Asian And Caucasian Patients With RA, And The Mean Rated 'Effectiveness' Of The Treatment On A Five Point Scale

Complementary Treatment (CAM)	**Number of patients trying the CAM**					**Mean rated effectiveness of CAM**		
	Gujerati patients		**Caucasian patients**		***P* value (χ^2)**	**Gujarati patients**	**Caucasian patients**	***P* value (Mann-Whitney U)**
	No.	**%**	**No.**	**%**				
Copper bracelets	32	52	24	39	0.15	1.2	1	0.08
Magnets	21	34	13	21	0.15	1.29	1.54	0.28
Herbal remedies	24	39	19	31	0.19	1.96	1.37	**0.025**
Acupuncture	18	30	9	15	**0.05**	2.28	2.56	0.70
Total number of patients trying CAM	48	79	42	69	0.22	N/A		

8. 3. DISCUSSION: COMPLEMENTARY MEDICINE, USE AND EFFICACY

Complementary medicines were widely used by all patients. This is in line with other studies, which suggest that between 40 to 80% RA sufferers will use CAM (Rao, Mihaliak et al. 1999; Buchbinder, Gingold et al. 2002). This usage has been shown to be very similar regardless of ethnic background (Herman, Allen et al. 2004), and we confirmed this in our study, with 69% Caucasians and 79% Gujaratis having tried CAM during their disease. The range of CAM used was extensive, with the most used being copper bracelets, which 52% Gujaratis and 39% Caucasians had tried, despite the complete lack of evidence for effect. Our patients did not find their bracelets helpful, as expected. Cost, ready availability and perceived lack of harm are factors that may have influenced the popularity of this CAM.

Magnets, usually as bracelets, were also in common usage, probably for similar reasons. 34% Gujaratis and 21% Caucasians had tried magnets. There is some weak evidence suggesting magnets may have some impact on inflammation (Johnson, Waite et al. 2004), but our study did not support this, with our patients rating magnets as no use at all.

Herbal remedies were popular with both groups, with 39% Gujaratis and 31% Caucasians trying various herbal remedies. Gujarati patients had often tried Ayurvedic preparations. A study in India confirmed that 43% RA patients used

CAM, and that they were most likely to use Ayurveda (Chandrashekhara, Anilkumar et al. 2002). In this study, the patients believed that as conventional medicine had no cure for RA, and that CAM had few adverse reactions, it was a safe and efficacious addition to their treatment. However, there is little evidence to support its use in inflammatory arthritis. A meta-analysis of Ayurvedic randomised controlled trials found only seven studies, four of which were flawed by comparing one treatment with another, rather than with placebo, and concluded that there is no evidence of its benefit in RA (Park and Ernst 2005). Although our Gujarati patients were more inclined to think charitably of its effects, they still rated it as only marginally effective, and less effective than their hospital prescribed medication. This lack of satisfaction in CAM has been found in other groups of RA patients. A study in Israel found that self perceived efficacy of CAM was much lower in RA than in other, less inflammatory pain syndromes, such as fibromyalgia (Breuer, Orbach et al. 2005).

The perception of greater benefit from acupuncture was found in both our patient groups. Acupuncture might be thought to have primarily an analgesic effect. A recent Cochrane review examined in benefits of acupuncture in rheumatoid arthritis (Casimiro, Barnsley et al. 2005), and concluded that there was no effect on disease activity or reduction in analgesic use. However, the small number of trials, and methodological difficulties, such as the use of electroacupuncture and traditional needle acupuncture limited their confidence in this conclusion. Our

patients did not agree that acupuncture was useless, but they still rated it lower than their prescription medication.

Overall, although our patients had extensively sampled from CAM, they found the treatments they tried less effective than their DMARD medication. This lack of satisfaction did not stop them from continuing to try CAM. In Australia, patients spent at least as much money on CAM as they did on their hospital prescriptions, despite a lower perceived benefit (Buchbinder, Gingold et al. 2002). Efficacy is not necessarily the motivating factor using CAM.

CHAPTER 9. PSYCHOLOGICAL DATA : DIFFERENCES BETWEEN GUJARATIS AND CAUCASIANS

9. 1. BACKGROUND

122 patients with RA, 61 Gujarati Asian and 61 Caucasian subjects were recruited (the revised data set, section 3.10.2), and age, sex and disease duration equivalent as discussed in previous chapters. They underwent an interview with the author and an interpreter, if necessary, as described in detail before (chapter 3). They were taken through the Self Reporting Questionnaire (SRQ) by the investigators as sensitively as possible. They were also taken through the List of Threatening Life Events as outlined previously, and asked about perceived efficacy of their medication. Results were collected and compared to previous data discussed in preceding chapters. Non-parametric statistical testing was used as the data was not normally distributed, and the sample sizes were relatively small. Non parametric testing does not assume normality, and is therefore a more appropriate test for the data.

9. 2. PSYCHOLOGICAL DIFFERENCES BETWEEN THE TWO GROUPS: RESULTS

9.2.1 Differences In Depression And Threatening Life Events

The Gujarati patients had highly significant scores on the SRQ than the Caucasian patients, with a mean of 9.44 in comparison to a Caucasian mean of 5.16 (table 31, $p<0.0001$, Mann-Whitney U, mean difference 4.28; 95% confidence interval 2.77 to 5.79). This was despite making the tool theoretically less sensitive by removing the items that referred to somatic symptoms. As the Asians had significantly more pain, they would have been expected to score these items as positive. The cut off for a probable psychiatric disorder is a value > or = 8. 64% (39) Gujarati patients scored a value of 8 or above, while 30% (18) Caucasians scored 8 or above. This was significantly different, $p=0.0002$ (chi-squared). No Gujarati patient scored 0. 10% (6) Caucasian patients scored 0.

There are many interacting factors in depression. Pain and disability can strongly influence mood, and it has already been shown that this group of Gujerati patients have significantly more pain and more disability than the Caucasian patients (section 5.2.3). Adverse or threatening life events significantly impact on mood. It is important to remember that the Asian patients are an immigrant community, and as such, may have experienced more threatening life events than the Caucasian patients. However, the study shows that the Asian patients had no significant difference in threatening life events experienced, compared

with the Caucasians (p=0.27, Mann-Whitney U, mean difference 0.28; 95% confidence interval -0.17 to 0.73).

Table 31. Depression And Threatening Life Events In Caucasian And Asian Patients

Depression and adverse life events	**Gujarati mean**	**Standard deviation**	**Caucasian mean**	**Standard deviation**	***P* value (Mann-Whitney U test)**
Life Events measured on list of threatening experiences	1.28	1.34	1.00	4.24	0.27
Depression on SRQ	9.44	4.17	5.16	1.14	**0.0000003**
Score on SRQ >or=8	**No.**	**%**	**No.**	**%**	***P* value (χ^2)**
	39	64	18	30	**0.0002**

9. 2. 2. Correlations Between Depression Scores And Other Variables

For the full tables of Pearson correlations, and tables with raw data for analyses, please see appendix 7. In the combined group of patients, depression correlated

moderately with ethnic group (r = 0.48, p <0.0005), and also with HAQ (r = 0.45, p <0.0005), pain (r = 0.50, p <0.0005) and EMS (r = 0.35, p <0.0005). It is understandable that pain and disability would be linked to depression. Depression also correlates with threatening life events (r = 0.43, p <0.0005), and negatively with perceived effectiveness of treatment (r = -0.46, p <0.0005).

In the Caucasians, depression correlated most strongly with pain (r = 0.48, p <0.0005), with threatening life events (r = 0.40, p <0.0005), and EMS (r =0.40, p <0.0005), as well as HAQ (r = 0.36, p= 0.001). Depression correlated negatively with perceived efficacy of treatment (r = -0.52, p <0.0005), and with presence of a partner (r = 0.36, p = 0.001). Presence of a partner is recognized to protect against depression in RA (Abdel-Nasser 1998). Perceived efficacy may be a surrogate marker for optimism and positive state of mind, which may be reduced in depressed individuals. In the Asian patients, depression was correlated most strongly with adverse life events (r = 0.48, p <0.0005), and moderately with HAQ (r = 0.36, p= 0.002) and with pain (r = 0.34, p= 0.004).

9. 2. 3. Univariant Analysis To Predict Depression in All Patients

Univariant analysis was used to identify variables that might predict depression in the combined group of patients, when the effect of other variables was not adjusted for. Variables tested were age, sex, disease duration, ethnic group, presence of partner, number of family members at home with the patients,

number of friends and family who regularly visit to help, years of education, score on the List of Threatening Life Events, units of alcohol consumed, pain, EMS, SJC, deformities, HAQ and perceived efficacy of conventional medication.

Disease duration, ethnic group, presence of a partner, number of friends and family who help the patient, threatening life events, alcohol consumed per week, pain, EMS, disability as measured by the HAQ and perceived efficacy of treatment were all significantly related to the depression scores recorded by the patients (see table 32).

9. 2. 4. Multiple Regression Analysis To Predict Depression in All Patients

Multiple regression analysis was used to determine variables that were uniquely predictive of depression when all other variables had been adjusted for. The same variables as noted above were entered. All variable accounted for 47.9% of the variance in depression (adjusted R^2), and the model as a whole was statistically significant (p <0.0005, F (16, 132) = 8.59). Ethnic group (p <0.0005), and number of threatening life events (p <0.0005) were the only uniquely predicting variables, when all other variables had been controlled for (see table 33).

Table 32. Univariant Analysis To Determine Variables Affecting Depression in All Patients

Variable	Adjusted R^2	*F* value	*P* value
Age	0.02	3.46	0.07
Sex	0.02	3.62	0.06
Disease duration	-0.01	0.03	**0.03**
Ethnic group	0.22	38.39	**<0.0005**
Presence of Partner	0.06	9.48	**0.003**
Family at home	-0.01	0.01	0.94
Number who help	0.04	6.60	**0.01**
Years of education			
Threatening Life events	0.18	29.48	**<0.0005**
Alcohol units consumed	0.05	7.43	**0.007**
Pain	0.25	44.17	**<0.0005**
EMS	0.11	18.05	**<0.0005**
SJC	0.00	1.30	0.26
Deformities	0.00	1.35	0.25
HAQ	0.20	34.10	**<0.0005**
Perceived efficacy of treatment	0.21	35.08	**<0.0005**

Table 33. Multiple Regression To Predict Depression In All Patients

Variable	Unstandardised Coefficients		Standardised Coefficient Beta	Significance (*p* value)
	B	Standard error		
Age	-0.01	0.03	-0.034	0.68
Sex	0.23	0.84	0.02	0.79
Disease duration	-0.05	0.05	-0.08	0.33
Ethnic group	2.99	0.82	0.32	**<0.0005**
Presence of Partner	-0.84	1.03	-0.06	0.42
Family at home	-0.33	0.37	-0.09	0.37
Number who help	0.20	0.19	0.08	0.30
Years of education	0.14	0.10	0.11	0.16
Threatening Life events	1.13	0.25	0.30	**<0.0005**
Alcohol units consumed	0.00	0.05	0.00	0.99
Pain	0.30	0.19	0.14	0.12
EMS	0.32	0.27	0.09	0.24
SJC	0.04	0.06	0.06	0.50
Deformities	0.02	0.07	0.02	0.79
HAQ	0.51	0.45	0.12	0.25
Perceived efficacy of treatment	-0.84	0.44	-0.15	0.06

9. 2. 5. Stepwise Regression To Create A Model To Predict Depression

Stepwise regression analysis was used top create a model to predict depression in all patients. Pain, threatening life events, ethnic group and perceived efficacy of treatment emerged as the predicting variables. The model as a whole predicted 48.2% (adjusted R^2) of the variance in depression. Pain was the most important predictor, responsible for 25.2% (R^2 change, see table 34) of the variance in depression. Threatening life events were responsible for a further 12.1%, and ethnic group for 10.1%. Perceived efficacy of treatment was responsible for 2.4% variance in depression. This is negatively correlated with depression ($r = -0.46$, $p < 0.0005$), and may reflect the general negativity of the depressed patients, rather than a specific link to ineffectiveness of treatment.

Table 34. Stepwise Regression Analysis To Predict Depression In All Patients

Variable	**Unstandardised Coefficients**		**Standardised Coefficient Beta**	***p* value**	**R^2 change**	***F* change**	***P* value for *F* change**
	B	**Standard error**					
Pain	0.55	0.15	0.26	**<0.0005**	0.25	44.17	**<0.0005**
Life events	1.21	0.24	0.32	**<0.0005**	0.12	25.01	**<0.0005**
Ethnic group	2.85	0.63	0.31	**<0.0005**	0.10	24.72	**<0.0005**
Perceived efficacy	-1.03	0.42	-0.18	**0.014**	0.02	6.17	**0.014**

9. 2. 6. Stepwise Regression Analysis To Predict Depression In Asian Patients

The patients were divided into their ethnic groups to see if different variables influenced depression in each group. In Asian patients, threatening life events and disability on the HAQ were the only variables that predicted depression. The model as a whole was poor, only predicting 28.8% of the variance in depression (adjusted R^2, see table 35). The model as a whole was significant (p <0.0005, F (2, 60) = 13.12). Threatening life events was the most important variable, being responsible for 23.1% of the variance in depression.

Table 35. Stepwise Regression To Predict Depression In Asian Patients

Variable	Unstandardised Coefficients		Standardised Coefficient Beta	*p* value	R^2 change	*F* change	*P* value for *F* change
	B	Standard error					
Life events	1.34	0.34	0.43	**<0.0005**	0.23	17.76	**<0.0005**
HAQ	1.24	0.48	0.29	**0.012**	0.08	6.75	**0.012**

9. 2. 7. Stepwise Regression To Predict Depression In Caucasian Patients

Stepwise regression analysis was also performed in the Caucasian group of patients, using the same variables to predict depression. The model as a whole was a better predictor than the Asian model, predicting 43.1% (adjusted R^2) of

the variance in depression. The predicting variables in the model were perceived efficacy of treatment, threatening life events, pain and age (see table 36). The model was significant, p <0.0005, F (4, 71) = 14.45.

Table 36. Stepwise Regression To Predict Depression In Caucasian Patients

Variable	Unstandardised Coefficients		Standardised Coefficient	*p* value	R^2 change	*F* change	*P* value for *F* change
	B	Standard error	Beta				
Perceived efficacy	-1.52	0.50	-0.32	**0.003**	0.27	25.45	**<0.0005**
Life events	1.08	0.33	0.30	**0.002**	0.09	9.53	**0.003**
Pain	0.49	0.18	0.28	**0.01**	0.06	7.07	**0.01**
Age	-0.07	0.03	-0.22	**0.02**	0.05	5.84	**0.02**

9. 2. 8. Logistic Regression to Predict Depression In All Patients

Backwards logistic regression was used to create a model to predict a depression score of >=8, which is the level that should trigger a psychiatric referral in this population (see section 3.8.1). This also allowed calculation of the odds ratios. The variables entered were age, sex, disease duration, ethnic group, years of education, family at home, number of friends and family who help patient, presence of a partner, SJC, deformities, HAQ, pain on VAS, EMS, threatening life events, perceived efficacy of treatment and alcohol consumption.

The model as a whole was significant (p <0.0005, χ^2 (4, N = 133) = 68.48), and correctly classified 79.7% of cases. The model predicted between 40.2% (Cox & Snell R^2) and 54.0% (Nagelkerke R^2) of the variance in depression scores on the SRQ. Ethnic group, EMS, pain and threatening life events were the predictive variables that made up the model. Ethnic group was the strongest predictive variable with an odds ratio of 3.76. This means that Asian patients were nearly four times as likely as Caucasians to have a depression score of >=8, despite adjusting for all other variables (see table 37).

Table 37. Backwards Logistic Regression To Predict Depression In All Patients

Variable	**B**	**S.E.**	**Wald**	**df**	***P* value**	**Odds ratio**	**95% Confidence interval for odds ratio**	
							Lower	**Upper**
Ethnic group	1.32	0.48	7.48	1	0.006	3.76	1.46	9.71
Age	0.50	0.22	4.96	1	0.026	1.65	1.06	2.56
Smoking history	0.37	0.13	8.15	1	0.004	1.45	1.13	1.88
Pain	1.01	0.24	17.94	1	<0.0005	2.73	1.72	4.35

9. 2. 9. Summary: Predicting Depression In The Leicester RA cohort

Ethnic group was a significant independent predictive factor for depression, despite adjusting for all potential variables that might affect depressive symptoms in the analysis, along with pain, threatening life events and perceived efficacy of treatment. This suggests that there were other factors uniquely affecting the Asian patients in terms of depression that were not studied in this analysis. Adverse life events and disability alone predicted depression in Asian patients, but poorly. Patients who felt their treatment was ineffective, had more adverse life events, more pain and were older were more likely to be depressed in the Caucasian group.

9. 3. DISCUSSION: THE PYSCHOLOGICAL IMPACT OF DISEASE

The Asian patients scored significantly more than the Caucasian patients on the WHO Self-Reporting Questionnaire. The WHO SRQ does not measure clinical depression, and is not a diagnostic indictor. It is important to remember that it is a screening tool, designed to pick out patients in communities for further investigation. Here, it was rendered less sensitive by omitting somatic questions, yet there was still a profoundly significant difference between the Gujarati patients and the Caucasians. Not only were the Gujaratis more depressed than the Caucasians, but their mean score at 9.44 was well above the cut off score of 8 for probable psychiatric disturbance in this population. It is certainly relevant

that nearly two thirds of all Gujarati patients in the study would have been followed up for formal psychiatric examination, had the WHO guidelines been followed.

9. 3. 1. Depression And Its Interaction With Pain And Disability

Depression is a potent confounder of pain and disability. The relationship of depression, pain and disability is complex, and bidirectional. Patients are both depressed because of their pain and disability, and, if they are depressed, likely to suffer greater pain levels and be less able to cope with functional impairment. In healthy volunteers, an experimentally induced sad mood or anxiety state increases pain perception (Ploghaus, Tracey et al. 1999). Pain has been shown to be correlated with depression in RA, even if the disease activity is controlled (Callahan, Kaplan et al. 1991). Disability leading to reduction in capacity to perform valued tasks such as visiting family leads to a significant increase in depression the following year (Katz and Yelin 1993). However, there is evidence to suggest that pain and disability on their own are unable to cause depression, except in advanced disease (Mindham, Bagshaw et al. 1981). Our Asian patients had highly significantly more pain and disability than their Caucasian counterparts, so although this might be expected to amplify any depressive symptoms, this should not be enough to account for the depression alone. Indeed, in the multivariant analysis, although disability predicted depression in Asian patients, it only accounted for 8% of the variance in HAQ. Ethnic group

was still a significant predictor of depression despite adjusting for disease activity markers, and adverse social circumstance. There are other factors that influence depression in the Asian population that were not uncovered by this study.

9. 3. 2. Disease Activity And Severity Factors

The evidence from the disease data is largely that the Gujarati patients seem to have a milder form of the disease, with less swollen joints, less seropositivity for rheumatoid factor, less nodulosis and a lower frequency of the shared epitope. They also have less smoke exposure, and a vegetarian diet rich in tumeric. At first glance, these factors might be expected to have contributed to a good outcome for our Gujarati patients, with a milder disease and thus less depression. This is not the case. They show significantly poorer outcomes in terms of the HAQ. Their apparently 'milder' disease neither improves their outcome, nor protects them from depression.

There were other factors that might have impacted on the Gujarati patients' greater depression. There is evidence that younger age at diagnosis and female gender may predispose to depression in RA (Ramjeet, Koutantji et al. 2005). The Gujarati patients had an earlier age of onset, and there were a higher proportion of women in the group, although this was not significantly different from the Caucasian patients. It seems less likely that these relatively small differences

were responsible for the large discrepancy in depressive symptoms, but they may have had an additive effect.

There is evidence from cardiovascular studies that inflammation may be related to depression. A high CRP was correlated with depression after adjusting for confounding factors in a large study (Kop, Gottdiener et al. 2002), but these findings have not been replicated in the rheumatoid population. It is possible that some of the inflammatory cytokines may be linked to depression in inflammatory arthritis, but this has not been studied in detail. A small study from Japan found that mirthful laughter, precipitated by asking RA patients to listen to a traditional Japanese comic story, altered the levels of pro-inflammatory and anti-inflammatory cytokines in a beneficial way, but did not look at outcome measures (Matsuzaki, Nakajima et al. 2006). Although the Gujaratis had a higher level of plasma viscosity, this was not correlated with depression ($r = -0.04$, $p = 0.38$). It seems unlikely that this was an important factor.

Fibromyalgia may also be a significant confounder in this group of patients. They were not examined for trigger points or other fibromyalgic symptoms. There is an increased incidence of fibromyalgia in patients with RA, up to 17%, and it is correlated with socioeconomic deprivation and a worse outcome (Wolfe and Michaud 2004). An excess of fibromyalgia in the Gujarati patients may account for their worse pain, disability and depression.

9. 3. 3. The Impact Of Social Stressors

Social stress has been shown to contribute significantly to risk of depression (Dickens, Jackson et al. 2003). This study has shown that Gujarati patients had many factors in their environment which should have protected them from depression. They had significantly more family at home, and a larger social network, both of which have been shown to be protective against depression (Zyrianova, Kelly et al. 2006). They were as likely as the Caucasians to be married, and had had no greater number of stressful life events. Marriage is recognized to protect against depression (Katz and Yelin 1993), and a higher rate of stressful life events correlates strongly with depression (Paykel 2001). However, these studies were largely performed in Western populations, and it may not be possible to extrapolate these findings to the immigrant Asian population. There may be other factors that would be protective in an individual with an Asian heritage, or in a first generation immigrant. Our patients may have been stressed, rather than protected by their larger social network, by being unable to fill their role, both at home and in the wider community. This may then predispose them to depression.

It is also worth considering the background frequency of depression in the Asian community, which may be considerable. The excess in suicide of young Asian immigrants in the UK is well recognized (Soni Raleigh and Balarajan 1992), and there is an excess of self harm in young South Asian women in the UK (Cooper

2006). It has been shown that premorbid personality factors are powerful predictors of depression in disease, and no attempt was made to assess this in this study. Covic et al showed that high tension and low self esteem were the strongest predictors of depression in an RA cohort (Covic, Tyson et al. 2006).

The Gujarati patients had significant depression, far greater than might be expected from markers of disease activity, and were not protected by their environment. Only 2% patients were being treated with anti-depressants, while 64% warranted referral to a psychiatrist. This is clear evidence of a missed opportunity to intervene. Dickens and Creed (Dickens and Creed 2001) suggest treating all such patients with anti-depressants, as 2/3 may respond quickly to treatment.

Health care professionals need to be aware of the high prevalence of depression in the RA population. Those working in ethnically mixed areas need to be especially aware of its presence in immigrant communities, who may be unable to communicate their emotions effectively in an unfamiliar language, setting and culture.

CHAPTER 10. DO ASIAN GUJARATI PATIENTS WITH RA HAVE MORE SEVERE DISEASE THAN CAUCASIAN PATIENTS WITH RA?

10.1. BACKGROUND

133 patients, 61 Gujarati and 73 Caucasian subjects with RA were recruited as described in chapter 3.10.2 (the complete data set). They were randomly recruited, and unmatched. Information as to conventional predictors of disease severity was collected as described in chapter 3.2 to 3.9.

Other studies have sought to explain the outcomes in RA by examining the impact of variables such as sero-positivity for RF, or presences of nodules, and looking to see if they predict outcome measures such as disability as measured by HAQ or erosions as measured by the Larsen or Sharp scores. In Caucasians, certain factors have been identified as predicting a poorer prognosis, as described in section 1.3.2. These include presence of RF, smoking history, nodules, presence of shared epitope and high inflammatory markers.

If regression analysis is used, the complete data set gathered can be utilised, as the difference in age and sex can be controlled for by the mathematical model. This gives another aspect to the data, and may help to remove any potential bias

that may have occurred by discarding the data pertaining to the more elderly Caucasian patients.

10.2. METHODS

10.2.1. Outcome Measures

In order to answer the question 'Is RA more severe in the Asian or the Caucasian patients?' outcome measures needed to be selected to differentiate between the groups. The OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) group has addressed this issue for the purpose of clinical trials in patients with RA, suggesting a composite score consisting of swollen joint count (SJC), tender joint count, disability score, physician and patient global assessment of disease activity, patient assessment of pain and laboratory test of an inflammatory marker such as CRP (Felson 1993). This has lead to the development of composite scoring systems such the various versions of the Disease Activity Score (DAS28), or the American College of Rheumatology Criteria (ACR 20, 50 or 70; the numbers represent the percentage improvement from baseline). These are used widely in clinical trials.

Individual clinical factors have also been used to assess outcome. An articular index has been shown to be a good predictor of joint damage (Harrison and Symmons 2000), and so swollen joint count may be a useful outcome measure. Progression of erosions is also an outcome measure for RA, and greater

radiographic damage has been related to increased disability (van der Heijde 2008). HAQ is a well validated outcome for RA, with a predictable deterioration and is recognized to predict progression (Wolfe and Sharpe 1998), as described in chapter 3.4.7.

There is increasing evidence that patient reported outcomes are as effective as physician assessed composite measures, such as the DAS28, particularly in the long term, and not as biased as previously thought (Pincus 2003; Mittendorf 2007; Pincus 2008). This lends weight to considering the HAQ as a good outcome measure of RA. The HAQ has also been shown to be a good predictor for long term quality of life in RA (Cohen 2006). HAQ also predicts mortality, both in RA (Wolfe 2003; Farragher 2007) and in the general population (Sokka 2004).

10.2.2. Predictive Variables

Previous chapters have assessed the factors that are thought to correlate with disease severity (sections 1.3.2, 1.4.5). They include sero-positivity for RF, presence of nodules, smoking history, presence of shared epitope, extra-articular manifestations (EAM) and SJC.

Other variables may also impact on the HAQ score. Disease duration, age and sex may confound the analysis. HAQ scores worsen predictably with disease duration (Krishnan 2004). Age would be expected to significantly confound the

HAQ, particularly as primary or secondary degenerative disease may affect it. Older patients may have accelerated disability (Onder 2002). Pain may also correlate strongly with HAQ, as described in chapter 5.3.3. Depression has been found to predict disability in RA (Rupp 2006). Ability to stay in work is an outcome many patients find important, and is strongly predicted by disability, and also by educational levels (Eberhardt 2007).

10.2.3. Analysis

Raw data tables for analyses can be found in appendix 7.

Meaning of values reported in the text:

% Variance	This is the spread of scores (e.g. HAQ scores) that a variable is able to predict (e.g. pain). This means that if you know the pain score, you would be able to accurately predict the disability score in a certain percentage of cases (e.g. 38%).
R^2	How much of the variance is explained by the model in the dependent variable.
Adjusted R^2	A more accurate estimate of the variance explained by the model in a small sample size, as the R^2 tends to be over optimistic.
F value	The ratio of two mean squares. When the F value is large and the significance level is small (typically smaller than 0.05) the null hypothesis (i.e. that there is no difference) can be rejected. In other

words, a small significance level indicates that the results probably are not due to random chance.

The significance level (*p* value) used to denote meaningful significance was < or = to 0.05.

10 .3. RESULTS: Predicting HAQ In The Complete Group Of Patients

10. 3.1. Predicting Disability

The data pertaining to the two ethnic groups was combined in the initial analysis. The variables examined with respect to their influence on the variance in HAQ were age, sex, disease duration, ethnic group, and markers of severity such as sero-positivity for RF, presence of nodules, smoking history, SJC, number of deformities, plasma viscosity, EMS, shared epitope, EAM, depression, years of education and pain.

10.3. 2. Univariant analysis

Univariant analysis was used to examine each variable separately, to ascertain which were individually significant, when other variables were not controlled for. This also allowed a measure of how much variance of HAQ could be attributed to each variable. This method does not control for any other variable, so there may be overlap between the affect of the variables. Table 38 shows the results. The

largest contributors were pain, which accounted for 38% of the unadjusted variance in HAQ. Depression accounted for 20%, number of deformities for 17.4% and SJC for 15.4% of the unadjusted variance in HAQ. EMS, ethnic group, years of education, smoking history, disease duration and presence of nodules were all also significant predictors of HAQ, when no other variables were controlled for. Shared epitope did not emerge as a predictor of HAQ.

Table 38. Univariant Analysis Of Individual Variables Influencing HAQ

Variable	Adjusted R^2	*P* value	*F* value
Age	0.02	0.07	3.29
Sex	0.004	0.22	1.54
Disease duration	0.08	**0.001**	11.67
Ethnic group	0.10	**0.0002**	15.23
Smoking history	0.04	**0.009**	7.07
Years of education	0.11	**<0.0005**	17.94
Presence of nodules	0.04	**0.02**	5.93
Sero-positivity	-0.004	0.49	0.48
SJC	0.15	**<0.0005**	25.07
Deformities	0.17	**<0.0005**	28.83
Plasma viscosity	0.03	**0.02**	5.53
Pain	0.38	**<0.0005**	82.48
Depression	0.20	**<0.0005**	34.10
EMS	0.11	**<0.0005**	17.71
Shared Epitope	0.00	0.31	1.04
EAM	-0.002	0.39	0.74

10 .3. 3. Multiple Regression To Predict HAQ In All Patients With RA

The combined data was examined using standard multiple regression, after preliminary analyses were conducted to ensure there were no violations of normality, linearity and multicollinearity. The variance in HAQ that could be explained by age, sex, disease duration, ethnic group and markers of severity such as sero-positivity for RF, presence of nodules, smoking history, SJC, number of deformities, plasma viscosity, EMS, shared epitope, EAM, depression and pain was calculated. All these variables were entered into Step 1, explaining 57.9% of variance in HAQ (adjusted R^2). The model as a whole was significant ($p<0.0005$). Raw data is in appendix 7.

Age, ethnic group, pain, and SJC were the only uniquely significantly associated variables (see table 39), when all other variables had been controlled for.

10. 3. 4. Correlations Between Variables (Appendix 7)

The full table of correlations can be found in appendix 7. HAQ was most strongly correlated with pain ($r = 0.62$, $p < 0.0005$). SJC ($r = 0.40$, $p < 0.0005$), deformities ($r = 0.42$, $p < 0.0005$) and depression ($r = 0.45$, $p < 0.0005$) also had moderate correlations with HAQ.

Disease duration had a large correlation with number of deformities (r = 0.61, p <0.0005), which would be expected. EMS did not correlate at all (r = 0.00, p =0.49) with disease duration, and correlated poorly with deformities (r = 0.07, p = 0.23) suggesting that it is not related to joint damage. Presence of nodules correlated with SJC (r = 0.43, p <0.0005) and deformities (r = 0.44, p <0.0005), and less strongly with seropositivity for RF (r = 0. 31, p <0.0005) and disease duration (r = 0.34, p <0.0005), findings that are expected, as nodules have been linked to more severe disease. Seropositivity for RF did not correlate strongly with any other variable, its correlation with nodules being the strongest finding. Shared epitope did not correlate strongly with RF, nodules or SJC. It had a weak correlation with ethnic group (r = 0.26, p = 0.004), which would be expected from the previous findings (section 6.3.2). SJC had a moderate correlation with deformities (r = 0.48, p <0.0005), showing that those who have had previous damage continue to have active disease – an expected finding. Interestingly, PV did not correlate strongly with any variable, and in particular, not with SJC as might be expected (r = 0.15, p = 0.05).

EMS correlated more strongly with pain (r = 0.47, p <0.0005) than with PV (r = 0.05, p = 0.03) or SJC (r = 0.18, p = 0.02), suggesting that it may not be as reliable as a marker of disease activity in this patient group, but may reflect other problems, such as coping with pain.

Table 39. Multiple Regression Analysis To Predict HAQ In All Patients

Variable	Unstandardised Coefficients		Standardised Coefficient Beta	*P* value
	B	Standard Error (S. E.)		
Age	0.02	0.01	0.21	**0.01**
Sex	-0.12	0.20	-0.05	0.54
Disease duration	0.003	0.01	0.03	0.77
Ethnic group	0.54	0.20	0.25	**0.01**
Years of education	-0.02	0.03	-0.06	0.44
Smoking history	-0.25	0.17	-0.12	0.14
Presence of nodules	0.02	0.21	0.01	0.91
Sero-positivity	-0.26	0.16	-0.13	0.11
EMS	0.04	0.07	0.05	0.56
Pain	0.15	0.04	0.35	**<0.0005**
Depression	0.03	0.02	0.11	0.18
SJC	0.06	0.02	0.33	**0.0002**
Deformities	0.03	0.02	0.07	0.09
Plasma viscosity	-0.16	0.54	-0.02	0.77
Shared Epitope	0.15	0.11	0.10	0.19
EAM	-0.16	0.19	-0.06	0.41

10. 3. 5. Hierarchical Regression Analysis: Controlling For Possible Confounding Variables

Hierarchical multiple regression analysis was performed, controlling for age, sex and disease duration, as these may all be confounding variables. It was particularly important to control for the effect of age, as the Caucasian group were older than the Asian group, which may have contributed to any differences in HAQ.

Age, sex and disease duration were controlled for by entering at Step 1. Adjusted R^2 was 0.08, showing that age, sex and disease duration together was responsible for 8% of the variance in HAQ. After entry of ethnic group, presence of nodules, sero-positivity, smoking history, years of education, plasma viscosity, SJC, deformities, depression, EAM, shared epitope and pain, the total variance then described by the model as a whole was 54.7% (adjusted R^2 0.55, $F = 8.31$, $p<0.0005$). Raw data is in appendix 7.

The variables entered at the second step explained an additional 51.4% of variance in HAQ (R^2 change =0.51, $p<0.0005$). Ethnic group, pain, SJC, and deformities all made a statistically significant contribution of variance in HAQ (see table 40).

Table 40. Hierarchical Regression Analysis To Predict The HAQ

Variable (Model 2)	Unstandardised coefficients		Standardised coefficient	Significance (*p* value)
	B	Standard error (S.E.)	Beta	
Age	0.02	0.01	0.18	0.27
Sex	-0.09	0.21	-0.03	0.65
Disease duration	0.00	0.01	0.01	0.92
Ethnic group	0.45	0.22	0.22	**0.05**
Years of education	-0.01	0.02	-0.04	0.61
Smoking history	-0.14	0.18	-0.06	0.46
Presence of nodules	0.12	0.20	0.05	0.56
Sero-positivity	-0.30	0.17	-0.14	0.08
SJC	0.04	0.02	0.21	**0.03**
Deformities	0.04	0.02	0.21	**0.04**
Plasma viscosity	0.50	0.57	0.07	0.38
Pain	0.18	0.04	0.40	**<0.0005**
Depression	0.02	0.02	0.08	0.36
EAM	-0.02	0.17	-0.01	0.89
EMS	0.04	0.07	0.04	0.60
Shared epitope	0.14	0.11	0.09	0.24

10 .3. 6. Creating And Testing A Model To Predict HAQ

Disease duration, ethnic group, smoking history, deformities, years of education, depression, nodules, SJC, PV, pain and EMS were all identified as significant in univariant analysis. Age approached significance. In order to create a model to predict HAQ, stepwise multiple regression analysis was utilised, using all the previously described variables.

Stepwise multiple regression analyses were used to assess the best fit model for predicting HAQ in all patients. The variables that were calculated as providing the best model to predict the variance in HAQ were, in order, pain, number of deformities, ethnic group, SJC, age, and sero-positivity for RF. Analyses showed that there was no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Combined, the variables predicted 57.2% of the variance in HAQ (adjusted R^2 0.57), and was significant; F (6, 97) = 22.30, p<0.0005. Table 41 shows the individual results for the variables, showing what additional percentage of variance of HAQ in the model each variable was responsible for (R^2 change). Complete data tables are in appendix 7. Pain had the greatest beta value (beta = 0.45), representing the unique contribution of pain to HAQ. Seropositivity for RF was protective (beta = -0.14).

Table 41. Stepwise Multiple Regression: The Best Fit Model To Predict HAQ

Variable	Unstandardised Coefficients		Standardised Coefficient	*P* value	R^2 change	*F* change	*P* value for *F* change
	B	S. E.	Beta				
Pain	0.21	0.03	0.45	**<0.0005**	0.39	60.44	**<0.0005**
Deformities	0.04	0.01	0.22	**0.006**	0.11	20.85	**<0.0005**
Ethnic group	0.56	0.16	0.27	**0.001**	0.03	5.06	**0.03**
SJC	0.04	0.01	0.26	**0.002**	0.04	7.49	**0.007**
Age	0.02	0.01	0.19	**0.01**	0.02	4.96	**0.03**
+ for RF	-0.29	0.15	-0.14	**0.05**	0.02	4.00	**0.05**

10. 3. 7. Calculating The Odds Ratio: Logistic Regression To Predict Disability In Patients With RA

HAQ scores were divided into two groups, those patients with scores greater than or equal to 2, and those with scores less than 2. This created two patient groups, one with moderate to severe disability (HAQ < or = 2), and one with no or mild disability (HAQ <2). The median HAQ score overall was 2. This allowed direct binary logistic regression to be used to calculate the odds ratio for each variable's impact on the HAQ, and to create a model for prediction of moderate to severe disability.

The odds ratio was calculated for each variable (see table 42; in the table 'df' denotes degrees of freedom). Ethnic group, EMS, pain, presence of nodules, depression score, SJC, number of deformities and PV were statistically significant predictors of HAQ > or = 2. Ethnic group (odds ratio = 3.63) and PV (odds ratio = 12.18) had the highest unadjusted odds ratios. Smoking and years of education were statistically significant protective factors against having a HAQ of > or = 2. This was surprising, as smoking has been shown to both increase the incidence and worsen the severity of RA (see section 1.3.2).

Entering all the above variables into the model to adjust for effect produced a statistically significant model, χ^2 (16, N = 98) = 68.02, p<0.0005. The model as a whole explained between 50.0% (Cox & Snell R^2) and 66.7% (Nagelkerke R^2) of the variance in disability, and correctly classified 82.7% of cases. Fewer variables made a unique statistically significant contribution to the model; ethnic group, pain, age and swollen joint count. The strongest predictor of HAQ > or =2 was ethnic group. Data set is in appendix 7.

Table 42. Logistic Regression With Unadjusted Odds Ratios Predicting Disability In Patients With RA

Variable	B	S.E.	Wald	df	*P* value	Odds ratio	95% Confidence interval for odds ratio	
							Lower	Upper
Ethnic group	1.29	.37	12.33	1	**<0.0005**	3.63	1.77	7.44
Sex	0.43	0.46	0.88	1	0.35	1.54	0.63	3.75
Age	0.02	0.01	1.63	1	0.20	1.02	0.99	1.05
Years of education	-0.21	0.07	9.67	1	**0.002**	0.81	0.71	0.93
Positive smoking history	-1.09	0.39	7.79	1	**0.005**	0.34	0.16	0.72
Disease Duration in years	0.04	0.02	2.78	1	0.10	1.04	0.99	1.08
EMS	0.61	0.19	10.19	1	**0.001**	1.83	1.26	2.66
Pain	0.64	0.12	30.77	1	**<0.0005**	1.90	1.52	2.39
Presence of Nodules	0.56	0.38	2.10	1	0.15	1.74	0.82	3.70
Depression	0.18	0.04	16.64	1	**<0.0005**	1.19	1.10	1.30
SJC	0.13	0.04	12.35	1	**<0.0005**	1.13	1.06	1.22
Deformities	0.11	0.03	10.20	1	**0.001**	1.12	1.04	1.19
Seropositivity for RF	0.28	0.35	0.62	1	0.43	0.76	0.38	1.50
PV	2.50	1.28	3.85	1	**0.05**	12.18	1.00	148.10
One copy of shared epitope	0.11	0.47	0.05	1	0.82	0.90	0.36	2.23
Two copies of shared epitope	0.29	0.60	0.24	1	0.63	0.75	0.23	2.43
Dose of shared epitope	0.14	0.30	0.23	1	0.63	0.87	0.49	1.55
EAM	0.50	0.43	1.35	1	0.25	1.64	0.71	3.79

10. 3. 8. Testing The Model With Logistic Regression

Backwards logistic regression was used to create a model to predict patients with a HAQ score of > or = 2, and to calculate the odds ratios. The model as a whole was significant, χ^2 (6, N = 133) = 60.62, p<0.0005. The model correctly classified 82.7% of cases. The model predicted between 46.1% (Cox & Snell R^2) and 61.5% (Nagelkerke R^2) of the variance in HAQ. Age, ethnic group, SJC and pain were again uniquely significant variables, but this model did not select sero-positivity for RF and deformities as predictive values. Smoking history was protective, being associated with a lower HAQ score. Shared epitope emerged as a predictor, but was not uniquely significant.

The strongest predictor of HAQ was ethnic group, with an odds ratio of 8.20. This indicates that Asian patients with RA were more than eight times more likely to have a HAQ> or =2 than Caucasian patients, controlling for all other factors in the model. Pain had the next highest odds ratio at 1.98, indicating that for each 10mm more on the pain VAS, an individual was twice as likely to have a HAQ of 2 or above (see table 43).

Table 43. Backwards Logistic Regression to Predict HAQ in All Patients With RA

Variable	B	S.E.	Wald	df	*P* value	Odds ratio	95% Confidence interval for odds ratio	
							Lower	Upper
Ethnic group	2.10	0.76	7.63	1	**0.006**	8.20	1.84	36.47
Age	0.06	0.03	5.18	1	**0.02**	1.06	1.01	1.12
Smoking history	-1.32	0.68	3.73	1	**0.05**	0.27	0.07	1.02
Pain	0.68	0.17	15.47	1	**<0.0005**	1.98	1.41	2.78
SJC	0.20	0.06	10.15	1	**0.001**	1.22	1.08	1.38
Dose of shared epitope	0.80	0.44	3.27	1	0.07	2.23	0.93	5.34

10. 3. 9. Summary Of Findings In All Patients

In summary, in the combined group of patients, ethnic background, age, seropositivity for RF, pain, number of deformities and SJC could be used as a composite to predict the level of disability each individual was likely to experience. Of these factors, pain was the strongest predictor. When trying to predict which patient would fall into a more severely disabled group, with a HAQ of 2 or above, age, ethnic group, pain and SJC were again highly predictive, but

shared epitope emerged as a predictor, while smoking history was a protective factor.

10. 4. RESULTS: Do Caucasian Patients Have Different Factors That Influence Their Disability?

The analysis was also performed separating the two ethnic groups, to examine whether different factors were responsible for HAQ in each ethnic group. The data was analysed in the same way the combined group was analysed.

10. 4.1. Univariant Analysis To Assess Contribution To Disability In Caucasians

Univariant analyses were conducted with each individual variable to see if any had a significant contribution to HAQ in Caucasians, when other variables were not controlled for. The results are recorded in table 44. Disease duration, EMS, pain, SJC, deformities, years of education, depression and presence of nodules all made significant contributions, with pain (50.1%) and SJC (42.2%) accounting for the largest percentage of variance in HAQ.

Table 44. Univariant Analysis Of Individual Variables Influencing HAQ In Caucasians

Variable	Adjusted R^2	*P* value	*F* value
Age	-0.004	0.41	0.70
Sex	-0.01	0.50	0.47
Disease duration	0.05	**0.03**	4.68
Years of education	0.07	**0.01**	6.46
Smoking history	0.002	0.30	1.11
Presence of nodules	0.22	**<0.0005**	21.11
Sero-positivity	-0.01	0.61	0.26
SJC	0.42	**<0.0005**	52.88
Deformities	0.19	**<0.0005**	17.82
Plasma viscosity	0.004	0.26	1.30
Pain	0.51	**<0.0005**	73.64
Depression	0.12	**0.002**	10.56
EMS	0.13	**0.001**	11.81
Shared Epitope	-0.02	0.94	0.01
EAM	-0.01	0.98	0.00

10. 4. 2. Correlations Between Variables In Caucasian Patients (Appendix 7)

The full table of Pearson correlations are in appendix 7. The Caucasian patients had strong correlations between pain (r = 0.72, p <0.0005), SJC (r = 0.66, p <0.0005) and HAQ. Nodules were also correlated to HAQ, but less strongly (r = 0.48, p <0.0005). Age was not correlated to HAQ (r = 0.10, p = 0.20), which is an unexpected finding. Disease duration was strongly correlated as expected to number of deformities (r = 0.66, p <0.0005) and moderately correlated to presence of nodules (r = 0.41, p <0.0005) and SJC (r = 0.44, p <0.0005). EMS was strongly correlated to pain (r = 0.50, p <0.0005), and moderately correlated to HAQ (r = 0.38, p <0.0005) and depression (r = 0.40, p <0.0005), but not to PV (r = -0.07, p = 0.28) or SJC (r = 0.21, p =0.04). This raises a question over EMS as an indicator of disease activity in these patients.

Presence of nodules was strongly correlated with SJC (r = 0.57, p <0.0005) and deformities (r = 0.52, p <0.0005). It was moderately correlated with seropositivity for RF (r = 0.36, p = 0.001). RF seropositivity only correlated modestly with SJC (r = 0.33, p = 0.003) and deformities (r = 0.31, p = 0.004). PV did not correlate strongly with any variabie, and did not correlate with SJC, as it might be expected to (r = 0.13, p = 0.14). Shared epitope did not correlate with SJC (-0.11, p = 0.20) or deformities (r = -0.10, p = 0.23), but did correlate weakly with EAM (r =0.25, p = 0.03). Shared epitope might have been expected to correlate more strongly

with SJC or deformities as it has been found to predict for erosive damage in other studies (section 1.4.5).

10. 4. 3. Multiple Regression Analysis To Predict HAQ in Caucasians

Multiple regression analysis was used to assess all potential factors that may predict disability in Caucasian patients with RA, controlling for the effects of all other variables. Initial analyses were conducted to ensure that there was no violation of normality, linearity, multicollinearity and homoscedasticity. Age, sex, disease duration, smoking history, years of education, EMS, pain, number of deformities, SJC, presence of nodules, seropositivity for RF, plasma viscosity, depression, EAM and shared epitope were all entered. The model as a whole explained 60.2% of the total variance of HAQ (adjusted R^2 0.60, F (15, 58) = 6.85) and was significant (p<0.0005). Pain and SJC were the only two variables that showed independent predictive significance, see table 45. All data is in appendix 7.

Table 45. Multiple Regression Of Variables To Predict HAQ In Caucasian Patients

Variable	Unstandardised Coefficients		Standardised Coefficient Beta	Significance (*p* value)
	B	Standard error		
Age	0.001	0.01	0.02	0.89
Sex	-0.17	0.23	-0.07	0.48
Disease duration	-0.01	0.01	-0.07	0.60
Years of Education	-0.01	0.04	-0.03	0.79
Smoking history	-0.04	0.18	-0.02	0.81
EMS	0.03	0.10	0.03	0.75
Pain	0.23	0.06	0.52	**<0.0005**
Presence of nodules	-0.08	0.25	-0.04	0.74
Sero-positivity	-0.24	0.21	-0.11	0.27
SJC	0.05	0.02	0.37	**0.008**
Deformities	0.04	0.03	0.24	0.12
Plasma viscosity	0.45	0.72	0.06	0.53
Shared Epitope	0.06	0.15	0.04	0.69
Depression	0.002	0.03	0.01	0.95
EAM	-0.24	0.24	-0.10	0.31

10. 4. 4. Hierarchical Multiple Regression To Predict HAQ Controlling For Age, Sex And Disease Duration

Hierarchical multiple regression analysis was used to control for age, sex and disease duration, by entering these variables at Step One, and the other variables at Step 2. In the model, age, sex and disease duration accounted for 3% of the variance of HAQ (adjusted R^2 0.03, p=0.2). Entering all other variables at the second step demonstrated that the model as a whole accounted for 62.2% of the variance of HAQ (Adjusted R^2 0.62, p<0.0005). The variables at the second step accounted for 60% of the variance of HAQ (R^2 change 0.60). Pain (p<0.0005) and SJC (p=0.008) were the only variables that made a statistically significant contribution to HAQ (see table 46). Complete data is in appendix 7.

Table 46. Hierarchical Regression Analysis to Predict the HAQ in Caucasians

Variable (Model 2)	**Unstandardised Coefficients**		**Standardised Coefficient Beta**	**Significance (*p* value)**
	B	**Standard error**		
Sex	-0.17	0.23	-0.07	0.48
Age	0.00	0.01	0.02	0.89
Disease duration	-0.01	0.01	-0.07	0.60
SJC	0.05	0.02	0.36	**0.008**
Pain	0.23	0.06	0.52	**<0.0005**

10. 4. 5. Testing the Model for Caucasians

Stepwise regression analysis was used to create a model to predict HAQ in Caucasian patients with RA. Pain and SJC emerged as the two predicting variables. Entering only pain and SJC into the model explained 64.9% of the variance in HAQ (adjusted R^2 0.65) and was significant ($p<0.0005$, F (2, 72) = 66.52). Pain had a higher beta value (beta = 0.53, $p<0.0005$) than SJC (beta = 0.42, $p<0.0005$, see table 47). Raw data is in appendix 7.

Table 47. Stepwise Regression To Create A Model For Predicting HAQ In Caucasian Patients

Variable	Unstandardised Coefficients		Standardised Coefficient Beta	Significance (*p* value)	R^2 change	*F* change	*P* value for *F* change
	B	Standard error					
SJC	0.06	0.01	0.42	**<0.0005**	0.51	59.96	**<0.0005**
Pain	0.23	0.03	0.53	**<0.0005**	0.15	23.91	**<0.0005**

10. 4. 6. Logistic Regression: Calculating The Odds Ratio To Predict HAQ For Caucasian Patients With RA

Direct logistic regression was also used to create a model to predict disability, in order to calculate the odds ratio for pain and disability. All variables (age, sex, disease duration, years of education, smoking, depression, nodules, RF sero-positivity, pain, SJC, PV, EMS, shared epitope, EAM) were initially entered, but pain and SJC were again found to be the only significant predictors. The full model containing all variables was statistically significant, χ^2 (13, N = 72) = 52.23, p<0.0005, and was able to classify 89.8% of cases. The model explained between 58.7% (Cox & Snell R^2) and 80.1% (Nalgelkerke R^2) of the variance in HAQ. Backwards logistic regression confirmed that pain and SJC were the variables that created the best fit model.

When only pain and SJC were entered, the model was statistically significant, χ^2 (2, N = 72) = 40.43, p<0.0005, and was able to classify 86.4% of cases. This model explained between 49.6% (Cox & Snell R^2) and 67.7% (Nalgelkerke R^2) of the variance in HAQ. The strongest predictor of HAQ > or = 2 was pain, with an odds ratio of 2.03 (see table 48). This indicates for every 10mm extra an individual scored on the pain VAS, an individual was twice as likely to have a HAQ of 2 or more. Complete data is in appendix 7.

Table 48. Model Predicting HAQ In Caucasians with RA showing Odds Ratio

Variable	B	S.E.	Wald	df	p	Odds ratio	95% Confidence interval for odds ratio	
							Lower	Upper
Pain	0.71	0.20	12.14	1	**<0.0005**	2.03	1.36	3.02
SJC	0.20	0.07	8.28	1	**<0.0005**	1.22	1.06	1.39

10. 4. 7. Summary Of Predictors Of HAQ In Caucasian Patients With RA

The disability of Caucasian patients with RA as measured by the HAQ can be most simply predicted by their pain scores on the VAS, and by the number of swollen joints they have. Other disease severity factors seem to be less important in this group.

10. 5. RESULTS: Predictors Of HAQ In Gujarati Asian Patients With RA

Gujarati patients were analysed separately, to examine whether the same or different factors could predict their disability score on the HAQ.

10. 5. 1. Univariant Analyses To Identify Variables That May Predict HAQ In Asian Patients

Univariant analyses were carried out to examine if any variable had a significant impact on the HAQ when other variables were not controlled for. The results are below in table 49. Age, disease duration, pain, deformities, years of education and depression were the unadjusted variables that significantly predicted HAQ.

Table 49. Univariant Analysis Of Individual Variables Influencing HAQ In Asians

Variable	Adjusted R^2	*P* value	*F* value
Age	0.28	**<0.0005**	24.78
Sex	-0.02	0.82	0.05
Disease duration	0.22	**<0.0005**	18.10
Years of education	0.07	**0.02**	5.65
Smoking history	-0.01	0.53	0.41
Presence of nodules	-0.01	0.56	0.35
Sero-positivity	-0.01	0.55	0.35
SJC	0.04	0.06	3.59
Deformities	0.22	**<0.0005**	18.05
Plasma viscosity	-0.002	0.36	0.87
Pain	0.12	**0.004**	9.25
EMS	0.04	0.08	3.18
Shared Epitope	-0.02	0.51	0.44
Depression	0.12	**0.004**	8.80
EAM	0.002	0.29	1.15

10. 5. 2. Correlations Between The Variables In Asian Patients When Predicting HAQ

The complete table of correlations is in appendix 7. In the Asian patients, HAQ was most strongly correlated with age (r = 0.54, $p<0.0005$), but was also correlated moderately strongly with disease duration (r = 0.48, $p<0.0005$), deformities (r = 0.48, $p<0.0005$), pain (r = 0.37, $p = 0.002$) and depression (r = 0.36, $p = 0.002$). HAQ was negatively correlated with years of education (r = -0.30, $p = 0.01$). In the Asian patients, the correlation with SJC was much weaker (r = 0.24, $p = 0.03$).

Disease duration was strongly correlated with deformities (r = 0.58, $p<0.0005$), which would be expected. EMS was correlated with pain (r = 0.37, $p = 0.002$), and only weakly correlated with SJC (r = 0.28, $p = 0.01$) and not correlated with PV (r = 0.03, $p = 0.41$). In this group, EMS does not seem to be related to inflammation.

Presence of nodules was correlated with deformities (r = 0.36, $p = 0.002$), and less strongly with disease duration (r = 0.25, $p = 0.03$). RF seropositivity was correlated most strongly with PV (r = 0.41, $p = 0.001$). Shared epitope was negatively correlated with pain (r = -0.50, $p = 0.001$) and with EMS (r = -0.29, $p = 0.03$). This was surprising, and may reflect that pain and EMS are influenced by multiple factors. Shared epitope was not correlated with SJC (r = -0.10, $p = 0.26$)

or deformities (r = -0.08, p = 0.31), which echoes the findings in the Caucasian patients. It has been closely linked to erosive disease (section 1.4.5), and so might be expected to correlate with SJC and deformities. PV is as strongly correlated with age (r = 0.32, p = 0.006) as it is with SJC (r = 0.34, p = 0.004), which suggests that PV may be affected by other variables than just disease activity in this patient group.

10. 5. 3. Multiple Regression To Identify Predictors Of HAQ

Using standard multiple regression, the same range of variables were entered into the analysis; age, sex, disease duration, SJC, presence of nodules, seropositivity for RF, pain, EMS, years of education, smoking history, depression, EAM and shared epitope. Only age was a significant factor in predicting HAQ (p=0.02). All variables only accounted for 36.3% in the variation of HAQ (adjusted R^2 0.36), and the model was statistically significant (p=0.03, F (15, 38) = 2.45, table 50). The only variable that made a unique statistically significant contribution when all other variables were controlled for was age (p=0.02). In the Caucasian patients, this model predicted 59.8% of the variance in HAQ. The Asian model was much weaker, suggesting that other factors outside this analysis were contributing to the variance of the HAQ in the Asian patients.

Table 50. Multiple Regression To Predict HAQ In Asian Gujarati Patients With RA

Variable	Unstandardised Coefficients		Standardised Coefficient Beta	Significance (*p* value)
	B	Standard error		
Age	0.05	0.02	0.55	**0.02**
Sex	-0.33	0.64	-0.10	0.61
Disease duration	-0.01	0.03	-0.04	0.83
Years of education	-0.01	0.05	-0.02	0.89
Smoking history	-0.10	0.64	-0.03	0.88
EMS	0.11	0.12	0.17	0.34
Pain	0.09	0.10	0.19	0.36
Depression	0.00	0.04	-0.01	0.97
Presence of nodules	0.29	0.48	0.11	0.55
Sero-positivity	-0.22	0.32	-0.11	0.50
SJC	0.05	0.05	0.19	0.33
Deformities	0.04	0.03	0.23	0.25
Plasma viscosity	-0.88	1.38	-0.14	0.53
Shared epitope	0.23	0.24	0.16	0.35
EAM	0.28	0.43	0.10	0.53

10. 5. 4. Testing The Model Used To Predict HAQ In The Gujarati Patients

Stepwise regression analysis was used to help create a model to predict HAQ in Asian patients with RA. Age, EMS and deformities were identified as the variables which could most accurately predict the HAQ in Asians. The model as a whole predicted 51% (adjusted R^2) of cases. Age was the most important predictor, responsible for 37.2% of the variance in HAQ (R^2 change, see table 51). Number of deformities was responsible for a further 18% variance in the HAQ, while EMS was responsible for 6%.

Table 51. Stepwise Multiple Regression: Creating A Model For Predicting HAQ In Gujarati Asian Patients

Variable	**Unstandardised Coefficients**		**Standardised Coefficient Beta**	***p* value**	**R^2 change**	***F* change**	***P* value for *F* change**
	B	**Standard error**					
Age	0.05	0.01	0.57	**<0.0005**	0.37	21.91	**<0.0005**
Deformities	0.05	0.02	0.31	**0.01**	0.18	8.28	**0.007**
EMS	0.16	0.08	0.25	**0.04**	0.06	4.57	**0.04**

10. 5. 5. Hierarchical Multiple Regression: Controlling For Age, Sex And Disease Duration When Predicting HAQ

Hierarchical multiple regression analysis was performed, adjusting for age, sex and disease duration, with all variables entered at step 2. This model was not significant. This may be because age was the most important variable to influence HAQ. Table with all data is in appendix 7.

EMS and deformities were examined separately, to see if the model still worked after controlling for age. Age, sex and disease duration were added at Step 1, explaining 28.4% of the variance in HAQ. After entering EMS and deformities, the total variance of HAQ described by the model as a whole was 45.0%, and this was significant ($p<0.0005$). EMS and deformities explained an extra 10.7% of the variance in HAQ (R^2 change 0.11, F change (2, 56) = 5.85, $p=0.004$). Data is in appendix 7.

10. 5. 6. Logistic Regression to Calculate the Odds Ratio When Predicting HAQ In Asians

Logistic regression was used with the same model, entering age, EMS and deformities to calculate odds ratios. The full model was statistically significant, χ^2 (3, N = 61) = 19.72, $p<0.0005$, showing that the model was able to distinguish between those with a HAQ > or =2, and those less disabled, with a HAQ <2. The

model as a whole explained between 27.6% (Cox & Snell R^2) and 38.9% (Nagelkerke R^2) of the variance in HAQ, and correctly classified 80.3% of cases. Age was the only uniquely significant variable (p=0.002). EMS had the highest odds ratio, 1.28 (see table 52), which suggests that for each additional hour of EMS, there was a 1.28 chance the patient would have a HAQ score of 2 or more.

Table 52. Logistic Regression To Predict HAQ In Gujarati Asians

Variable	B	S.E.	Wald	df	*P* value	Odds ratio	95% Confidence interval for odds ratio	
							Lower	Upper
Age	0.12	0.04	9.68	1	**0.002**	1.12	0.12	0.04
Deformities	0.11	0.07	2.62	1	0.11	1.12	0.11	0.07
EMS	0.24	0.27	0.83	1	0.36	1.28	0.24	0.27

10. 5. 7. Summary: Predicting The HAQ In Gujarati Asians With RA

For Gujarati Asians, the factors predicting HAQ were different to those predicting HAQ in the Caucasian patients. Age, number of deformities and EMS are the most important predicting factors. SJC and pain were less important than in Caucasian patients.

10. 6. RESULTS: What Variables Predict Number Of Swollen Joints In Patients With RA?

Univariant analysis was performed to investigate which variables predicted SJC. Age, sex, disease duration may potentially affect SJC. Known markers of disease severity such as presence of nodules, RF seropositivity, shared epitope dose, smoking history, PV, and EAM may also influence SJC. Number of deformities may be related as it may represent prior disease. SJC has already been shown to predict HAQ, so it would be expected that HAQ would be strongly related to SJC, and so it was not included in the analysis.

10. 6. 1. Univariant Analysis To Predict SJC In All Patients With RA

Univariant analysis was carried out to see if any variable had an effect on the SJC (see table 53). Age, disease duration, ethnic group, presence of nodules, seropositivity for RF, number of deformities and EMS were all statistically significant predictors of the SJC.

Table 53. Univariant Analysis To Examine Variables Predicting SJC In All Patients With RA

Variable	Adjusted R^2	*F* value	*P* value
Age	0.03	4.32	**0.04**
Sex	0.004	1.50	0.22
Disease duration	0.12	19.73	**<0.0005**
Ethnic group	0.03	5.04	**0.03**
Smoking history	-0.01	0.05	0.83
Presence of nodules	0.18	29.31	**<0.0005**
Sero-positivity	0.06	9.10	**0.003**
Deformities	0.23	40.20	**<0.0005**
Plasma viscosity	0.01	2.91	0.09
EMS	0.03	4.50	**0.04**
Shared Epitope	-0.01	0.08	0.78
EAM	0.00	1.19	0.28

10. 6. 2. Creating A Model To Predict SJC In All Patients

Stepwise multiple regression analysis was performed to create a model to predict SJC. SJC was the dependent variable, and age, sex, disease duration, ethnic group, presence of nodules, RF seropositivity, shared epitope dose, number of deformities, smoking history, PV, and EAM were entered as independent variables.

Number of deformities, presence of nodules, and PV emerged as the variables that formed the best fit model to predict SJC in all patients (see table 54). The number of deformities made the biggest contribution to the variance of SJC (adjusted $R^2 = 0.23$). Presence of nodules contributed 5.6%, and PV 3.5% of the variance of SJC. The model as a whole was statistically significant (F (3, 97) = 15.15, p <0.0005) and predicted 30.4% of the variance in SJC (adjusted R^2). Raw data is in appendix 7.

Table 54. Stepwise Multiple Regression: Creating A Model To Predict SJC In All Patients With RA

Variable	**Unstandardised Coefficients**		**Standardised Coefficient Beta**	***p* value**	**R^2 change**	***F* change**	***P* value for *F* change**
	B	**Standard error**					
Deformities	0.39	0.10	0.37	**<0.0005**	0.24	29.46	**<0.0005**
Nodules	3.66	1.25	0.28	**0.004**	0.06	7.54	**0.007**
PV	7.82	3.55	0.19	**0.03**	0.04	4.85	**0.03**

10. 6. 3. SJC In Caucasians: Predicting Factors

The patients were separated into ethnic groups and analysed separately to see if the same factors predicted SJC in each group, as this variable may have been more objective.

Stepwise multiple regression analysis was used in the Caucasian patients. There was no violation of normality, linearity, multicollinearity and homoscedasticity. The model was statistically significant as a whole ($p<0.0005$, F (2, 58) = 26.08), and deformities and nodules were predictive of SJC (see table 55). Number of deformities made the largest contribution, predicting 39.2% (adjusted R^2) of the variance in SJC, while presence of nodules accounted for 7.9% (R^2 change). Surprisingly, PV was not part of the model. It may be that PV is influenced by other factors, and is less good as a predictor of disease activity in this group.

Table 55. Stepwise Multiple Regression: Creating A Model To Predict SJC In Caucasian Patients With RA

Variable	**Unstandardised Coefficients**		**Standardised Coefficient Beta**	***p* value**	**R^2 change**	***F* change**	***P* value for *F* change**
	B	**Standard error**					
Deformities	0.56	0.14	0.46	**<0.0005**	0.40	38.47	**<0.0005**
Nodules	4.52	1.54	0.33	**0.005**	0.08	8.58	**0.005**

10. 6. 4. SJC In Gujarati Asian Patients: Predicting Factors

Gujarati Asian patients were analysed separately by stepwise multiple regression analysis to see if the predicting factors for SJC were conserved across the ethnic groups (see table 56).

There was no violation of normality, linearity, multicollinearity or homoscedasticity. In Asian patients, PV and deformities only predicted the SJC. The model as a whole was significant (p = 0.009, F (1, 38) = 5.45), but was a very poor model, predicting only 19% of cases (adjusted R^2).

Table 56. Stepwise Multiple Regression To Predict SJC In Asian Patients With RA

Variable	Unstandardised Coefficients		Standardised Coefficient Beta	*p* value	R^2 change	*F* change	*P* value for *F* change
	B	Standard error					
PV	12.18	4.54	0.40	**0.01**	0.11	4.72	**0.04**
Deformities	0.28	0.12	0.35	**0.02**	0.12	5.60	**0.02**

10. 6. 5. Summary: Predicting SJC In RA Patients In Different Ethnic Groups

The number of deformities, presence of nodules, and higher PV were all predictive factors for SJC in the combined patient group. Ethnicity did not emerge as a predictive factor.

When the ethnic groups were examined separately, presence of nodules and number of deformities predicted SJC in Caucasians, and PV and number of deformities predicted SJC in the Asians. In Asian patients the model was poor. SJC in the Asian patients may be influenced by factors not examined in this analysis.

10. 7. Examining The Difference In Disease Severity Between Gujarati Asians And Caucasians: Using Multivariate Analysis Of Variance

An experiment was conducted to attempt to create a disease outcome measure similar to that recommended by OMERACT (section 10. 2.1). Four dependent variables were selected from the variables measured: SJC, PV, pain and disability as measured by the HAQ score. A one way between groups multivariate analysis of variance (MANOVA) was performed to investigate ethnic differences in disease severity. The independent variable was ethnic group. Preliminary assumption testing was conducted to check for normality, linearity,

univariate and multivariate outliers, homogeneity of variance-covariance matrices, and multicollinearity, with no serious violations noted.

There was a statistically significant difference between Caucasians and Gujarati Asians on the combined dependent variables, F (4, 128) = 13.80, p<0.0005; Wilks' Lambda = 0.70; partial eta squared = 0.30. When the results for the dependent variables were considered separately, only pain (F (1, 131) = 16.03, p <0.0005, partial eta squared = 0.11) and HAQ (F (1, 131) = 15.23, p<0.0005, partial eta squared = 0.10) reached statistical significance, using a Bonferroni adjusted alpha level (p value) of 0.001 (see table 57). This means that 10.9% of the difference in pain and 10.4% of the difference in HAQ could be explained by ethnic group. These are medium effect sizes (Cohen 1988). Examining the means showed that Asians reported higher pain and HAQ scores than Caucasians. By this analysis, Asians had significantly more severe disease than Caucasians, but it is interesting to note that this was achieved because of higher pain and disability scores. These were the two subjective variables.

Table 57. MANOVA To Examine Difference In Disease Severity Between Asians And Caucasians

Variable	*F* value	Significance	Partial eta squared	Mean		S.E.	
				Cauc-asians	Asians	Cauc-asians	Asians
SJC	5.04	0.03	0.037	10.4	8.07	0.70	0.77
Pain	16.03	**<0.0005**	0.109	3.67	5.14	0.25	0.27
HAQ	15.23	**<0.0005**	0.104	1.26	1.93	0.12	0.13
PV	10.09	0.002	0.071	1.70	1.78	0.02	0.02

10. 8. DISCUSSION

There are difficulties assessing outcome measures in RA. Composite measures involving a mixture of physician derived, patient derived and laboratory derived scales have been developed by the OMERACT group for use in clinical trials (Felson 1993). These are designed to be able to detect differences in response to treatment, rather than designed to assess disease outcomes for the individual patient. Disability as measured by the HAQ is a reliable and well validated direct outcome measure of an inflammatory arthritis, but may be impacted on by other factors than just the manifestations of the disease itself, and this shows in the results.

10. 8. 1. Disease Severity In The Combined Group Of Patients: Factors That Predict HAQ And SJC

In the combined group of patients, a model was calculated for predicting the HAQ. It utilised pain, SJC, number of deformities, age, seropositivity for RF and ethnic group, the scores for which, when combined, allowed prediction of 59.7% of the variance in HAQ.

Pain may reflect current disease activity, as well as past damage, and has been found to be strongly predictive of HAQ in RA (Rupp 2006). It may also be impacted on significantly by other factors, such as depression (see section 5.3.3). It was the strongest predictor of disability as measured by HAQ in the combined group of patients. It might be expected that more pain would worsen disability, and this has been found in other studies (Strating 2007). Age is well recognized to impact on the HAQ, which deteriorates predictably with aging (Sokka 2006). Number of deformities is a surrogate marker for previous joint damage, and SJC may represent the current activity of the disease. Seropositivity for RF has been associated with more erosive disease (Bukhari, Lunt et al. 2002), which may account for its predictive value in this sample.

Interestingly PV did not accurately predict the HAQ. It might be expected that markers of inflammation might predict disease severity. This may be because other factors impact on its value, making it a less accurate reflection of disease

activity in this group of patients. Presence of nodules was also not found to be predictive of HAQ. This suggests that other factors were much more important in governing disability, making the impact of nodules less relevant. Nodules were a predictor for SJC, and thus still a predictor for disease activity, but they did not have as much impact on disability as a final outcome.

Dividing HAQ into 2 groups to represent moderate to severe disability (> or = 2) and mild to no disability (<2) preserved pain, SJC, age and ethnic group as predictors, but shared epitope also emerged as a weak predictor. It has been shown in studies to be related to erosive disease (Gorman, Lum et al. 2004), which is linked to deformity and disability. Smoking was found to be protective, which was not expected, as other studies have shown a link between smoking and disease severity (Manfredsdottir, Vikingsdottir et al. 2006). This may represents its close relationship with ethnicity (Pearson correlation = -0.41), as very few Asian patients smoked in comparison to the Caucasian patients (see section 4.2.9). It may be a surrogate marker for another factor, such as affluence or sociability, which is not accounted for here.

Predictive measures for SJC were number of deformities, presence of nodules, and PV in all patients. A high PV would be expected to reflect more disease activity, and the presence of nodules has been associated with more severe disease (Turesson, O'Fallon et al. 2003). Number of deformities may have been a surrogate marker for previous disease severity. It is expected that those

patients who have more severe disease in the past might have more joint deformities, so it is not surprising that patients with a history of severe disease might continue to have many swollen joints.

Ethnicity was an independent predictive factor for disability as measured by the HAQ. This suggests that there may be other factors which control disability that are related to ethnicity, which were not examined in this study. It is possible that cultural differences may have had an impact. This may include negative attitudes to chronic disease, or adverse learned coping mechanisms, that may impact on their disability. Although this has not been studied in rheumatoid, a study in Leicester looked at attitudes of Gujarati patients after myocardial infarction (Webster 2002). It found that Gujarati patients had poor expectations and a lack of plans for the future after the event, and a belief in fate. They were also dissatisfied with their GP (general practitioner). This was also found in a study in London which examined influences for hospital admission for asthma in Asian and Caucasian patients (Griffiths 2001). South Asian patients had less confidence in their GP, and less confidence in controlling their asthma. This lack of trust in the medical services available to them, and disempowerment in controlling the disease process may also be important in the Gujarati patients with RA, and may contribute to their poorer outcomes.

10. 8. 2. Ethnicity: Differences Between The Ethnic Groups In Variables Predicting Outcome Measures

In the Caucasians, the best fit model for predicting HAQ consisted of pain and SJC. This finding has been echoed in other Northern European RA populations (Strating 2007). This is not a surprising finding: pain perceived and joints affected are likely to impact on an individual's ability to function in day to day life. What is more puzzling is that these variables were not preserved in Gujarati Asian patients. In the Asian RA patients, HAQ could be best predicted with age, number of deformities and length of EMS. It may be that age has a more profound effect on the helplessness of Asian patients, encouraging them to seek the 'sick role' in their families and depend more on those around them, sapping their coping ability. The fact that deformities rather than SJC acted as a predictor suggests that past damage is more a factor than current disease activity. This may reflect on the lack of ability of the Asian patients to adapt to their permanent disabilities, so that they are constantly challenged by them. EMS is often thought to be an indicator of active disease. EMS in this study did not correlate with other markers of disease activity such as the PV or the SJC. It did correlate with pain, both in the Caucasians and the Asians. It may be more a function of pain than of disease activity. This was echoed in a study in North America, where EMS was found to reflect disability and pain more accurately than ESR or joint counts (Yazici 2004). 89% of their patient group was Caucasian, the rest of the ethnic mix was unreported.

In predicting SJC, the results are less surprising. In the Caucasian patients, SJC is best predicted by number of deformities and presence of nodules. Nodules are recognized to be associated with more severe disease (section 1.3.2), and number of deformities demonstrates previous damage. In the Asian patients, only 19% of the variance in SJC could be predicted and that was by PV and number of deformities. This suggests that factors other than those examined may be influencing the SJC in Asian patients. It may be that CRP would be a better serological marker to look at in this population, as PV was more closely correlated with age than with SJC in these patients. Nodules seem to be less common in Asian patients (section 5.2.2), so their lack of predictive power may just reflect the lower prevalence of nodules in the Asian patients.

The results in my study show that Gujarati Asian patients with RA have poorer outcomes of RA than Caucasians in terms of disability. In these patients, disability seems to be influenced by different aspects of the disease process than in Caucasian patients, and therefore interventions aimed at, for example, reducing SJC, may not translate into improved mobility. Pain is also less important than age or past deformities in the Asian patients. There may be other aspects to coping with chronic disease that influence disability, and future studies should seek to examine this in more detail. There are marked differences between the Asians and the Caucasians in aspects such as their diet (see

section 4.4.3), their mood (see section 9.2.1), and their socioeconomic status (see section 4.3), all of which may be having an impact.

This study suggests that Asian patients will continue to have poor outcomes in terms of disability despite intervention by the treating physician to reduce SJC and PV, the clinical indices most commonly measured in the clinic.

10. 8. 3. Differences Between Ethnic Groups In Disease Severity: Using A Composite Measure

As an experiment, Caucasians and Gujarati Asians were compared using multivariant analysis of variance (MANOVA), using the variables available that matched most closely with the recommendations of the OMERACT group. This was a combination of pain, PV, HAQ and SJC: a mixture of clinical, physician derived and patient derived scores and laboratory results. This might be expected to give the most accurate picture of 'disease severity', as it seeks to use all these factors, rather than just picking out one or two that may be influenced by factors outside the actual disease itself. Using this test, there was a significant difference between the two groups; one ethnic group had significantly worse disease, as measured by this method. Looking at the individual scores, it was pain and HAQ that reached significance, both reaching a medium effect size, with Asians scoring worse (higher) scores for both these variables. This means that by this analysis, using a combination of relevant variables to assess

disease severity, Gujarati Asian patients had more severe disease than Caucasian patients. It is important to note that the higher scores were the patient derived scores. The result has been strongly influenced by the subjective scores. The previous analyses have shown that HAQ is influenced by different factors in the two ethnic groups, and so this result may be showing a poorer outcome, but not necessarily more severe disease.

10. 8. 4. Gujarati Asians: Less Likely to Have Known Markers Of Disease Severity, But Do They Have Milder Disease?

The factors that in a Caucasian population might alert a treating physician to the onset or presence of more severe disease are less common in the Leicester Gujarati Asian patients with RA. As seen in chapter 5.2.2, Asian patients were significantly less likely to have nodules, or to be sero-positive for RF. Asian patients had a lower frequency of the shared epitope (chapter 6.3.2). They are less likely to smoke (chapter 4.2.9). They have less severe extra-articular manifestations (chapter 5.2.4), and lower SJC (chapter 5.2.2). It has been suggested that Asian patients in the UK have less severe disease than their Caucasian contemporaries (Griffiths, Situnayake et al. 2000). The findings made by Griffiths et al were largely replicated by my study; they found fewer nodules, a lower frequency of shared epitope, and much higher disability and pain levels in their South Asian patients.

In both the HAQ and the combined outcome measures (Pain, SJC, PV and HAQ), the Gujarati Asian patients did badly. It has already been shown that they are less likely to express the factors that might alert a physician to more severe disease, such as rheumatoid nodules or RF. This study shows that although they do not have these markers, they still have severe disability. It seems that in this group of patients, traditional disease severity markers are less important when assessing an individual's risk of developing disabling disease. Other factors such as self empowerment, adequate coping strategies and confidence in both primary and secondary care may be more important. These factors need to be looked at in more depth in this vulnerable group of patients, and interventions need to be developed that address needs. These interventions will need to be appropriate and sensitive to the cultural context. Only then will the needs of the immigrant Asian patients be adequately addressed.

CHAPTER 11. CONCLUSION AND FURTHER DIRECTIONS

This study aimed to build up a picture of rheumatoid arthritis in the patient population of Leicester, with reference to its two biggest ethnic groups – Anglo-Saxon/Celtic British, and Gujarati Asian. It showed clear differences between the two groups, socioeconomically, with respect to disease severity, with respect to HLA type, and most profoundly, in terms of their psychological distress.

11. 1. SUMMARY OF RESULTS:

An age, sex and disease duration matched population of Gujarati Asian and Caucasian patients in Leicester with RA have the following similarities and differences:

11.2. Socioeconomic Status:

1. They have equivalent marital status, education and housing.
1. Gujarati patients have more family at home, a larger social network of helpers, more children at home, and more in-laws living with them.
2. Gujarati patients drink and smoke less than the Caucasians, and are likely to be vegetarian, and eating a traditional Indian diet.
3. Gujarati patients are likely to be unable to work because of reported disability, and to have worked in less skilled occupations

4. Gujarati patients are more likely to have social services support, and to have more forms of social services support.

11. 3. Rheumatoid Disease:

5. Gujarati patients have a lower swollen joint count, less nodulosis and less sero-positivity for RF.
6. Gujarati patients have longer EMS, more pain, more disability and more 'mild' extra-articular manifestations than Caucasians.
7. Gujarati patients have a higher PV and a lower Hb than Caucasians.
8. Gujarati patients had an earlier age of disease onset than Caucasians.

11. 4. HLA And Shared Epitope Status:

9. Gujarati patients were less likely to have a copy of the shared epitope. If they had a copy, it was likely to be HLA DRB1*10, while Caucasian patients expressed HLA DRB1*04 and DRB1*01.

11. 5. Treatment:

10. There were no differences in treatments given in both groups, either in interventions, number or type of DMARDs used, steroid use, analgesics or anti-depressants. Patients were equally compliant.

11. Gujarati patients were more likely to complain of a rash as a side effect of their medication, but no more likely to get side effects than Caucasians.
12. Gujarati patients were more likely to be taking calcium and vitamin D supplements
13. Gujarati patients rated their treatment as significantly less effective than the Caucasian patients.
14. Although the majority of patients had tried complementary medicine, the Gujarati patients were more likely to have tried acupuncture. Both groups felt acupuncture was the most effective of the CAM. Gujarati patients rated herbal remedies as more effective than Caucasians did, but neither rated CAM above their hospital initiated DMARD treatment.

11. 6. Psychological status:

15. Gujarati patients were highly significantly more depressed on the SRQ than Caucasians, despite having no differences in threatening life events.

11. 7. Do Asian patients with RA have more severe disease than Caucasian patients?

16. Ethnic group was an independent risk factor for disability, despite controlling for markers of disease severity, with Asians being more disabled. SJC and pain

could predict Caucasian disability well, but Asian patients' disability was influenced by factors outside those studied.

11. 8. Summary And Future Directions

This study has shown that the rheumatoid disease is different in the two ethnic communities. Disease processes in British Caucasians cannot be directly extrapolated to the immigrant Gujarati community, as they refuse to fit those parameters. In particular, disease is likely to have a profound impact on function in Asian patients. Asian patients have different clinical needs to Caucasians, and treating physicians need to be alert for depressive symptoms, and to treat pain effectively. Traditional markers of disease severity seem to be less frequent, but their disease has a significant impact, and should not be underestimated in terms of how it affects them.

With such a large, ethnically discrete community, there is the opportunity to perform more detailed in depth analysis of aspects of the psychological distress suffered. Future generations of Gujarati patients will offer the scope to repeat this work, to see if the negative effects of lack of acculturation and migrant status become less marked. Knowledge of anti-CCP antibody status and CRP measurements would be useful in these populations, as PV does not seem to correlate closely with other markers of disease activity.

LIST OF FIGURES

Fig. 12 Percentage of Asian and Caucasian patients who had side effects with one or more DMARD

LIST OF TABLES

LIST OF ABBREVIATIONS

ABgene	Company supplying commercial reagents
ACR	American College of Rheumatology
ANOVA	Analysis of variance
ARA	American Rheumatism Association
ARC	Arthritis Research Campaign
AW1	Commercial buffer made by Quigen
AW2	Commercial buffer made by Quigen
CAM	Complementary and alternative medicine
CCP	Cyclic citrullinated peptide
CD	Cluster of differentiation
χ^2	chi-squared
CLP	Commercial company supplying chemicals and reagents
COX 2	Cyclic oxygenase 2 inhibitor
CRP	C-reactive protein
DAS	Disease Activity Score
df	Degrees of Freedom
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
EAM	Extra-articular manifestations
EDTA	Ethylenediaminetetraacetic acid
EMS	Early morning stiffness
ERAS	Early Rheumatoid Arthritis Study

ESR	Erythrocyte sedimentation rate
F value	Ratio of mean squares
Ficoll	Hydrophilic polysaccharide made by GE Heathcare
GP	General practitioner
HAQ	Health Assessment Questionnaire
Hb	Haemoglobin
HLA	Human Leukocyte antigen
MANOVA	Multivariant analysis of variance
MHC	Major histocompatibility complex
N/A	Not applicable
No.	Number
NOAR	Norfolk Arthritis Register
NSAID	Non-steroidal anti-inflammatory drug
Od	Once daily
OMERACT	Outcome measures in rheumatoid arthritis clinical trials
P	Probability (*p* value represents significance)
PCR-SSP	Polymerase chain reaction with sequence specific primers
PV	Plasma viscosity
R	Regression
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SD	Standard deviation
S. E.	Standard error

SRQ	Self Reporting Questionnaire
T cell	Thymus cell
Tris-HCl	2-Amino-2-(hydroxymethyl)-1,3-propanediol, hydrochloride
Tween 20	Polyoxyethylene (20) sorbitan monolaurate
VAS	Visual analogue scale
WHO	World Health Organisation

APPENDIX 1: Information leaflet given to patient

IS RHEUMATOID ARTHRITIS DIFFERENT IN GUJERATI ASIAN AND CAUCASIAN POPULATIONS?

Principal Investigator Dr. Cai Neville

You may contact Dr. Cai Neville at Dept. Of Rheumatology,
Leicester Royal Infirmary,
Infirmary Square,
Leicester,
LE1 5WW.
Tel. 0116 2585253

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that it not clear or if you would like more information. Take time to decide whether or not you wish to tale part.

Thank you for reading this.

1. What is the purpose of the study ?

This study is to compare the differences between Gujerati Asian patients with rheumatoid arthritis and Caucasian patients. No-one has ever looked into this, and we feel that there are significant differences in disease, disability, treatments, inheritance, and blood markers between the two groups. We would like to examine these differences in some detail so that doctors can have a better understanding of rheumatoid arthritis in Asian patients.

We are also hoping that by comparing Asian patients to white patients, we may get an idea of why people get this illness in the first place. As Asians have been living here for fewer generations than white people, we are hoping to find differences that may give clues as to the trigger for the disease. Could it be something in the environment of the area? This may help us in our search for the reasons why we get rheumatoid arthritis. This will be immensely helpful to all patients, regardless of ethnic background.

3. What will be involved if I take part in the study ?

We would ask you to come to the hospital for an interview covering such issues as pain, disability, previous and planned drug and surgical treatment,

family history of joint problems, current joint problems, cough, breathlessness, and other questions related to the disease.

Our interviewer will also examine you to assess your joints and other systems that can be affected by rheumatoid, such as heart, lungs and skin.

Many different diseases are associated with a certain degree of inheritance, meaning that if your parents have that illness, you have a greater chance of contracting it than someone who is not related to anyone with that disease. While we don't as yet have very much information about the *genes* associated with rheumatoid arthritis, we do know that there are protein markers connected to it. These markers are something we call 'HLA', and they are essentially proteins that everybody has on each of their cells.

The interesting and useful thing about these proteins is that in the same way that we all look different from each other, these proteins are slightly different in each of us. In the way that you look similar to your family, so you are more likely to have the same types of these proteins. Of course, they are not as varied as the way we look, and it is possible to have exactly the same combination as someone who *isn't* related to you. You probably know how we already exploit this in medicine, by using these same proteins to match up people for organ transplants.

In rheumatoid arthritis, there are several specific types of these HLA markers that Caucasian people with the disease seem to be more likely to have. We don't know if Asian people with rheumatoid share these markers, or if they have a different type of HLA associated with the disease. This knowledge would help us to a better understanding of the disease and hopefully give us more clues as to how and why people develop it.

We would like you to have a blood test to test your HLA proteins for markers of rheumatoid arthritis. This is to show if these are different in the Asian and Caucasian populations. This examines the way our genes control how we end up. It is NOT the same as 'DNA fingerprinting', as it doesn't directly test your genes, and doesn't give us nearly enough information even to identify one person from another. The only information we are looking for is the types of this protein, 'HLA', that are known to be connected to rheumatoid arthritis. We are not looking for connections to any other kind of disease.

We would also like to test your blood for markers of disease activity and to see if you are anaemic. We will also test your blood for 'rheumatoid factor' and other antibodies that show what kind of arthritis you have. If you have not had your hands x-rayed in the last two years, we will arrange an x-ray. These are the tests that we use to monitor rheumatoid arthritis in our patients normally. You will probably have had these tests on many previous clinic visits.

Rheumatoid arthritis can affect the lungs in many ways. We will be asking you about breathing difficulties. If you have ever had problems with your breathing, we may ask you to undergo breathing tests. These involve blowing hard into a complicated piece of apparatus that can tell us how well your lungs are working, and if the arthritis has affected them in any way. If you have difficulty with your breathing, or the blowing tests show that your lungs are affected, we may arrange a CT scan of your lungs. This would be to get a more detailed picture of your lungs to help us work out how and where they have been affected. We would normally arrange these tests in clinic for anyone we thought had breathing problems, so it may be that you have already had these sorts of tests. If you have had them recently as part of your usual treatment, we would not repeat them.

If, at that time, your joints required injection or aspiration, or you needed other medical treatment or investigation that you might usually have in a clinic visit, we would perform that at the same time.

4. Will information obtained in the study be confidential ?

If you receive any treatment (i.e. joint injections) as a consequence of your visit, this will be documented in your medical notes, and it will be treated with the usual degree of confidentiality under the data protection act.

All interviews as part of the study will be recorded separately, and *will not be identified* under your name.

The HLA testing carried out will only be to identify known markers for rheumatoid arthritis, and will not be examined for evidence of other conditions. The results will not be entered into your medical notes or recorded under your name.

We will inform you GP of your participation in this study unless you have some reason for wanting us not to.

5. What if I am harmed by the study ?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

6. What happens if I do not wish to participate in this study or wish to withdraw from the study ?

If you do not wish to participate in this study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected.

APPENDIX 2: **PATIENT CONSENT FORM**

IS RHEUMATOID ARTHRITIS DIFFERENT IN GUJERATI ASIANS THAN IN CAUCASIANS?

Principal Investigator Dr. Cai Neville, MRCP.

This form should be read in conjunction with the Patient Information Leaflet (Version 1, September 2000)

I agree to take part in the above study as described in the Patient Information Leaflet.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant sections of my medical records, but that all the information will be treated as confidential.

I understand that, as part of the study, my HLA will be tested for types that are associated with rheumatoid arthritis, but not other diseases. I understand that

this indirectly tests my genes in a limited way, and *only* in connection with rheumatoid arthritis.

I understand medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

I have read the patient information leaflet on the above study and have had the opportunity to discuss the details with Dr. Cai Neville and ask any questions. The nature and the purpose of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Signature of patient

.....Date.....

(Name in BLOCK LETTERS)

.....

I confirm I have explained the nature of the Trial, as detailed in the Patient Information Leaflet, in terms which in my judgement are suited to the understanding of the patient.

Signature of Investigator

.....Date.....

(Name in BLOCK LETTERS)

.....

APPENDIX 3: **INTERVIEW QUESTIONAIRE**

D.O.B:

Hospital no:

Sex:

Marital status:

Country and region of birth:

Country of parents' birth:

Country of grandparents' birth:

Year of immigration:

Ethnic group	White	British / Irish
	Mixed	W&Bl.Car / W&Bl.Af / W&Ind / W&Other
	Asian	Guj / Ind / Pak / Bang / Other
	Black	African / Caribbean
	Other	
Employment:	Working full time	
	Working part time	
	Unemployed but seeking work	
	Domestic work in the home full time	
	Not working because ill-health/disability	
	Student	
	Retired	

Education:	Yrs of full time education
	Age on leaving
Housing:	Owned / rented / council / hostel or b&b
Occupational hx:	
Disability benefit:	Income support / carer / car sticker / rent / disability living allowance / mobility allowance / none / other
Family:	No of family members who live at home
	Part/spouse / children / in-laws / grandparents / other
	No who help
	Tasks help needed for washing / dressing / toileting / mobility / cooking / shopping
Past medical hx:	DM / asthma / epil / MI / ↑BP / CVA / angina / thyroid / RF / TB / DVT / PE / migraines / gynae
	Ops
	Other
Smoking:	X / Y / N
EtOH:	Un/wk =
Diet:	Veg / normal / Indian trad / other
FH:	RA / DM / Cancer / IHD / Other

History of disease

Date of onset:

Age at onset of symptoms:

Diagnosis made:

Duration of disease:

Medication

DMARD started date:

DMARDS tried: Reason for stopping/SEs:

?MTX

?SSZ

?D-pen

?Lefl

?HCQ

?Other

Current medication:

Use of Pred, freq and dose:

Analgesics/NSAIDs: Perceived efficacy:

Excellent / good / ok / worked a bit / no use

Compliance: Ever miss tablets

How often

Why

Complimentary therapies: Helpful?

Cu bracelet

Magnets

Acupuncture

Glucosamine

Herbal remedies

Other

Hospital adm for flares/Rx:

Intra-articular inj: Date: Site:

Surgical intervention:

Current status of disease

EMS in hours:

Disability (ref to HAQ)

Pain

WORSE POSSIBLE NO PAIN

Extra articular involvement:

Rash

Alopecia

Skin nodules

Dry eyes and mouth

Red eye/scleromalacia

Vasculitis

Raynauds

Digital gangrene

Nails

SOB

Prev pl. eff

Lung nodules

Known Fib / Bronchiec / bronchiolitis oblit

Peric. Eff

Cardiac nodules / Dysrhythm

Renal

Gut

Periph neuro / Mononeuritis / Migraines

Carpal tunnel

Other

Symptoms of depression

Do you often have headaches?

Is your appetite poor?

Do you sleep badly?

Are you easily frightened?

Do your hands shake?

Do you feel tense, nervous or worried?

Do you have trouble thinking clearly?

Do you feel unhappy?

Do you cry more than usual?

Do you find it difficult to enjoy your daily activities?

Do you find it difficult to make decisions?

Are you unable to play a useful part in life?

Have you lost interest in things?

Do you feel that you are a worthless person?

Has the thought of ending your life been in your mind?

Do you feel tired all the time?

Are you easily tired?

In the last 12 months:

Has a close relative had a serious illness/injury?

Has a first degree relative/close friend died?

Have you separated from your spouse?

Have you split up from a serious relationship?

Have you had serious problems with a close friend/relative/ neighbour?

Have you lost your job?

Are you unemployed/seeking work?

Have you had a major financial crisis?

Have you had trouble with the police or a court appearance?

Have you had something valuable lost or stolen?

Have you been mugged or assaulted in or out of your area of residence?

Have you been the victim of a racist attack?

Are you satisfied with the service from your GP?

Are you satisfied with the service you get from your consultant?

Do you feel that your doctor listens to your problems?

Do you have someone you can turn to when something is bothering you, or you are feeling low?

Do your parents and parents-in-law live >30 mins away?

Acculturation

Which languages do you speak?	Eng / Guj / Other
Which language do you use at home	E / G / O
With friends	E / G / O
With neighbours	E / G / O
At work	E / G / O

Which religion are you? Not / Christ / Hind / Musl / Other

Do you see Britain as your home?

If not, which country do you see as home?

Do you feel a part of British society?

Examination

Joints swollen:	DIP	R	L
	PIP	R	L
	MCP	R	L
	Wrist	R	L
	Elbow	R	L
	Shoulder	R	L
	MTP	R	L
	Ankle	R	L
	Knee	R	L
	Hip	R	L
	Other	R	L

Deformities:	Ulnar dev	R	L
	Swan neck	R	L
	Boutoniere	R	L

	Wrist sublux	R	L		
	Wrist fix	R	L		
	Fix flex fing	R	L		
	Fix elb	R	L		
	Shoul fix	R	L		
	Neck fix	R	L		
	Knee fix flex	R	L		
	Ankle fix	R	L		
	MTP sublux	R	L		
	LNs				
Cardio:	HR			BP	
	JVP			?Oedema	Periph
	pulses				
	HS				
Resp:	RR				
	Chest				
GIT:					
Skin:	Rash?				

Ix:	Hb	Na
	WCC	K
	Plts	U
	PV	Cr
		Gluc
	RF	Alb
	ANA	ALP
	ENA	ALT
		Bili
		CRP

Hand XRs

HLA type

?PFT/HRCT/CXR

HAQ

APPENDIX 4: MODIFIED STANDFORD HEALTH ASSESSMENT QUESTIONAIRRE (HAQ)

We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

PLEASE TICK THE ONE RESPONSE WHICH BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	Unable to do
1. DRESSING AND GROOMING				
Are you able to:				
Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
Shampoo your hair?	_____	_____	_____	_____
2. RISING				
Are you able to:				
Stand up from an armless straight chair?	_____	_____	_____	_____
Get in and out of bed?	_____	_____	_____	_____
1. EATING				
Are you able to:				

Cut your meat?	_____	_____	_____	_____
Lift a full cup or glass to your mouth?	_____	_____	_____	_____
Open a new carton of milk (or soap powder)?	_____	_____	_____	_____

2. WALKING

Are you able to:				
Walk outdoors on flat ground?	_____	_____	_____	_____
Climb up five steps?	_____	_____	_____	_____

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Cane	____	Devices used for dressing (button hook,	
Walking frame	____	zipper pull, long handled shoe-horn)	____
Crutches	____	Built-up or special utensils	_____
Wheelchair	____	Special or built-up chair	_____

Other _____

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

Dressing and grooming	____	Eating	_____

Rising ____ Walking _____

PLEASE TICK THE ONE RESPONSE WHICH BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	Unable to do
3. HYGIENE				
Are you able to:				
Wash and dry your entire body?	_____	_____	_____	_____
Take a bath?	_____	_____	_____	_____
Get on and off the toilet?	_____	_____	_____	_____
4. REACH				
Are you able to:				
Reach and get down a 5lb object (e.g. bag of potatoes) from just above your head?	_____	_____	_____	_____
Bend down to pick up clothing from the floor?	_____	_____	_____	_____
5. GRIP				
Are you able to:				
Open car doors?	_____	_____	_____	_____
Open jars which have been previously opened?	_____	_____	_____	_____
Turn taps on and off?	_____	_____	_____	_____
6. ACTIVITIES				

Are you able to:

Run errands and shop? _____ _____ _____ _____

Get in and out of a car? _____ _____ _____ _____

Do chores such as vacuuming,

housework, or light gardening? _____ _____ _____ _____

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Raised toilet seat _____ Bath rail _____

Bath seat _____ Long handled appliance for reach _____

Jar opener (for jars previously opened) Other _____

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

Hygiene _____ Gripping and opening things _____

Reach _____ Errands and housework _____

APPENDIX 5: **The WHO SELF-REPORTING QUESTIONAIRRE**

1. Do you often have headaches?
2. Is your appetite poor?
3. Do you sleep badly?
4. Are you easily frightened?
5. Do your hands shake?
6. Do you feel tense, nervous or worried?
7. Is your digestion poor?
8. Do you have trouble thinking clearly?
9. Do you feel unhappy?
10. Do you cry more than usual?
11. Do you find it difficult to enjoy your daily activities?
12. Do you find it difficult to make decisions?
13. Is your daily work suffering?
14. Are you unable to play a useful part in life?
15. Have you lost interest in things?
16. Do you feel that you are a worthless person?
17. Has the thought of ending your life been in your mind?
18. Do you feel tired all the time?
19. Do you have uncomfortable feelings in your stomach?
20. Are you easily tired?

APPENDIX 6: THE LIST OF THREATENING LIFE EVENTS

In the last 12 months:

1. Has a close relative had a serious illness/injury?
2. Has a first degree relative/close friend died?
3. Have you separated from your spouse?
4. Have you split up from a serious relationship?
5. Have you had serious problems with a close friend/relative/ neighbour?
6. Have you lost your job?
7. Are you unemployed/seeking work?
8. Have you had a major financial crisis?
9. Have you had trouble with the police or a court appearance?
10. Have you had something valuable lost or stolen?
11. Have you been mugged or assaulted in or out of your area of residence?
12. Do you have someone you can turn to when something is bothering you, or you are feeling low?

Do your parents and parents-in-law live >30 mins away?

Pearson correlation (r)	HAQ	Age	Sex	Disease duration	Ethnic group	Yrs of education	Smoking history	Presence of nodules	Sero-positivity for RF	SJC	Deformities	PV	Pain	Depression	EAM	EMS	Shared epitope
HAQ	1.00	.16	.11	.29	.32	-.35	-.23	.21	-.06	.40	.42	.20	.62	.45	.08	.35	-.10
Age	.16	1.00	-.13	.23	-.32	-.27	.18	.14	.23	.18	.25	.11	-.03	-.16	.03	-.14	-.08
Sex	.11	-.13	1.00	-.04	.16	-.02	-.39	-.08	-.16	.11	.07	.06	.10	.16	-.05	.14	-.12
Disease duration	.29	.23	-.04	1.00	-.07	-.12	-.04	.37	.08	.36	.61	.04	.09	-.01	.13	.00	-.04
Ethnic group	.32	-.32	.16	-.07	1.00	-.25	-.41	-.27	-.18	-.19	-.05	.27	.33	.48	.03	.21	-.26
Yrs of education	-.35	-.27	-.02	-.12	-.25	1.00	.13	-.03	-.06	-.21	-.14	-.22	-.26	-.14	-.14	-.11	.09
Smoking history	-.23	.18	-.39	-.04	-.41	.13	1.00	.14	.12	-.02	-.10	-.07	-.16	-.20	-.04	-.09	.06
Presence of nodules	.21	.14	-.08	.37	-.27	-.03	.14	1.00	.31	.43	.44	-.08	.16	-.05	.09	-.08	.02
Seropositivity for RF	-.06	.23	-.16	.08	-.18	-.06	.12	.31	1.00	.25	.16	.22	-.03	-.20	.07	-.12	-.05
SJC	.40	.18	.11	.36	-.19	-.21	-.02	.43	.25	1.00	.48	.15	.21	.10	.10	.18	-.03
Deformities	.42	.25	.07	.61	-.05	-.14	-.10	.44	.16	.48	1.00	-.05	.16	.10	.11	.07	-.06
PV	.20	.11	.06	.04	.27	-.22	-.07	-.08	.22	.15	-.05	1.00	.14	.13	-.02	.05	-.12
Pain	.62	-.03	.10	.09	.33	-.26	-.16	.16	-.03	.21	.16	.14	1.00	.50	.03	.47	-.22
Depression	.45	-.16	.16	-.01	.48	-.14	-.20	-.05	-.20	.10	.10	.13	.50	1.00	.03	.35	-.07
EAM	.08	.03	-.05	.13	.03	-.14	-.04	.09	.07	.10	.11	-.02	.03	.03	1.00	-.04	.14
EMS	.35	-.14	.14	.00	.21	-.11	-.09	-.08	-.12	.18	.07	.05	.47	.35	-.04	1.00	-.07
Shared epitope	-.10	-.08	-.12	-.04	-.26	.09	.06	.02	-.05	-.03	-.06	-.12	-.22	-.07	.14	-.07	1.00
Sig (1-tailed)																	
HAQ	.	.036	.108	.000	.000	.000	.004	.008	.245	.000	.000	.010	.000	.000	.195	.000	.155
Age	.036	.	.074	.004	.000	.001	.017	.052	.005	.020	.002	.107	.380	.033	.380	.060	.204
Sex	.108	.074	.	.329	.035	.428	.000	.192	.035	.111	.206	.241	.133	.030	.295	.055	.123
Disease duration	.000	.004	.329	.	.197	.090	.318	.000	.176	.000	.000	.309	.162	.436	.072	.485	.340
Ethnic group	.000	.000	.035	.197	.	.002	.000	.001	.018	.013	.296	.001	.000	.000	.357	.007	.004
Yrs of education	.000	.001	.428	.090	.002	.	.062	.379	.248	.007	.052	.006	.001	.054	.054	.100	.192
Smoking history	.004	.017	.000	.318	.000	.062	.	.051	.084	.413	.135	.209	.032	.011	.316	.156	.278
Presence of nodules	.008	.052	.192	.000	.001	.379	.051	.	.000	.000	.000	.187	.030	.293	.148	.181	.440
Seropositive for RF	.245	.005	.035	.176	.018	.248	.084	.000	.	.002	.030	.005	.360	.009	.200	.088	.295
SJC	.000	.020	.111	.000	.013	.007	.413	.000	.002	.	.000	.045	.009	.128	.138	.018	.392
Deformities	.000	.002	.206	.000	.296	.052	.135	.000	.030	.000	.	.287	.037	.124	.097	.225	.281
PV	.010	.107	.241	.309	.001	.006	.209	.187	.005	.045	.287	.	.053	.067	.398	.299	.110
Pain	.000	.380	.133	.162	.000	.001	.032	.030	.360	.009	.037	.053	.	.000	.359	.000	.014
Depression	.000	.033	.030	.436	.000	.054	.011	.293	.009	.128	.124	.067	.000	.	.362	.000	.238
EAM	.195	.380	.295	.072	.357	.054	.316	.148	.200	.138	.097	.398	.359	.362		.326	.084
EMS	.000	.060	.055	.485	.007	.100	.156	.181	.088	.018	.225	.299	.000	.000	.326	.	.243
Shared epitope	.155	.204	.123	.340	.004	.192	.278	.440	.295	.392	.281	.110	.014	.238	.084	.243	.

Table Of Pearson Correlations For All Variables When Predicting HAQ In All Patients

Significance for all tables of Pearson correlations was 1 tailed as I did not expect disability to improve

Pearson correlation	HAQ	Age	Sex	Disease duration	Yrs education	Smoking history	EMS	Pain	Nodules	Seropositivity for RF	SJC	Deformities	PV	Shared epitope	Depression	EAM
HAQ	1.00	.10	.08	.25	-.29	-.13	.38	.72	.48	.06	.66	.45	.13	.01	.36	.00
Age	.10	1.00	-.12	.14	-.42	.13	-.19	-.02	.12	.21	.11	.33	.11	-.20	-.22	-.03
Sex	.08	-.12	1.00	-.12	.14	-.23	.15	.05	-.06	-.16	.16	.09	.08	-.20	.11	-.12
Disease duration	.25	.14	-.12	1.00	-.11	-.04	-.03	.07	.41	.15	.44	.66	.12	-.11	-.09	.21
Yrs education	-.29	-.42	.14	-.11	1.00	.05	-.04	-.26	-.26	-.07	-.26	-.17	-.07	-.07	.13	-.04
Smoking history	-.13	.13	-.23	-.04	.05	1.00	.01	-.08	.06	.03	-.14	-.11	-.04	.00	.01	-.04
EMS	.38	-.19	.15	-.03	-.04	.01	1.00	.50	.11	-.13	.21	.04	-.07	.21	.40	.06
Pain	.72	-.02	.05	.07	-.26	-.08	.50	1.00	.46	.01	.44	.17	.06	.03	.48	.05
Nodules	.48	.12	-.06	.41	-.26	.06	.11	.46	1.00	.36	.57	.52	.18	-.04	.16	.10
Seropositivity for RF	.06	.21	-.16	.15	-.07	.03	-.13	.01	.36	1.00	.33	.31	.16	-.17	-.09	.15
SJC	.66	.11	.16	.44	-.26	-.14	.21	.44	.57	.33	1.00	.63	.13	-.11	.19	.11
Deformities	.45	.33	.09	.66	-.17	-.11	.04	.17	.52	.31	.63	1.00	.13	-.10	.08	.23
PV	.13	.11	.08	.12	-.07	-.04	-.07	.06	.18	.16	.13	.13	1.00	-.08	.05	-.11
Shared epitope	.01	-.20	-.20	-.11	-.07	.00	.21	.03	-.04	-.17	-.11	-.10	-.08	1.00	.14	.25
Depression	.36	-.22	.11	-.09	.13	.01	.40	.48	.16	-.09	.19	.08	.05	.14	1.00	-.08
EAM	.00	-.03	-.12	.21	-.04	-.04	.06	.05	.10	.15	.11	.23	-.11	.25	-.08	1.00
Sig (1-tailed)																
HAQ	.	.203	.249	.017	.007	.148	.000	.000	.000	.305	.000	.000	.129	.471	.001	.489
Age	.203	.	.152	.116	.000	.143	.059	.439	.168	.036	.172	.002	.181	.060	.031	.413
Sex	.249	.152	.	.159	.118	.027	.112	.327	.306	.089	.084	.215	.245	.060	.171	.167
Disease duration	.017	.116	.159	.	.178	.360	.399	.282	.000	.103	.000	.000	.162	.211	.223	.035
Yrs education	.007	.000	.118	.178	.	.348	.381	.014	.014	.293	.015	.077	.292	.307	.136	.383
Smoking history	.148	.143	.027	.360	.348	.	.479	.254	.319	.405	.124	.175	.363	.497	.454	.385
EMS	.000	.059	.112	.399	.381	.479	.	.000	.177	.133	.036	.365	.280	.058	.000	.318
Pain	.000	.439	.327	.282	.014	.254	.000	.	.000	.457	.000	.077	.306	.419	.000	.330
Nodules	.000	.168	.306	.000	.014	.319	.177	.000	.	.001	.000	.000	.063	.371	.088	.200
Seropositivity for RF	.305	.036	.089	.103	.293	.405	.133	.457	.001	.	.003	.004	.091	.101	.237	.099
SJC	.000	.172	.084	.000	.015	.124	.036	.000	.000	.003	.	.000	.142	.202	.059	.186
Deformities	.000	.002	.215	.000	.077	.175	.365	.077	.000	.004	.000	.	.145	.225	.257	.027
PV	.129	.181	.245	.162	.292	.363	.280	.306	.063	.091	.142	.145	.	.281	.329	.177
Shared epitope	.471	.060	.060	.211	.307	.497	.058	.419	.371	.101	.202	.225	.281	.	.139	.031
Depression	.001	.031	.171	.223	.136	.454	.000	.000	.088	.237	.059	.257	.329	.139	.	.257
EAM	.489	.413	.167	.035	.383	.385	.318	.330	.200	.099	.186	.027	.177	.031	.257	.

Table of Pearson Correlations For Caucasian Patients When Predicting HAQ

APPENDIX 7

Pearson correlation	HAQ	Age	Sex	Disease duration	Yrs education	Smoking history	EMS	Pain	Nodules	Seropositivity for RF	SJC	Deformities	PV	Shared epitope	Depression	EAM
HAQ	1.00	.54	.03	.48	-.30	-.08	.23	.37	.08	-.08	.24	.48	.12	-.11	.36	.14
Age	.54	1.00	-.01	.37	-.35	-.07	.04	.26	-.04	.14	.15	.15	.32	-.09	.26	.11
Sex	.03	-0.01	1.00	.19	-.12	-.68	.08	.04	.02	-.09	.09	.06	-.05	.22	.09	.03
Disease duration	.48	.37	.19	1.00	-.20	-.18	.07	.22	.25	-.07	.15	.58	.00	.00	.22	.01
Yrs education	-.30	-.35	-.12	-.20	1.00	.02	-.08	-.13	.08	-.15	-.33	-.15	-.23	.17	-.17	-.22
Smoking history	-.08	-.07	-.68	-.18	.02	1.00	-.01	.08	-.02	.09	-.04	-.16	.17	-.16	-.04	-.03
EMS	.23	.04	.08	.07	-.08	-.01	1.00	.37	-.19	-.04	.28	.11	.03	-.29	.19	-.13
Pain	.37	.26	.04	.22	-.13	.08	.37	1.00	-.08	.06	-.01	.20	.06	-.50	.34	-.02
Nodules	.08	-.04	.02	.25	.08	-.02	-.19	-.08	1.00	.14	.01	.36	-.23	-0.11	.01	.11
Seropositivity for RF	-.08	.14	-.09	-.07	-.15	.09	-.04	.06	.14	1.00	.08	-.01	.41	.03	-.19	.01
SJC	.24	.15	.09	.15	-.33	-.04	.28	-.01	.01	.08	1.00	.28	.34	-.10	.29	.11
Deformities	.48	.15	.06	.58	-.15	-.16	.11	.20	.36	-.01	.28	1.00	-.18	-.08	.21	.01
PV	.12	.32	-.05	.00	-.23	.17	.03	.06	-.23	.41	.34	-.18	1.00	-.05	-.04	.03
Shared epitope	-.11	-.09	.22	.00	.17	-.16	-.29	-.50	-.11	.03	-.10	-.08	-.05	1.00	-.18	-.04
Depression	.36	.26	.09	.22	-.17	-.04	.19	.34	.01	-.19	.29	.21	-.04	-.18	1.00	.11
EAM	.14	.11	.03	.01	-.22	-.03	-.13	-.02	.11	.01	.11	.01	0.03	-0.04	.11	1.00
Sig (1-tailed)																
HAQ	.	.000	.412	.000	.010	.263	.040	.002	.278	.278	.032	.000	.178	.256	.002	.144
Age	.000	.	.467	.002	.003	.290	.383	.023	.392	.146	.122	.125	.006	.291	.024	.197
Sex	.412	.467	.	.074	.179	.000	.282	.382	.438	.237	.244	.316	.340	.094	.249	.412
Disease duration	.000	.002	.074	.	.062	.083	.285	.041	.027	.305	.126	.000	.487	.490	.042	.455
Yrs education	.010	.003	.179	.062	.	.429	.271	.153	.263	.119	.005	.124	.035	.145	.100	.046
Smoking history	.263	.290	.000	.083	.429	.	.468	.262	.438	.237	.389	.102	.089	.171	.384	.412
EMS	.040	.383	.282	.285	.271	.468	.	.002	.075	.385	.014	.200	.411	.034	.070	.160
Pain	.002	.023	.382	.041	.153	.262	.002	.	.283	.331	483	.061	.330	.001	.004	.454
Nodules	.278	.392	.438	.027	.263	.438	.075	.283	.	.140	.462	.002	.036	.255	.481	.189
Seropositivity for RF	.278	.146	.237	.305	.119	.237	.385	.331	.140	.	.278	.478	.001	.437	.070	.471
SJC	.032	.122	.244	.126	.005	.389	.014	.483	.462	.278	.	.014	.004	.263	.012	.210
Deformities	.000	.125	.316	.000	.124	.102	.200	.061	.002	.478	.014	.	.085	.310	.055	.474
PV	.178	.006	.340	.487	.035	.089	.411	.330	.036	.001	.004	.085	.	.379	.378	.412
Shared epitope	.256	.291	.094	.490	.145	.171	.034	.001	.255	.437	.263	.310	.379	.	.143	.407
Depression	.002	.024	.249	.042	.100	.384	.070	.004	.481	.070	.012	.055	.378	.143	.	.193
EAM	.144	.197	.412	.455	.046	.412	.160	.454	.189	.471	.032	.000	.178	.256	.002	.144

APPENDIX 7

Table of Pearson Correlations For Asian Patients When Predicting HAQ

Pearson correlation	Depression	Age	Sex	Disease duration	Ethnic gp	Partner	Family at home	No who help	Yrs ed	Life events	Alcohol	Pain	EMS	SJC	Deformities	HAQ	Perceived efficacy
Depression	1.000	-.160	.164	-.014	.477	-.260	-.007	.219	-.140	.429	-.232	.502	.348	.099	.101	.454	-.460
Age	-.160	1.000	-.126	.230	-.321	.047	-.429	-.111	-.265	-.013	.008	-.027	-.136	.179	.249	.157	.085
Sex	.164	-.126	1.000	-.039	.157	-.088	-.018	.199	-.016	.045	-.279	.097	.140	.106	.072	.108	-.036
Disease duration	-.014	.230	-.039	1.000	-.074	-.031	-.123	.114	-.117	.048	-.022	.086	-.003	.362	.610	.286	.016
Ethnic Gp	.477	-.321	.157	-.074	1.000	.007	.347	.342	-.251	.091	-.259	.330	.214	-.193	-.047	.323	-.306
Partner	-.260	.047	-.088	-.031	.007	1.000	.389	-.069	.084	-.239	.071	-.231	-.097	-.022	-.076	-.134	.242
Family no.	-.007	-.429	-.018	-.123	.347	.389	1.000	.401	.025	-.087	-.042	-.078	.073	-.237	-.169	-.159	.018
No who help	.219	-.111	.199	.114	.342	-.069	.401	1.000	-.195	.054	-.188	.200	.156	-.028	-.021	.147	-.028
Yrs ed	-.140	-.265	-.016	-.117	-.251	.084	.025	-.195	1.000	-.108	.065	-.261	-.112	-.215	-.142	-.347	.161
Life events	.429	-.013	.045	.048	.091	-.239	-.087	.054	-.108	1.000	-.101	.172	.065	.087	.102	.179	-.205
Alcohol	-.232	.008	-.279	-.022	-.259	.071	-.042	-.188	.065	-.101	1.000	-.242	-.114	-.007	-.013	-.248	.214
Pain	.502	-.027	.097	.086	.330	-.231	-.078	.200	-.261	.172	-.242	1.000	.465	.206	.155	.622	-.457
EMS	.348	-.136	.140	-.003	.214	-.097	.073	.156	-.112	.065	-.114	.465	1.000	.182	.066	.345	-.307
SJC	.099	.179	.106	.362	-.193	-.022	-.237	-.028	-.215	.087	-.007	.206	.182	1.000	.485	.401	-.089
Deformities	.101	.249	.072	.610	-.047	-.076	-.169	-.021	-.142	.102	-.013	.155	.066	.485	1.000	.425	-.086
HAQ	.454	.157	.108	.286	.323	-.134	-.159	.147	-.347	.179	-.248	.622	.345	.401	.425	1.000	-.403
Percieved efficacy	-.460	.085	-.036	.016	-.306	.242	.018	-.028	.161	-.205	.214	-.457	-.307	-.089	-.086	-.403	1.000
Sig (1 tailed)																	
Depression	.	.033	.030	.436	.000	.001	.467	.006	.054	.000	.004	.000	.000	.128	.124	.000	.000
Age	.033	.	.074	.004	.000	.295	.000	.102	.001	.443	.466	.380	.060	.020	.002	.036	.166
Sex	.030	.074	.	.329	.035	.157	.417	.011	.428	.305	.001	.133	.055	.111	.206	.108	.342
Disease duration	.436	.004	.329	.	.197	.362	.080	.095	.090	.291	.400	.162	.485	.000	.000	.000	.427
Ethnic Gp	.000	.000	.035	.197	.	.467	.000	.000	.002	.148	.001	.000	.007	.013	.296	.000	.000
Partner	.001	.295	.157	.362	.467	.	.000	.215	.167	.003	.209	.004	.134	.400	.191	.063	.003
Family no.	.467	.000	.417	.080	.000	.000	.	.000	.387	.160	.314	.186	.201	.003	.026	.034	.417
No who help	.006	.102	.011	.095	.000	.215	.000	.	.012	.268	.015	.011	.036	.375	.405	.045	.376
Yrs ed	.054	.001	.428	.090	.002	.167	.387	.012	.	.107	.228	.001	.100	.007	.052	.000	.032
Life events	.000	.443	.305	.291	.148	.003	.160	.268	.107	.	.123	.024	.229	.161	.122	.020	.009
Alcohol	.004	.466	.001	.400	.001	.209	.314	.015	.228	.123	.	.002	.095	.470	.440	.002	.007
Pain	.000	.380	.133	.162	.000	.004	.186	.011	.001	.024	.002	.	.000	.009	.037	.000	.000
EMS	.000	.060	.055	.485	.007	.134	.201	.036	.100	.229	.095	.000	.	.018	.225	.000	.000
SJC	.128	.020	.111	.000	.013	.400	.003	.375	.007	.161	.470	.009	.018	.	.000	.000	.154
Deformities	.124	.002	.206	.000	.296	.191	.026	.405	.052	.122	.440	.037	.225	.000	.	.000	.161
HAQ	.000	.036	.108	.000	.000	.063	.034	.045	.000	.020	.002	.000	.000	.000	.000	.	.000
Percieved efficacy	.000	.166	.342	.427	.000	.003	.417	.376	.032	.009	.007	.000	.000	.154	.161	.000	.

Table of Pearson Correlations for all Patients for Depression

APPENDIX 7 CONTINUED

Multiple Regression to predict HAQ in all patients: raw data

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.805*	.648	.579	.673	.648	9.327	16	81	.000

*Predictors: (Constant), EAM, age, pain, smoking history, PV, sex, disease duration, ethnic group, seropositivity for RF, Shared Epitope, yrs education, EMS, depression, nodules, SJC, deformities

ANOVA

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	67.676	16	4.230	9.327	.000
Residual	36.732	81	.453		
Total	104.408	97			

Predictors as before

Model	Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
	B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
(Constant)	-.588	1.083		-.543	.588	-2.743	1.567					
Age	.017	.007	.210	2.627	.010	.004	.031	.159	.280	.173	.651	1.536
Sex	-.121	.197	-.046	-.614	.541	-.512	.271	.077	-.068	-.040	.780	1.283
Disease duration	.003	.011	.027	.300	.765	-.019	.025	.276	.033	.020	.577	1.732
Yrs education	.537	.204	.254	2.627	.010	.130	.943	.269	.280	.173	.411	2.434
Smoking history	-.020	.025	-.061	-.784	.435	-.070	.031	-.329	-.087	-.052	.720	1.390
EMS	-.249	.168	-.115	-1.483	.142	-.582	.085	-.239	-.163	-.098	.688	1.452
Pain	.024	.207	.011	.113	.910	-.389	.436	.267	.013	.007	.585	1.710
Nodules	-.260	.162	-.125	-1.607	.112	-.582	.062	-.083	-.176	-.106	.730	1.370
Seropositive for RF	.039	.066	.050	.587	.559	-.092	.169	.363	.065	.039	.694	1.441
SJC	.154	.042	.347	3.718	.000	.072	.237	.603	.382	.245	.544	1.840
Deformities	.026	.019	.110	1.360	.178	-.012	.063	.410	.149	.090	.576	1.736
PV	.057	.015	.331	3.685	.000	.026	.087	.454	.379	.243	.550	1.819
Shared epitope	.031	.018	.170	1.740	.086	-.004	.066	.409	.190	.115	.469	2.134
Depression	-.155	.544	-.021	-.285	.777	-1.236	.927	.108	-.032	-.019	.740	1.351
EAM	.145	.110	.096	1.316	.192	-.074	.363	-.104	.145	.087	.815	1.227

Hierarchical Regression analysis to predict HAQ in all patients

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.328	.108	.079	.997	.108	3.782	3	94	.013
2	.788	.621	.547	.700	.514	8.456	13	81	.000

Model 1. Predictors: (Constant), Age, sex, disease duration
Model 2. Predictors: (Constant), age, sex, disease duration, pain, smoking history, PV, ethnic group, seropositivity for RF, Shared Epitope, yrs education, EMS, depression, nodules, SJC, deformities, EAM,

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	11.283	3	3.761	3.782	.013
	Residual	93.485	94	.995		
	Total	104.768	97			
2	Regression	65.107	16	4.069	8.311	.000
	Residual	39.661	81	.490		
	Total	104.768	97			

Predictors as above

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	.388	.549		.706	.482	-.703	1.479					
	Age	.009	.009	.112	1.113	.032	-.007	.026	.157	.114	.108	.933	1.071
	Sex	.356	.264	.132	1.347	.181	-.169	.881	.108	.138	.131	.984	1.016
	Disease duration	.033	.013	.265	2.649	.009	.008	.058	.286	.264	.258	.947	1.056
2	(Constant)	-1.667	1.094		-1.524	.131	-3.843	.509					
	Age	.016	.007	.185	2.183	.269	.001	.030	.157	.236	.149	.651	1.536
	Sex	-.094	.208	-.035	-.452	.653	-.509	.321	.108	-.050	-.031	.780	1.283
	Disease duration	.001	.011	.009	.096	.924	-.021	.024	.286	.011	.007	.577	1.732
	Yrs education	-.013	.024	-.042	-.519	.605	-.061	.036	-.347	-.058	-.035	.720	1.390
	Smoking history	-.136	.182	-.062	-.747	.457	-.499	.227	-.226	-.083	-.051	.688	1.452
	Depression	.019	.020	.084	.931	.355	-.021	.059	.454	.103	.064	.576	1.736
	EMS	.036	.067	.043	.529	.598	-.098	.169	.345	.059	.036	.694	1.441
	Pain	.185	.043	.397	4.283	.000	.099	.270	.622	.430	.293	.544	1.840
	SJC	.035	.016	.207	2.241	.028	.004	.067	.401	.242	.153	.550	1.819
	Deformities	.038	.018	.211	2.116	.037	.002	.073	.425	.229	.145	.469	2.134
	Seropositive for RF	-.296	.166	-.143	-1.781	.079	-.627	.035	-.060	-.194	-.122	.730	1.370
	Nodules	.117	.202	.052	.580	.564	-.285	.519	.208	.064	.040	.585	1.710
	PV	.500	.568	.070	.879	.382	-.631	1.631	.201	.097	.060	.740	1.351
	Shared epitope	.136	.115	.090	1.183	.240	-.092	.363	-.104	.130	.081	.815	1.227
	EAM	-.024	.172	-.010	-.142	.888	-.367	.318	.075	-.016	-.010	.922	1.084
	Ethnic group	.447	.222	.215	2.018	.047	.006	.888	.323	.219	.138	.411	2.434

Stepwise multiple regression to predict HAQ in all patients

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.622	.386	.380	.818	.386	60.440	1	96	.000
2	.705	.497	.486	.745	.110	20.852	1	95	.000
3	.723	.523	.507	.730	.026	5.061	1	94	.027
4	.747	.558	.539	.706	.036	7.495	1	93	.007
5	.762	.581	.558	.691	.023	4.959	1	92	.028
6	.774	.598	.572	.680	.018	3.996	1	91	.049

Predictors in models

1. (Constant) Pain
2. (Constant) Pain, deformities
3. (Constant) Pain, deformities, ethnic group
4. (Constant) Pain, deformities, ethnic group, SJC
5. (Constant) Pain, deformities, ethnic group, SJC, age
6. (Constant) Pain, deformities, ethnic group, SJC, age, seropositivity for RF

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	40.477	1	40.477	60.440	.000
	Residual	64.292	96	.670		
	Total	104.768	97			
2	Regression	52.049	2	26.024	46.895	.000
	Residual	52.720	95	.555		
	Total	104.768	97			
3	Regression	54.742	3	18.247	34.287	.000
	Residual	50.026	94	.532		
	Total	104.768	97			
4	Regression	58.473	4	14.618	29.366	.000
	Residual	46.295	93	.498		
	Total	104.768	97			
5	Regression	60.841	5	12.168	25.485	.000
	Residual	43.928	92	.477		
	Total	104.768	97			
6	Regression	62.689	6	10.448	22.595	.000
	Residual	42.080	91	.462		
	Total	104.768	97			

Predictors as above

Stepwise multiple regression to predict HAQ in all patients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	.316	.181		1.743	.085	-.044	.676					
	Pain	.289	.037	.622	7.774	.000	.215	.363	.622	.622	.622	1.000	1.000
2	(Constant)	.041	.176		.233	.816	-.308	.390					
	Pain	.265	.034	.569	7.729	.000	.197	.333	.622	.621	.563	.976	1.025
	Deformities	.060	.013	.336	4.566	.000	.034	.086	.425	.424	.332	.976	1.025
3	(Constant)	-.022	.174		-.126	.900	-.368	.324					
	Pain	.237	.036	.510	6.647	.000	.166	.308	.622	.565	.474	.862	1.160
	Deformities	.063	.013	.354	4.874	.000	.037	.089	.425	.449	.347	.965	1.036
	Ethnic group	.355	.158	.171	2.250	.027	.042	.668	.323	.226	.160	.881	1.135
4	(Constant)	-.224	.184		-1.216	.227	-.589	.142					
	Pain	.214	.036	.461	6.033	.000	.144	.285	.622	.530	.416	.814	1.229
	Deformities	.045	.014	.254	3.217	.002	.017	.073	.425	.316	.222	.761	1.314
	Ethnic group	.470	.158	.226	2.968	.004	.155	.784	.323	.294	.205	.819	1.220
	SJC	.039	.014	.226	2.738	.007	.011	.067	.401	.273	.189	.695	1.438
5	(Constant)	-.999	.392		-2.548	.012	-1.777	-.220					
	Pain	.211	.035	.453	6.052	.000	.142	.280	.622	.534	.409	.812	1.231
	Deformities	.039	.014	.217	2.737	.007	.011	.067	.425	.274	.185	.727	1.376
	Ethnic group	.581	.163	.280	3.568	.001	.257	.904	.323	.349	.241	.742	1.347
	SJC	.039	.014	.227	2.804	.006	.011	.066	.401	.281	.189	.695	1.438
	Age	.014	.006	.164	2.227	.028	.001	.026	.157	.226	.150	.840	1.190
6	(Constant)	-.972	.386		-2.519	.014	-1.739	-.205					
	Pain	.207	.034	.446	6.047	.000	.139	.276	.622	.535	.402	.810	1.234
	Deformities	.039	.014	.221	2.831	.006	.012	.067	.425	.284	.188	.726	1.377
	Ethnic group	.559	.161	.269	3.482	.001	.240	.878	.323	.343	.231	.739	1.354
	SJC	.044	.014	.256	3.166	.002	.016	.071	.401	.315	.210	.672	1.487
	Age	.016	.006	.186	2.536	.013	.003	.028	.157	.257	.168	.822	1.217
	Sero+ RF	-.292	.146	-.141	-1.999	.049	-.583	-.002	-.060	-.205	-.133	.892	1.121

Logistic regression analysis to predict HAQ in all patients
Omnibus Tests of Model Coefficients

		Chi square	df	significance
Step 1	Step	68.019	16	.000
	Block	68.019	16	.000
	Model	68.019	16	.000

Model summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	67.797	.500	.667

Classification table

Observed		Predicted		
		HAQ <2	HAQ >=2	Percentage correct
Step 1	HAQ <2	42	8	84.0
	HAQ >=2	9	39	81.3
	Overall percentage			82.7

Variables in the equation

		B	S. E.	Wald	df	Sig	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
Step 1	**Ethnic group**	3.168	1.104	8.239	1	.004	23.748	2.731	206.509
	Sex	-1.165	1.001	1.354	1	.245	.312	.044	2.219
	Age	.080	.035	5.412	1	.020	1.084	1.013	1.160
	Yrs education	-.031	.147	.044	1	.834	.970	.727	1.294
	Smoker	-1.592	.866	3.379	1	.066	.204	.037	1.111
	Disease duration	-.064	.061	1.114	1	.291	.938	.832	1.057
	EMS	.078	.285	.076	1	.783	1.082	.618	1.892
	Pain	.725	.228	10.126	1	.001	2.064	1.321	3.225
	Nodules	.105	.972	.012	1	.914	1.110	.165	7.465
	Depression	-.029	.085	.119	1	.730	.971	.823	1.147
	SJC	.258	.085	9.204	1	.002	1.294	1.096	1.529
	Deformities	.114	.090	1.616	1	.204	1.121	.940	1.338
	Sero + RF	-1.373	.811	2.869	1	.090	.253	.052	1.241
	PV	-3.291	2.680	1.507	1	.220	.037	.000	7.118
	Shared epitope	.757	.515	2.164	1	.141	2.133	.777	5.851
	EAM	-.177	.963	.034	1	.854	.838	.127	5.535
	Constant	-3.862	5.404	.511	1	.475	.021		

Backwards Logistic regression analysis to predict HAQ in all patients

Omnibus Tests of Model Coefficients

		Chi square	df	significance
Step 1	Step	68.019	16	.000
	Block	68.019	16	.000
	Model	68.019	16	.000
Step 2	Step	-.012	1	.914
	Block	68.008	15	.000
	Model	68.008	15	.000
Step 3	Step	-.042	1	.838
	Block	67.966	14	.000
	Model	67.966	14	.000
Step 4	Step	-.030	1	.863
	Block	67.936	13	.000
	Model	67.936	13	.000
Step 5	Step	-.077	1	.781
	Block	67.859	12	.000
	Model	67.859	12	.000
Step 6	Step	-.094	1	.759
	Block	67.765	11	.000
	Model	67.765	11	.000
Step 7	Step	-1.353	1	.245
	Block	66.412	10	.000
	Model	66.412	10	.000
Step 8	Step	-.815	1	.367
	Block	65.597	9	.000
	Model	65.597	9	.000
Step 9	Step	-.797	1	.372
	Block	64.800	8	.000
	Model	64.800	8	.000
Step 10	Step	-1.630	1	.202
	Block	63.170	7	.000
	Model	63.170	7	.000
Step 11	Step	-2.553	1	.110
	Block	60.618	6	.000
	Model	60.618	6	.000

A negative Chi-squares value indicates that the Chi-squares value has decreased from the previous step.

Model summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	67.797	.500	.667
2	67.808	.500	.667
3	67.850	.500	.667
4	67.880	.500	.667
5	67.957	.500	.666
6	68.051	.499	.666
7	69.404	.492	.656
8	70.219	.488	.651
9	71.016	.484	.645
10	72.646	.475	.634
11	75.199	.461	.615

Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Classification table

Observed		Predicted		
		HAQ <2	HAQ >=2	Percentage correct
Step 1	HAQ <2	42	8	84.0
	HAQ >=2	9	39	81.3
	Overall percentage			82.7
Step 2	HAQ <2	42	8	84.0
	HAQ >=2	9	39	81.3
	Overall percentage			82.7
Step 3	HAQ <2	42	8	84.0
	HAQ >=2	9	39	81.3
	Overall percentage			82.7
Step 4	HAQ <2	42	8	84.0
	HAQ >=2	9	39	81.3
	Overall percentage			82.7
Step 5	HAQ <2	41	9	82.0
	HAQ >=2	9	39	81.3
	Overall percentage			81.6
Step 6	HAQ <2	41	9	82.0
	HAQ >=2	9	39	81.3
	Overall percentage			81.6
Step 7	HAQ <2	40	10	80.0
	HAQ >=2	8	40	83.3
	Overall percentage			81.6
Step 8	HAQ <2	41	9	82.0
	HAQ >=2	9	39	81.3
	Overall percentage			81.6
Step 9	HAQ <2	40	10	80.0
	HAQ >=2	9	39	81.3
	Overall percentage			80.6
Step 10	HAQ <2	40	10	80.0
	HAQ >=2	9	39	81.3
	Overall percentage			80.6
Step 11	HAQ <2	41	9	82.0
	HAQ >=2	8	40	83.3
	Overall percentage			82.7

Variables

		B	S. E.	Wald	df	Sig	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
Step 1	Age	.080	.035	5.412	1	.020	1.084	1.013	1.160
	Sex	-1.165	1.001	1.354	1	.245	.312	.044	2.219
	Disease duration	-.064	.061	1.114	1	.291	.938	.832	1.057
	Ethnic group	3.168	1.104	8.239	1	.004	23.748	2.731	206.509
	Yrs education	-.031	.147	.044	1	.834	.970	.727	1.294
	Smoking	-1.592	.866	3.379	1	.066	.204	.037	1.111
	EMS	.078	.285	.076	1	.783	1.082	.618	1.892
	Pain	.725	.228	10.126	1	.001	2.064	1.321	3.225
	Nodules	.105	.972	.012	1	.914	1.110	.165	7.465
	Sero + RF	-1.373	.811	2.869	1	.090	.253	.052	1.241
	SJC	.258	.085	9.204	1	.002	1.294	1.096	1.529
	Deformities	.114	.090	1.616	1	.204	1.121	.940	1.338
	Depression	-.029	.085	.119	1	.730	.971	.823	1.147
	PV	-3.291	2.680	1.507	1	.220	.037	.000	7.118
	Shared epitope	.757	.515	2.164	1	.141	2.133	.777	5.851
	EAM	-.177	.963	.034	1	.854	.838	.127	5.535
	Constant	-3.862	5.404	.511	1	.475	.021		
Step 2	Age	.080	.034	5.468	1	.019	1.083	1.013	1.158
	Sex	-1.180	.991	1.417	1	.234	.307	.044	2.145
	Disease duration	-.063	.059	1.126	1	.289	.939	.836	1.055
	Ethnic group	3.140	1.071	8.600	1	.003	23.113	2.833	188.547
	Yrs education	-.030	.147	.042	1	.838	.970	.728	1.294
	Smoking	-1.592	.867	3.372	1	.066	.204	.037	1.113
	EMS	.073	.281	.067	1	.795	1.075	.621	1.864
	Pain	.729	.224	10.541	1	.001	2.072	1.335	3.217
	Sero + RF	-1.351	.784	2.968	1	.085	.259	.056	1.204
	SJC	.259	.085	9.327	1	.002	1.296	1.097	1.530
	Deformities	.116	.088	1.740	1	.187	1.123	.945	1.336
	Depression	-.028	.083	.110	1	.740	.973	.826	1.145
	PV	-3.294	2.676	1.515	1	.218	.037	.000	7.041
	Shared epitope	.758	.515	2.167	1	.141	2.133	.778	5.848
	EAM	-.196	.947	.043	1	.836	.822	.129	5.258
	Constant	-3.847	5.402	.507	1	.476	.021		
Step 3	Age	.082	.032	6.445	1	.011	1.086	1.019	1.157
	Sex	-1.189	.986	1.456	1	.228	.304	.044	2.102
	Disease duration	-.063	.059	1.141	1	.285	.939	.836	1.054
	Ethnic group	3.180	1.054	9.107	1	.003	24.043	3.048	189.625
	Smoking	-1.611	.862	3.494	1	.062	.200	.037	1.081
	EMS	.075	.280	.072	1	.788	1.078	.622	1.868
	Pain	.730	.224	10.593	1	.001	2.075	1.337	3.220
	Sero + RF	-1.337	.782	2.922	1	.087	.263	.057	1.216
	SJC	.261	.084	9.709	1	.002	1.299	1.102	1.531
	Deformities	.116	.088	1.725	1	.189	1.123	.945	1.334
	Depression	-.027	.083	.107	1	.744	.973	.827	1.145
	PV	-3.182	2.599	1.499	1	.221	.041	.000	6.764

	Shared epitope	.751	.510	2.163	1	.141	2.119	.779	5.762
	EAM	-.161	.926	.030	1	.862	.851	.139	5.227
	Constant	-4.521	4.261	1.126	1	.289	.011		
Step 4	Age	.082	.032	6.433	1	.011	1.085	1.019	1.156
	Sex	-1.212	.980	1.528	1	.216	.298	.044	2.033
	Disease duration	-.066	.057	1.345	1	.246	.936	.837	1.047
	Ethnic group	3.162	1.048	9.093	1	.003	23.609	3.024	184.307
	Smoking	-1.617	.861	3.522	1	.061	.199	.037	1.074
	EMS	.077	.279	.076	1	.782	1.080	.625	1.867
	Pain	.723	.220	10.827	1	.001	2.061	1.340	3.170
	Sero + RF	-1.346	.781	2.972	1	.085	.260	.056	1.202
	SJC	.261	.084	9.711	1	.002	1.299	1.102	1.531
	Deformities	.119	.086	1.907	1	.167	1.126	.951	1.334
	Depression	-.026	.083	.097	1	.755	.975	.829	1.146
	PV	-3.099	2.556	1.470	1	.225	.045	.000	6.761
	Shared epitope	.729	.493	2.182	1	.140	2.072	.788	5.450
	Constant	-4.577	4.261	1.154	1	.283	.010		
Step 5	Age	.080	.031	6.480	1	.011	1.083	1.019	1.152
	Sex	-1.187	.977	1.476	1	.224	.305	.045	2.071
	Disease duration	-.065	.057	1.319	1	.251	.937	.839	1.047
	Ethnic group	3.162	1.049	9.086	1	.003	23.616	3.022	184.542
	Smoking	-1.563	.839	3.469	1	.063	.209	.040	1.085
	Pain	.743	.209	12.664	1	.000	2.102	1.396	3.165
	Sero + RF	-1.371	.777	3.111	1	.078	.254	.055	1.165
	SJC	.261	.084	9.630	1	.002	1.298	1.101	1.531
	Deformities	.119	.086	1.921	1	.166	1.126	.952	1.333
	Depression	-.025	.083	.094	1	.760	.975	.829	1.146
	PV	-3.116	2.564	1.477	1	.224	.044	.000	6.748
	Shared epitope	.746	.488	2.337	1	.126	2.110	.810	5.493
	Constant	-4.498	4.247	1.121	1	.290	.011		
Step 6	Age	.079	.031	6.506	1	.011	1.082	1.018	1.149
	Sex	-1.208	.976	1.533	1	.216	.299	.044	2.022
	Disease duration	-.063	.056	1.254	1	.263	.939	.841	1.048
	Ethnic group	3.064	.987	9.639	1	.002	21.409	3.095	148.117
	Smoking	-1.581	.838	3.558	1	.059	.206	.040	1.064
	Pain	.721	.194	13.774	1	.000	2.056	1.405	3.008
	Sero + RF	-1.327	.765	3.004	1	.083	.265	.059	1.189
	SJC	.256	.081	9.884	1	.002	1.292	1.101	1.515
	Deformities	.114	.084	1.844	1	.174	1.121	.951	1.322
	PV	-3.025	2.530	1.430	1	.232	.049	.000	6.914
	Shared epitope	.734	.485	2.293	1	.130	2.083	.806	5.384
	Constant	-4.542	4.242	1.147	1	.284	.011		
Step 7	Age	.073	.030	5.869	1	.015	1.076	1.014	1.142
	Sex	-.915	.941	.946	1	.331	.400	.063	2.533
	Ethnic group	2.974	.968	9.441	1	.002	19.567	2.935	130.425
	Smoking	-1.436	.807	3.166	1	.075	.238	.049	1.157
	Pain	.694	.184	14.182	1	.000	2.002	1.395	2.873
	Sero + RF	-1.159	.734	2.494	1	.114	.314	.074	1.322

	SJC	.242	.080	9.153	1	.002	1.274	1.089	1.490
	Deformities	.061	.068	.790	1	.374	1.063	.929	1.215
	PV	-2.936	2.449	1.438	1	.231	.053	.000	6.448
	Shared epitope	.773	.477	2.631	1	.105	2.166	.851	5.512
	Constant	-4.871	4.196	1.348	1	.246	.008		
Step 8	Age	.078	.030	6.744	1	.009	1.081	1.019	1.146
	Sex	-.814	.920	.783	1	.376	.443	.073	2.688
	Ethnic group	2.952	.968	9.306	1	.002	19.139	2.873	127.504
	Smoking	-1.480	.799	3.433	1	.064	.228	.048	1.089
	Pain	.698	.184	14.383	1	.000	2.009	1.401	2.881
	Sero + RF	-.971	.685	2.010	1	.156	.379	.099	1.450
	SJC	.262	.076	11.767	1	.001	1.299	1.119	1.509
	PV	-3.387	2.410	1.975	1	.160	.034	.000	3.806
	Shared epitope	.805	.475	2.878	1	.090	2.237	.882	5.671
	Constant	-4.397	4.109	1.145	1	.285	.012		
Step 9	Age	.077	.029	6.809	1	.009	1.080	1.019	1.144
	Ethnic group	2.868	.944	9.224	1	.002	17.610	2.766	112.126
	Smoking	-1.169	.700	2.787	1	.095	.311	.079	1.226
	Pain	.687	.180	14.550	1	.000	1.987	1.396	2.827
	Sero + RF	-.822	.656	1.569	1	.210	.440	.121	1.591
	SJC	.251	.074	11.574	1	.001	1.286	1.112	1.486
	PV	-3.193	2.346	1.852	1	.174	.041	.000	4.077
	Shared epitope	.841	.467	3.244	1	.072	2.319	.928	5.791
	Constant	-5.385	4.018	1.796	1	.180	.005		
Step 10	Age	.070	.028	6.290	1	.012	1.072	1.015	1.132
	Ethnic group	2.707	.907	8.905	1	.003	14.981	2.532	88.642
	Smoking	-1.185	.689	2.959	1	.085	.306	.079	1.180
	Pain	.684	.177	14.999	1	.000	1.981	1.402	2.800
	SJC	.233	.072	10.537	1	.001	1.262	1.097	1.453
	PV	-3.551	2.302	2.379	1	.123	.029	.000	2.615
	Shared epitope	.867	.463	3.500	1	.061	2.379	.960	5.900
	Constant	-4.570	3.865	1.398	1	.237	.010		
Step 11	Age	.059	.026	5.177	1	.023	1.061	1.008	1.117
	Ethnic group	2.104	.762	7.633	1	.006	8.198	1.843	36.467
	Smoking	-1.315	.681	3.732	1	.053	.268	.071	1.019
	Pain	.682	.173	15.467	1	.000	1.978	1.408	2.778
	SJC	.197	.062	10.154	1	.001	1.218	1.079	1.375
	Shared epitope	.804	.445	3.266	1	.071	2.234	.934	5.340
	Constant	-9.501	2.417	15.448	1	.000	.000		

Multiple Regression to predict HAQ in Caucasians only

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.840*	.705	.602	.635	.705	6.848	15	43	.000

*Predictors: (Constant), EAM, age, pain, smoking history, PV, sex, disease duration, Seropositivity for RF, Shared Epitope, yrs education, EMS, depression, nodules, SJC, deformities

ANOVA

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	41.453	15	2.764	6.848	.000
Residual	17.353	43	.404		
Total	58.806	58			

Predictors as before

Model	Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
	B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
(Constant)	-.801	1.451		-.552	.584	-3.728	2.126					
Age	.001	.009	.016	.145	.885	-.017	.020	.100	.022	.012	.568	1.760
Sex	-.165	.234	-.070	-.707	.484	-.638	.307	.081	-.107	-.059	.694	1.441
Disease duration	-.007	.013	-.065	-.528	.600	-.033	.019	.250	-.080	-.044	.458	2.186
Yrs education	-.009	.035	-.028	-.268	.790	-.080	.061	-.291	-.041	-.022	.640	1.563
Smoking history	-.044	.180	-.022	-.243	.809	-.408	.320	-.125	-.037	-.020	.843	1.186
EMS	.031	.096	.034	.326	.746	-.162	.225	.380	.050	.027	.634	1.578
Pain	.225	.056	.516	4.050	.000	.113	.337	.716	.525	.335	.422	2.369
Nodules	-.084	.250	-.042	-.337	.737	-.588	.420	.481	-.051	-.028	.452	2.212
Seropositive for RF	-.236	.210	-.114	-1.122	.268	-.659	.188	.061	-.169	-.093	.663	1.508
SJC	.054	.019	.365	2.796	.008	.015	.093	.656	.392	.232	.402	2.486
Deformities	.043	.027	.242	1.594	.118	-.011	.098	.450	.236	.132	.297	3.362
PV	.452	.717	.055	.631	.532	-.994	1.898	.135	.096	.052	.898	1.114
Shared epitope	.059	.147	.039	.405	.687	-.236	.355	.010	.062	.034	.725	1.380
Depression	.002	.027	.007	.066	.947	-.052	.055	.362	.010	.005	.601	1.664
EAM	-.244	.235	-.097	-1.038	.305	-.718	.230	.003	-.156	-.086	.789	1.267

Hierarchical multiple regression to predict HAQ in Caucasians

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.285	.081	.031	.991	.081	1.620	3	55	.195
2	.840	.705	.622	.635	.604	7.574	12	43	.000

Model 1. Predictors: (Constant), Age, sex, disease duration
Model 2. Predictors: (Constant), age, sex, disease duration, pain, smoking history, PV, ethnic group, seropositivity for RF, Shared Epitope, yrs education, EMS, depression, nodules, SJC, deformities, EAM,

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	4.775	3	1.592	1.620	.195
	Residual	54.030	55	.982		
	Total	58.806	58			
2	Regression	41.453	15	2.764	6.848	.000
	Residual	17.353	43	.404		
	Total	58.806	58			

Predictors as above

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	.353	.736		.479	.634	-1.123	1.828					
	Age	.007	.011	.078	.596	.553	-.015	.028	.100	.080	.077	.968	1.033
	Sex	.285	.308	.121	.926	.359	-.332	.903	.081	.124	.120	.974	1.026
	Disease duration	.027	.014	.254	1.933	.058	-.001	.055	.250	.252	.250	.969	1.032
2	(Constant)	-.801	1.451		-.552	.584	-3.728	2.126					
	Age	.001	.009	.016	.145	.885	-.017	.020	.100	.022	.012	.568	1.760
	Sex	-.165	.234	-.070	-.707	.484	-.638	.307	.081	-.107	-.059	.694	1.441
	Disease duration	-.007	.013	-.065	-.528	.600	-.033	.019	.250	-.080	-.044	.458	2.186
	Yrs education	-.009	.035	-.028	-.268	.790	-.080	.061	-.291	-.041	-.022	.640	1.563
	Smoking history	-.044	.180	-.022	-.243	.809	-.408	.320	-.125	-.037	-.020	.843	1.186
	Depression	.002	.027	.007	.066	.947	-.052	.055	.362	.010	.005	.601	1.664
	EMS	.031	.096	.034	.326	.746	-.162	.225	.380	.050	.027	.634	1.578
	Pain	.225	.056	.516	4.050	.000	.113	.337	.716	.525	.335	.422	2.369
	SJC	.054	.019	.365	2.796	.008	.015	.093	.656	.392	.232	.402	2.486
	Deformities	.043	.027	.242	1.594	.118	-.011	.098	.450	.236	.132	.297	3.362
	Seropositive for RF	-.236	.210	-.114	-1.122	.268	-.659	.188	.061	-.169	-.093	.663	1.508
	Nodules	-.084	.250	-.042	-.337	.737	-.588	.420	-.084	.250	-.042	.452	2.212
	PV	.452	.717	.055	.631	.532	-.994	1.898	.452	.717	.055	.898	1.114
	Shared epitope	-.244	.235	-.097	-1.038	.305	-.718	.230	-.244	.235	-.097	.789	1.267
	EAM	.059	.147	.039	.405	.687	-.236	.355	.059	.147	.039	.725	1.380

Stepwise Multiple regression to predict HAQ in Caucasians

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.716	.513	.504	.709	.513	59.964	1	57	.000
2	.811	.658	.646	.599	.146	23.909	1	56	.000

1. Predictors (constant) pain
2. Predictors (constant) pain, SJC

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	30.148	1	30.148	59.964	.000
	Residual	28.658	57	.503		
	Total	58.806	58			
2	Regression	38.722	2	19.361	53.987	.000
	Residual	20.083	56	.359		
	Total	58.806	58			

Predictors as above

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	.119	.174		.681	.499	-.230	.468					
	Pain	.312	.040	.716	7.744	.000	.231	.393	.716	.716	.716		
2	(constant)	-.240	.165		-1.459	.150	-.570	.090					
	Pain	.231	.038	.531	6.116	.000	.156	.307	.716	.633	.478		
	SJC	.063	.013	.424	4.890	.000	.037	.089	.656	.547	.382		

Backward logistic regression analysis to predict HAQ in Caucasians
Omnibus test of model coefficients

		Chi square	df	significance
Step 1	Step	54.572	15	.000
	Block	54.572	15	.000
	Model	54.572	15	.000
Step 2	Step	-.012	1	.914
	Block	54.561	14	.000
	Model	54.561	14	.000
Step 3	Step	-.178	1	.673
	Block	54.382	13	.000
	Model	54.382	13	.000
Step 4	Step	-.167	1	.683
	Block	54.215	12	.000
	Model	54.215	12	.000
Step 5	Step	-.846	1	.358
	Block	53.369	11	.000
	Model	53.369	11	.000
Step 6	Step	-.788	1	.375
	Block	52.581	10	.000
	Model	52.581	10	.000
Step 7	Step	-1.204	1	.273
	Block	51.377	9	.000
	Model	51.377	9	.000
Step 8	Step	-1.941	1	.164
	Block	49.436	8	.000
	Model	49.436	8	.000
Step 9	Step	-1.640	1	.200
	Block	47.796	7	.000
	Model	47.796	7	.000
Step 10	Step	-.769	1	.381
	Block	47.027	6	.000
	Model	47.027	6	.000
Step 11	Step	-1.112	1	.292
	Block	45.915	5	.000
	Model	45.915	5	.000
Step 12	Step	-2.082	1	.149
	Block	43.833	4	.000
	Model	43.833	4	.000
Step 13	Step	-1.418	1	.234
	Block	42.415	3	.000
	Model	42.415	3	.000
Step 14	Step	-1.989	1	.158
	Block	40.426	2	.000
	Model	40.426	2	.000

A negative Chi-squares value indicates that the Chi-squares value has decreased from the previous step.

Backward logistic regression analysis to predict HAQ in Caucasians

Model summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	23.363	.603	.823
2	23.375	.603	.823
3	23.553	.602	.821
4	23.721	.601	.820
5	24.567	.595	.812
6	25.355	.590	.805
7	26.559	.581	.793
8	28.499	.567	.774
9	30.140	.555	.757
10	30.908	.549	.749
11	32.021	.541	.738
12	34.103	.524	.715
13	35.521	.513	.699
14	37.510	.496	.677

Estimation terminated at iteration number 9 because parameter estimates changed by less than .001.
Estimation terminated at iteration number 8 because parameter estimates changed by less than .001.
Estimation terminated at iteration number 7 because parameter estimates changed by less than .001.
Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Classification table

Observed		Predicted		
		HAQ <2	HAQ >=2	Percentage correct
Step 1	HAQ <2	34	3	91.9
	HAQ >=2	2	20	90.9
	Overall percentage			91.5
Step 2	HAQ <2	34	3	91.9
	HAQ >=2	2	20	90.9
	Overall percentage			91.5
Step 3	HAQ <2	35	2	94.6
	HAQ >=2	2	20	90.9
	Overall percentage			93.2
Step 4	HAQ <2	35	2	94.6
	HAQ >=2	2	20	90.9
	Overall percentage			93.2
Step 5	HAQ <2	34	3	91.9
	HAQ >=2	3	19	86.4
	Overall percentage			89.8
Step 6	HAQ <2	35	2	94.6
	HAQ >=2	3	19	86.4
	Overall percentage			91.5
Step 7	HAQ <2	34	3	91.9
	HAQ >=2	3	19	86.4
	Overall percentage			89.8
Step 8	HAQ <2	34	3	91.9
	HAQ >=2	4	18	81.8
	Overall percentage			88.1
Step 9	HAQ <2	33	4	89.2
	HAQ >=2	4	18	81.8
	Overall percentage			86.4
Step 10	HAQ <2	34	3	91.9
	HAQ >=2	5	17	77.3
	Overall percentage			86.4
Step 11	HAQ <2	33	4	89.2
	HAQ >=2	6	16	72.7
	Overall percentage			83.1
Step 12	HAQ <2	34	3	91.9
	HAQ >=2	4	18	81.8
	Overall percentage			88.1
Step 13	HAQ <2	33	4	89.2
	HAQ >=2	6	16	72.7
	Overall percentage			83.1
Step 14	HAQ <2	34	3	91.9
	HAQ >=2	5	17	77.3
	Overall percentage			86.4

Variables in the equation

		B	S. E.	Wald	df	Sig	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
Step 1	Sex	-5.589	3.148	3.152	1	.076	.004	.000	1.788
	Age	.011	.098	.012	1	.914	1.011	.834	1.224
	Yrs education	-.164	.501	.107	1	.744	.849	.318	2.264
	Smoker	-2.931	1.823	2.586	1	.108	.053	.001	1.899
	Disease duration	-.166	.208	.634	1	.426	.847	.563	1.275
	EMS	1.256	.848	2.193	1	.139	3.510	.666	18.496
	Pain	1.020	.666	2.348	1	.125	2.773	.752	10.222
	Nodules	-3.444	3.143	1.201	1	.273	.032	.000	15.123
	Depression	-.193	.184	1.103	1	.294	.825	.575	1.182
	SJC	.707	.336	4.424	1	.035	2.027	1.049	3.917
	Deformities	.365	.304	1.438	1	.230	1.440	.793	2.615
	Sero + RF	-1.968	1.896	1.078	1	.299	.140	.003	5.742
	PV	7.420	6.888	1.160	1	.281	1668.965	.002	1218646954.797
	Shared epitope	-1.179	1.543	.584	1	.445	.307	.015	6.331
	EAM	-.763	1.780	.184	1	.668	.466	.014	15.264
	Constant	-15.546	18.050	.742	1	.389	.000		
Step 2	Sex	-5.599	3.153	3.153	1	.076	.004	.000	1.787
	Yrs education	-.188	.443	.180	1	.672	.829	.348	1.974
	Smoker	-2.838	1.592	3.180	1	.075	.059	.003	1.325
	Disease duration	-.168	.207	.663	1	.416	.845	.563	1.268
	EMS	1.249	.836	2.231	1	.135	3.488	.677	17.968
	Pain	1.019	.669	2.320	1	.128	2.771	.747	10.282
	Nodules	-3.428	3.142	1.191	1	.275	.032	.000	15.331
	Depression	-.202	.165	1.501	1	.221	.817	.592	1.129
	SJC	.699	.328	4.539	1	.033	2.011	1.058	3.826
	Deformities	.376	.288	1.699	1	.192	1.456	.828	2.563
	Sero + RF	-1.973	1.892	1.087	1	.297	.139	.003	5.674
	PV	7.526	6.900	1.190	1	.275	1856.247	.002	1386063533.950
	Shared epitope	-1.269	1.318	.927	1	.336	.281	.021	3.724
	EAM	-.746	1.772	.177	1	.674	.474	.015	15.289
	Constant	-14.681	16.052	.836	1	.360	.000		
Step 3	Sex	-5.778	3.135	3.397	1	.065	.003	.000	1.442
	Yrs education	-.176	.437	.161	1	.688	.839	.356	1.976
	Smoker	-2.988	1.546	3.733	1	.053	.050	.002	1.044
	Disease duration	-.213	.185	1.316	1	.251	.808	.562	1.163
	EMS	1.234	.802	2.365	1	.124	3.435	.713	16.558
	Pain	1.022	.669	2.330	1	.127	2.778	.748	10.314
	Nodules	-3.308	3.115	1.128	1	.288	.037	.000	16.401
	Depression	-.198	.164	1.458	1	.227	.820	.595	1.131
	SJC	.665	.301	4.897	1	.027	1.945	1.079	3.507
	Deformities	.404	.286	1.999	1	.157	1.498	.856	2.622
	Sero + RF	-1.835	1.878	.955	1	.328	.160	.004	6.330
	PV	8.252	6.641	1.544	1	.214	3836.324	.009	1723151490.870
	Shared epitope	-1.309	1.293	1.026	1	.311	.270	.021	3.402
	Constant	-15.448	15.719	.966	1	.326	.000		

Step 4	Sex	-5.941	3.225	3.394	1	.065	.003	.000	1.462
	Smoker	-3.078	1.571	3.839	1	.050	.046	.002	1.001
	Disease duration	-.220	.185	1.409	1	.235	.803	.559	1.154
	EMS	1.175	.794	2.189	1	.139	3.237	.683	15.340
	Pain	1.168	.611	3.650	1	.056	3.214	.970	10.651
	Nodules	-3.860	2.964	1.695	1	.193	.021	.000	7.028
	Depression	-.211	.161	1.732	1	.188	.809	.591	1.109
	SJC	.704	.305	5.330	1	.021	2.023	1.112	3.679
	Deformities	.433	.282	2.366	1	.124	1.542	.888	2.679
	Sero + RF	-1.587	1.802	.775	1	.379	.205	.006	6.992
	PV	9.268	6.196	2.237	1	.135	10591.117	.056	1992387125.247
	Shared epitope	-1.212	1.269	.911	1	.340	.298	.025	3.582
	Constant	-19.999	11.508	3.020	1	.082	.000		

Step 5	Sex	-6.605	3.448	3.668	1	.055	.001	.000	1.167
	Smoker	-3.380	1.555	4.726	1	.030	.034	.002	.717
	Disease duration	-.279	.183	2.324	1	.127	.757	.529	1.083
	EMS	1.332	.840	2.514	1	.113	3.790	.730	19.673
	Pain	1.264	.610	4.285	1	.038	3.538	1.070	11.704
	Nodules	-5.092	2.762	3.398	1	.065	.006	.000	1.381
	Depression	-.184	.157	1.380	1	.240	.832	.611	1.131
	SJC	.735	.315	5.427	1	.020	2.085	1.124	3.867
	Deformities	.487	.285	2.909	1	.088	1.627	.930	2.845
	PV	10.686	6.569	2.646	1	.104	43743.782	.112	17079186405.864
	Shared epitope	-1.030	1.205	.730	1	.393	.357	.034	3.788
	Constant	-23.102	11.970	3.725	1	.054	.000		
Step 6	Sex	-5.007	2.402	4.346	1	.037	.007	.000	.741
	Smoker	-2.845	1.332	4.565	1	.033	.058	.004	.790
	Disease duration	-.249	.161	2.395	1	.122	.780	.569	1.069
	EMS	.862	.543	2.526	1	.112	2.369	.818	6.860
	Pain	1.083	.511	4.490	1	.034	2.954	1.085	8.044
	Nodules	-4.168	2.245	3.448	1	.063	.015	.000	1.260
	Depression	-.153	.146	1.093	1	.296	.858	.644	1.143
	SJC	.610	.231	7.006	1	.008	1.841	1.172	2.893
	Deformities	.403	.242	2.777	1	.096	1.496	.931	2.404
	PV	7.555	4.620	2.673	1	.102	1909.650	.223	16365252.866
	Constant	-18.048	8.608	4.396	1	.036	.000		
Step 7	Sex	-4.406	2.162	4.153	1	.042	.012	.000	.845
	Smoker	-2.679	1.315	4.153	1	.042	.069	.005	.903
	Disease duration	-.176	.135	1.694	1	.193	.839	.643	1.093
	EMS	.605	.451	1.800	1	.180	1.832	.757	4.435
	Pain	.902	.454	3.951	1	.047	2.464	1.013	5.994
	Nodules	-4.016	2.266	3.143	1	.076	.018	.000	1.528
	SJC	.572	.213	7.192	1	.007	1.771	1.166	2.689
	Deformities	.315	.213	2.184	1	.139	1.370	.902	2.079
	PV	6.715	4.543	2.185	1	.139	824.339	.112	6067987.378
	Constant	-16.750	8.488	3.894	1	.048	.000		
Step 8	Sex	-3.755	2.039	3.392	1	.066	.023	.000	1.273

	Smoker	-2.216	1.220	3.300	1	.069	.109	.010	1.191
	Disease duration	-.137	.120	1.297	1	.255	.872	.689	1.104
	Pain	.995	.429	5.378	1	.020	2.705	1.167	6.271
	Nodules	-3.831	2.175	3.103	1	.078	.022	.000	1.540
	SJC	.535	.200	7.133	1	.008	1.707	1.153	2.528
	Deformities	.275	.201	1.865	1	.172	1.316	.887	1.954
	PV	5.160	4.119	1.569	1	.210	174.221	.054	559196.352
	Constant	-14.396	7.756	3.445	1	.063	.000		
Step 9	Sex	-2.520	1.506	2.801	1	.094	.080	.004	1.539
	Smoker	-1.777	1.062	2.799	1	.094	.169	.021	1.357
	Pain	.838	.349	5.757	1	.016	2.312	1.166	4.586
	Nodules	-3.190	1.809	3.110	1	.078	.041	.001	1.426
	SJC	.536	.199	7.263	1	.007	1.709	1.157	2.524
	Deformities	.097	.113	.730	1	.393	1.102	.882	1.376
	PV	3.754	3.485	1.160	1	.281	42.675	.046	39531.412
	Constant	-12.956	6.923	3.502	1	.061	.000		
Step 10	Sex	-2.169	1.332	2.651	1	.104	.114	.008	1.556
	Smoker	-1.701	1.016	2.802	1	.094	.182	.025	1.337
	Pain	.705	.279	6.385	1	.012	2.024	1.171	3.496
	Nodules	-2.455	1.439	2.911	1	.088	.086	.005	1.441
	SJC	.526	.183	8.234	1	.004	1.692	1.181	2.423
	PV	3.545	3.393	1.091	1	.296	34.631	.045	26791.720
	Constant	-11.887	6.424	3.424	1	.064	.000		
Step 11	Sex	-1.719	1.238	1.927	1	.165	.179	.016	2.030
	Smoker	-1.576	.984	2.564	1	.109	.207	.030	1.424
	Pain	.649	.259	6.295	1	.012	1.913	1.153	3.176
	Nodules	-2.019	1.326	2.317	1	.128	.133	.010	1.787
	SJC	.485	.173	7.869	1	.005	1.623	1.157	2.277
	Constant	-5.715	1.911	8.946	1	.003	.003		
Step 12	Smoker	-1.241	.911	1.854	1	.173	.289	.048	1.725
	Pain	.565	.229	6.069	1	.014	1.759	1.122	2.757
	Nodules	-1.259	1.104	1.301	1	.254	.284	.033	2.471
	SJC	.396	.139	8.131	1	.004	1.486	1.132	1.951
	Constant	-6.153	1.773	12.047	1	.001	.002		
Step 13	Smoker	-1.205	.882	1.867	1	.172	.300	.053	1.688
	Pain	.536	.219	5.998	1	.014	1.709	1.113	2.624
	SJC	.308	.104	8.720	1	.003	1.360	1.109	1.668
	Constant	-5.656	1.622	12.154	1	.000	.003		
Step 14	Pain	.520	.211	6.089	1	.014	2.028	1.113	2.541
	SJC	.305	.103	8.834	1	.003	1.217	1.109	1.659
	Constant	-6.058	1.582	14.662	1	.000	.002		

Multiple Regression to predict HAQ in Asians only

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.784	.615	.363	.780	.615	2.446	15	23	.026

*Predictors: (Constant), EAM, AGE, PAIN, smoker2, PLASMA VISCOSITY, SEX no, DISEASE DURATION /YRS, SERO2, Shared Epitope, YRS EDUCATION, EMS/hrs, DEPRESSION /19, NODULES, SWOLLEN JOINT COUNT, DEFORMITIES

ANOVA

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	22.348	15	1.490	2.446	.026
Residual	14.010	23	.609		
Total	36.359	38			

Predictors as before

Model	Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
	B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
(Constant)	.050	2.306		.022	.983	-4.720	4.820					
Age	.048	.018	.551	2.626	.015	.010	.086	.610	.480	.340	.380	2.630
Sex	-.326	.638	-.102	-.511	.614	-1.645	.993	-.132	-.106	-.066	.417	2.397
Disease duration	-.007	.031	-.042	-.215	.831	-.071	.058	.401	-.045	-.028	.443	2.260
Yrs education	-.008	.053	-.025	-.143	.888	-.117	.102	-.286	-.030	-.018	.562	1.779
Smoking history	-.100	.636	-.035	-.158	.876	-1.417	1.216	-.108	-.033	-.020	.345	2.897
EMS	.114	.116	.175	.981	.337	-.126	.353	.252	.200	.127	.528	1.894
Pain	.091	.097	.185	.938	.358	-.110	.292	.343	.192	.121	.429	2.329
Depression	-.002	.041	-.007	-.038	.970	-.085	.082	.417	-.008	-.005	.524	1.908
Nodules	.292	.480	.109	.609	.549	-.701	1.285	.130	.126	.079	.521	1.921
Seropositive for RF	-.217	.319	-.112	-.680	.503	-.878	.443	-.189	-.140	-.088	.613	1.632
SJC	.046	.046	.192	1.005	.325	-.049	.142	.135	.205	.130	.461	2.169
Deformities	.038	.033	.228	1.179	.251	-.029	.106	.449	.239	.153	.446	2.243
PV	-.885	1.380	-.138	-.641	.528	-3.741	1.971	-.050	-.132	-.083	.361	2.772
Shared epitope	.231	.241	.156	.959	.347	-.267	.729	-.108	.196	.124	.630	1.587
EAM	.276	.430	.095	.642	.527	-.613	1.164	.130	.133	.083	.757	1.321

Hierarchical multiple regression in Asians to predict HAQ

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.624	.390	.338	.784	.390	7.453	3	35	.001
2	.757	.573	.295	.809	.183	.823	12	23	.627

Model 1. Predictors: (Constant), Age, sex, disease duration
Model 2. Predictors: (Constant), age, sex, disease duration, pain, smoking history, PV, ethnic group, seropositivity for RF, Shared Epitope, yrs education, EMS, depression, nodules, SJC, deformities, EAM,

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	13.761	3	4.587	7.453	.001
	Residual	21.540	35	.615		
	Total	35.301	38			
2	Regression	20.229	15	1.349	2.058	.058
	Residual	15.071	23	.655		
	Total	35.301	38			

Predictors as above

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	-.368	.707		-.521	.606	-1.805	1.068					
	Age	.036	.012	.420	2.944	.006	.011	.061	.544	.446	.389	.857	1.167
	Sex	-.088	.405	-.029	-.216	.830	-.909	.734	.029	-.037	-.029	.958	1.044
	Disease duration	.050	.022	.335	2.307	.027	.006	.094	.485	.363	.305	.827	1.209
2	(Constant)	-1.948	2.053		-.949	.353	-6.195	2.300					
	Age	.029	.015	.343	1.985	.059	-.001	.060	.544	.382	.270	.620	1.612
	Sex	-.429	.635	-.143	-.675	.506	-1.743	.885	.029	-.139	-.092	.414	2.416
	Disease duration	.008	.028	.053	.277	.784	-.051	.067	.485	.058	.038	.516	1.938
	Yrs education	-.027	.042	-.104	-.628	.536	-.114	.061	-.296	-.130	-.086	.679	1.473
	Smoking history	-.240	.613	-.080	-.392	.699	-1.509	1.029	-.083	-.081	-.053	.444	2.254
	Depression	.018	.038	.078	.479	.637	-.060	.096	.360	.099	.065	.698	1.433
	EMS	.107	.113	.155	.946	.354	-.127	.341	.226	.193	.129	.688	1.453
	Pain	.113	.103	.220	1.099	.283	-.100	.327	.368	.223	.150	.464	2.154
	SJC	-.006	.036	-.028	-.153	.880	-.081	.069	.239	-.032	-.021	.556	1.800
	Deformities	.051	.031	.321	1.640	.115	-.013	.115	.484	.324	.223	.485	2.060
	Seropositive for RF	-.409	.324	-.213	-1.262	.220	-1.080	.262	-.077	-.254	-.172	.653	1.531
	Nodules	.241	.454	.093	.530	.601	-.699	1.180	.077	.110	.072	.600	1.667
	PV	.964	1.156	.159	.834	.413	-1.428	3.356	.120	.171	.114	.511	1.959
	Shared epitope	.262	.269	.180	.975	.340	-.294	.818	-.108	.199	.133	.544	1.838
	EAM	.180	.298	.087	.603	.552	-.438	.797	.138	.125	.082	.892	1.121

Hierarchical regression : only entering EMS and deformities after adjusting for age in Asians
Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.624	.390	.358	.772	.390	12.138	3	57	.000
2	.705	.497	.451	.714	.107	5.845	2	55	.005

Model 1. Predictors: (Constant), Age, sex, disease duration
Model 2. Predictors: (Constant), age, sex, disease duration, EMS, deformities
ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	21.727	3	7.242	12.138	.000
	Residual	34.010	57	.597		
	Total	55.738	60			
2	Regression	27.689	5	5.538	10.859	.000
	Residual	28.049	55	.510		
	Total	55.738	60			

Predictors as above

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	-.368	.554		-.664	.509	-1.479	.742					
	Age	.036	.010	.420	3.757	.000	.017	.055	.544	.446	.389	.857	1.167
	Sex	-.088	.317	-.029	-.276	.784	-.723	.547	.029	-.037	-.029	.958	1.044
	Disease duration	.050	.017	.335	2.945	.005	.016	.084	.485	.363	.305	.827	1.209
2	(Constant)	-.640	.519		-1.233	.223	-1.680	.400					
	Age	.038	.009	.442	4.264	.000	.020	.056	.544	.498	.408	.850	1.177
	Sex	-.067	.294	-.022	-.228	.821	-.657	.523	.029	-.031	-.022	.949	1.054
	Disease duration	.018	.019	.123	.965	.339	-.020	.057	.485	.129	.092	.562	1.779
	EMS	.114	.066	.165	1.712	.093	-.019	.247	.226	.225	.164	.983	1.018
	Deformities	.052	.019	.330	2.797	.007	.015	.090	.484	.353	.268	.656	1.523

Stepwise multiple regression to predict HAQ in Asians

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.610	.372	.355	.786	.372	21.907	1	37	.000
2	.700	.489	.461	.718	.117	8.283	1	36	.007
3	.740	.548	.510	.685	.059	4.569	1	35	.040

Predictors: 1. (constant) age
2. (constant) age, deformities
3. (constant) age, deformities, EMS

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	13.522	1	13.522	21.907	.000
	Residual	22.837	37	.617		
	Total	36.359	38			
2	Regression	17.793	2	8.896	17.251	.000
	Residual	18.566	36	.516		
	Total	36.359	38			
3	Regression	19.937	3	6.646	14.164	.000
	Residual	16.422	35	.469		
	Total	36.359	38			

Coefficients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	-.971	.620		-1.565	.126	-2.227	.286					
	Age	.053	.011	.610	4.680	.000	.030	.076	.610	.610	.610	1.000	1.000
2	(Constant)	-.979	.567		-1.727	.093	-2.129	.171					
	Age	.048	.011	.546	4.506	.000	.026	.069	.610	.600	.537	.966	1.035
	Deformities	.059	.020	.349	2.878	.007	.017	.100	.449	.432	.343	.966	1.035
3	(Constant)	1.281	.559		-2.293	.028	-2.416	-.147					
	Age	.050	.010	.570	4.910	.000	.029	.070	.610	.639	.558	.957	1.045
	Deformities	.052	.020	.309	2.638	.012	.012	.092	.449	.407	.300	.942	1.062
	EMS	.160	.075	.247	2.138	.040	.008	.313	.252	.340	.243	.970	1.031

Logistic regression using age, EMS and deformities to predict HAQ in Asians

Omnibus test of model coefficients

		Chi square	df	significance
Step 1	Step	19.721	3	.000
	Block	19.721	3	.000
	Model	19.721	3	.000

Model summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	55.952	.276	.389

Classification table

Observed		Predicted		
		HAQ <2	HAQ >=2	Percentage correct
Step 1	HAQ <2	11	8	57.9
	HAQ >=2	4	38	90.5
	Overall percentage			80.3

Variables in the equation

		B	S. E.	Wald	df	Sig	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
Step 1	**Age**	.115	.037	9.682	1	.002	1.122	1.044	1.207
	Deformities	.113	.070	2.620	1	.106	1.119	.977	1.283
	EMS	.244	.267	.834	1	.361	1.276	.756	2.154
	Constant	-5.829	1.915	9.268	1	.002	.003		

Stepwise regression to predict SJC in all patients

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.485	.235	.227	5.340	.235	29.457	1	96	.000
2	.540	.291	.276	5.166	.056	7.544	1	95	.007
3	.571	.326	.304	5.065	.035	4.846	1	94	.030

Predictors: 1. (constant) deformities
2. (constant) deformities, nodules,
3. (constant) deformities, nodules, PV

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	839.825	1	839.825	29.457	.000
	Residual	2737.008	96	28.511		
	Total	3576.834	97			
2	Regression	1041.171	2	520.585	19.504	.000
	Residual	2535.663	95	26.691		
	Total	3576.834	97			
3	Regression	1165.493	3	388.498	15.145	.000
	Residual	2411.341	94	25.653		
	Total	3576.834	97			

Coefficients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	6.129	.799		7.666	.000	4.542	7.715					
	Deformities	.505	.093	.485	5.427	.000	.320	.689	.485	.485	.485	1.000	1.000
2	(Constant)	5.854	.780		7.507	.000	4.306	7.403					
	Deformities	.382	.100	.367	3.809	.000	.183	.582	.485	.364	.329	.803	1.245
	Nodules	3.492	1.272	.265	2.747	.007	.968	6.017	.428	.271	.237	.803	1.245
3	(Constant)	-7.780	6.241		-1.247	.216	-20.171	4.610					
	Deformities	.386	.098	.371	3.921	.000	.190	.581	.485	.375	.332	.803	1.245
	Nodules	3.664	1.249	.278	2.933	.004	1.184	6.143	.428	.290	.248	.800	1.250
	PV	7.819	3.552	.187	2.201	.030	.767	14.871	.147	.221	.186	.994	1.006

Stepwise regression to predict SJC in Caucasians

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.635	.403	.392	5.291	.403	38.465	1	57	.000
2	.694	.482	.464	4.971	.079	8.579	1	56	.005

Predictors: 1. (constant) deformities
2. (constant) deformities, nodules,
3. (constant) deformities, nodules,

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1076.745	1	1076.745	38.465	.000
	Residual	1595.601	57	27.993		
	Total	2672.345	58			
2	Regression	1288.717	2	644.358	26.079	.000
	Residual	1383.629	56	24.708		
	Total	2672.345	58			

Coefficients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	5.364	1.065		5.036	.000	3.231	7.497					
	Deformities	.764	.123	.635	6.202	.000	.517	1.010	.635	.635	.635	1.000	1.000
2	(Constant)	4.854	1.016		4.779	.000	2.820	6.889					
	Deformities	.556	.136	.462	4.092	.000	.284	.828	.635	.480	.393	.726	1.377
	Nodules	4.519	1.543	.331	2.929	.005	1.428	7.610	.572	.364	.282	.726	1.377

Stepwise regression to predict SJC in Asians

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.336	.113	.089	4.636	.113	4.716	1	37	.036
2	.482	.232	.190	4.372	.119	5.599	1	36	.023

Predictors: 1. (constant) PV
2. (constant) PV, deformities

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	101.361	1	101.361	4.716	.036
	Residual	795.273	37	21.494		
	Total	896.634	38			
2	Regression	208.398	2	104.199	5.450	.009
	Residual	688.236	36	19.118		
	Total	896.634	38			

Coefficients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	-10.189	8.439		-1.207	.235	-27.287	6.910					
	PV	10.276	4.732	.336	2.172	.036	.688	19.864	.336	.336	.336	1.000	1.000
2	(Constant)	-15.271	8.243		-1.852	.072	-31.989	1.448					
	PV	12.182	4.535	.399	2.686	.011	2.985	21.379	.336	.409	.392	.968	1.033
	Deformities	.280	.119	.351	2.366	.023	.040	.521	.280	.367	.346	.968	1.033

MANOVA

Multivariate tests

Effect		Value	F	Hypothesis df	Error df	Sig	Partial eta squared
Intercept	Pillai's Trace	.994	5074.201	4.000	128.000	.000	.994
	Wilks' Lambda	.006	5074.201	4.000	128.000	.000	.994
	Hotelling's Trace	158.569	5074.201	4.000	128.000	.000	.994
	Roy's Largest Root	158.569	5074.201	4.000	128.000	.000	.994
Ethnic group	Pillai's Trace	.301	13.796	4.000	128.000	.000	.301
	Wilks' Lambda	.699	13.796	4.000	128.000	.000	.301
	Hotelling's Trace	.431	13.796	4.000	128.000	.000	.301
	Roy's Largest Root	.431	13.796	4.000	128.000	.000	.301

Tests of between subjects means

Source	Dependent variable	Type III sum of squares	df	Mean square	F	Sig	Partial eta squared
Corrected model	SJC (1)	180.386	1	180.386	5.042	.026	.037
	Pain (2)	71.962	1	71.962	16.031	.000	.109
	HAQ (3)	14.848	1	14.848	15.228	.000	.104
	PV (4)	.199	1	.199	10.086	.002	.071
Intercept	SJC	11263.334	1	11263.334	314.802	.000	.706
	Pain	2564.431	1	2564.431	571.262	.000	.813
	HAQ	337.795	1	337.795	346.460	.000	.726
	PV	398.801	1	398.801	20203.822	.000	.994
Ethnic group	SJC	180.386	1	180.386	5.042	.026	.037
	Pain	71.962	1	71.962	16.031	.000	.109
	HAQ	14.848	1	14.848	15.228	.000	.104
	PV	.199	1	.199	10.086	.002	.071
Error	SJC	4687.057	131	35.779			
	Pain	588.067	131	4.489			
	HAQ	127.724	131	.975			
	PV	2.586	131	.020			
Total	SJC	16447.000	133				
	Pain	3171.070	133				
	HAQ	471.000	133				
	PV	402.850	133				
Corrected total	SJC	4867.444	132				
	Pain	660.029	132				
	HAQ	142.571	132				
	PV	2.785	132				

1. R Squared = .037 (Adjusted R Squared = .030)
2. R Squared = .109 (Adjusted R Squared = .102)
3. R Squared = .104 (Adjusted R Squared = .097)

Multiple Regression to predict depression in all patients

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.736	.542	.479	3.359	.542	8.587	16	116	.000

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1550.096	16	96.881	8.587	.000
	Residual	1308.716	116	11.282		
	Total	2858.812	132			

Model	Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
	B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
(Constant)	4.664	3.438		1.357	.178	-2.145	11.473					
Age	-.013	.032	-.034	-.409	.684	-.076	.050	-.160	-.038	-.026	.556	1.798
Sex	.228	.839	.019	.272	.786	-1.433	1.890	.164	.025	.017	.815	1.227
Disease duration	-.047	.047	-.083	-1.006	.316	-.140	.046	-.014	-.093	-.063	.574	1.742
Ethnic gp	2.994	.817	.322	3.665	.000	1.376	4.612	.477	.322	.230	.512	1.953
Partner	-.836	1.026	-.064	-.814	.417	-2.868	1.197	-.260	-.075	-.051	.631	1.586
Family	-.331	.366	-.086	-.903	.368	-1.056	.395	-.007	-.084	-.057	.439	2.280
No who help	.203	.194	.084	1.050	.296	-.180	.587	.219	.097	.066	.616	1.623
Yrs education	.140	.100	.105	1.402	.164	-.058	.339	-.140	.129	.088	.709	1.411
Life events	1.132	.251	.298	4.502	.000	.634	1.630	.429	.386	.283	.903	1.108
Alcohol	.000	.053	.001	.008	.994	-.104	.105	-.232	.001	.001	.810	1.235
Pain	.299	.189	.144	1.583	.116	-.075	.673	.502	.145	.099	.479	2.089
EMS	.321	.271	.087	1.184	.239	-.216	.858	.348	.109	.074	.724	1.381
SJC	.043	.063	.056	.684	.495	-.082	.169	.099	.063	.043	.579	1.727
Deformities	.019	.072	.024	.267	.790	-.124	.163	.101	.025	.017	.480	2.084
HAQ	.515	.448	.115	1.149	.253	-.373	1.403	.454	.106	.072	.394	2.540
Perceived efficacy	-.841	.439	-.146	-1.914	.058	-1.712	.029	-.460	-.175	-.120	.674	1.485

Stepwise multiple regression to predict depression in all patients

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.502	.252	.246	4.040	.252	44.170	1	131	.000
2	.611	.373	.363	3.714	.121	25.014	1	130	.000
3	.688	.474	.461	3.415	.101	24.717	1	129	.000
4	.706	.498	.482	3.349	.024	6.167	1	128	.014

Predictors:
1. (constant) Pain
2. (constant) Pain, life events
3. (constant) Pain, life events, ethnic group
4. (constant) Pain, life events, ethnic group, perceived efficacy

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	720.860	1	720.860	44.170	.000
	Residual	2137.952	131	16.320		
	Total	2858.812	132			
2	Regression	1065.856	2	532.928	38.640	.000
	Residual	1792.956	130	13.792		
	Total	2858.812	132			
3	Regression	1354.152	3	451.384	38.699	.000
	Residual	1504.660	129	11.664		
	Total	2858.812	132			
4	Regression	1423.313	4	355.828	31.728	.000
	Residual	1435.499	128	11.215		
	Total	2858.812	132			

Coefficients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	2.497	.768		3.252	.001	.978	4.016					
	Pain	1.045	.157	.502	6.646	.000	.734	1.356	.502	.502	.502	1.000	1.000
2	(Constant)	1.493	.734		2.034	.044	.041	2.944					
	Pain	.919	.147	.441	6.261	.000	.628	1.209	.502	.481	.435	.970	1.031
	Life events	1.341	.268	.353	5.001	.000	.811	1.872	.429	.402	.347	.970	1.031
2	(Constant)	1.095	.680		1.611	.110	-.249	2.440					
	Pain	.692	.142	.332	4.855	.000	.410	.974	.502	.393	.310	.871	1.149
	Life events	1.296	.247	.341	5.251	.000	.807	1.784	.429	.420	.335	.969	1.032
	Ethnic gp	3.132	.630	.337	4.972	.000	1.886	4.379	.477	.401	.318	.890	1.124
2	(Constant)	5.619	1.940		2.897	.004	1.781	9.457					
	Pain	.550	.151	.264	3.641	.000	.251	.848	.502	.306	.228	.746	1.341
	Life events	1.211	.244	.318	4.955	.000	.727	1.694	.429	.401	.310	.950	1.053
	Ethnic gp	2.849	.628	.306	4.534	.000	1.605	4.092	.477	.372	.284	.860	1.162
	Perceived eff	-1.032	.416	-.180	-2.483	.014	-1.854	-.210	-.460	-.214	-.156	.749	1.335

Stepwise regression to predict depression in Asians

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.481	.231	.218	3.683	.231	17.758	1	59	.000
2	.558	.311	.288	3.515	.080	6.750	1	58	.012

Predictors: 1. (constant) Life events
2. (constant) Life events, HAQ

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	240.844	1	240.844	17.758	.000
	Residual	800.205	59	13.563		
	Total	1041.049	60			
2	Regression	324.264	2	162.132	13.119	.000
	Residual	716.785	58	12.358		
	Total	1041.049	60			

Coefficients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	7.535	.654		11.529	.000	6.228	8.843					
	Life events	1.492	.354	.481	4.214	.000	.783	2.200	.481	.481	.481	1.000	1.000
2	(Constant)	5.327	1.055		5.051	.000	3.216	7.438					
	Life events	1.341	.343	.432	3.913	.000	.655	2.027	.481	.457	.426	.971	1.029
	HAQ	1.241	.478	.287	2.598	.012	.285	2.197	.360	.323	.283	.971	1.029

Stepwise regression to predict depression in Caucasians

Model summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.516	.267	.256	3.495	.267	25.453	1	70	.000
2	.596	.356	.337	3.300	.089	9.531	1	69	.003
3	.645	.416	.391	3.164	.061	7.071	1	68	.010
4	.681	.463	.431	3.057	.047	5.838	1	67	.018

Predictors:
1. (constant) Perceived efficacy
2. (constant) Perceived efficacy, life events,
3. (constant) Perceived efficacy, life events, pain
4. (constant) Perceived efficacy, life events, pain, age

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	310.920	1	310.920	25.453	.000
	Residual	855.080	70	12.215		
	Total	1166.000	71			
2	Regression	414.701	2	207.350	19.043	.000
	Residual	751.299	69	10.888		
	Total	1166.000	71			
3	Regression	485.463	3	161.821	16.169	.000
	Residual	680.537	68	10.008		
	Total	1166.000	71			
4	Regression	540.010	4	135.002	14.449	.000
	Residual	625.990	67	9.343		
	Total	1166.000	71			

Coefficients

Model		Unstandardised coefficients		Standardised coefficients	t.	Sig	95% confidence interval		Correlations			Collinearity statistics	
		B	S. E.	Beta			Lower bound	Upper bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	14.283	1.885		7.575	.000	10.522	18.043					
	Perceived efficacy	-2.448	.485	-.516	-5.045	.000	-3.416	-1.480	-.516	-.516	-.516	1.000	1.000
2	(Constant)	11.957	1.933		6.186	.000	8.101	15.813					
	Perceived efficacy	-2.144	.469	-.452	-4.576	.000	-3.079	-1.210	-.516	-.483	-.442	.956	1.046
	Life events	1.112	.360	.305	3.087	.003	.393	1.831	.400	.348	.298	.956	1.046
3	(Constant)	7.557	2.484		3.042	.003	2.599	12.515					
	Perceived efficacy	-1.466	.517	-.309	-2.837	.006	-2.497	-.435	-.516	-.325	-.263	.723	1.384
	Life events	1.104	.345	.303	3.197	.002	.415	1.793	.400	.361	.296	.956	1.046
	Pain	.500	.188	.285	2.659	.010	.125	.876	.475	.307	.246	.746	1.340
4	(Constant)	12.179	3.069		3.968	.000	6.052	18.306					
	Perceived efficacy	-1.515	.500	-.319	-3.031	.003	-2.512	-.517	-.516	-.347	-.271	.721	1.386
	Life events	1.081	.334	.297	3.240	.002	.415	1.748	.400	.368	.290	.955	1.047
	Pain	.486	.182	.277	2.669	.010	.122	.849	.475	.310	.239	.745	1.341
	Age	-.073	.030	-.217	-2.416	.018	-.133	-.013	-.222	-.283	-.216	.998	1.002

Descriptive Statistics Of Complete Data Set: Age And Disease Duration

Variable	Gujarati Mean	SD	Range	Caucasian Mean	SD	Range	P value (independent t-test
Age/years	52.1	11.2	30 to 74	60.0	12.1	27 to 80	0.01
Disease duration	10.0	6.4	1 to 27	11.3	9.5	1 to 40	0.38

Descriptive Statistics Of Complete Data Set: Sex

	Gujarati	Caucasian	X^2
Female	54	55	0.07
Male	7	17	

Raw data for all patients

Number	Ethnic Gp	Sex	Age	Marital	Employ	Yrs ed	Age end ed	Family at home	Partner	No who help	Smoker	EtOH /wk	Diet	Date onset	Age at onset	Diag made	Delay / mths
1	A	F	57	M	G	5	15	1	1	6	N	0	1	1979	33	1979	1
2	A	F	72	W	D	0	N/A	3	0	10	N	0	1	1980	49	1980	2
3	A	F	45	M	D	12	16	2	1	1	N	0	2	1989	33	1989	3
4	A	F	48	M	D	13	18	3	1	3	N	0	4	1988	35	1988	4
5	A	F	53	M	E	5	10	6	1	8	N	0	2	1995	48	2001	5
6	A	M	45	M	E	5	15	3	1	3	X	21	4	1996	43	1997	6
7	A	F	53	M	A	16	10	1	1	1	N	0	2	1995	46	1996	7
8	A	F	60	M	E	6	12	2	1	3	N	0	1	1994	54	1995	8
9	A	F	64	M	E	11	16	2	1	1	N	0	1	1982	45	1985	9
10	A	F	64	W	D	9	14	0	0	6	N	0	1	1986	48	1989	10
11	A	F	30	M	E	9	14	3	1	2	N	0	1	1996	24	1996	11
12	A	M	44	M	E	12	17	2	1	2	Y	0	2	2000	42	2002	12
13	A	M	33	M	A	18	23	3	1	1	N	1	3	2001	32	2001	13
14	A	M	74	M	G	11	25	1	1	1	N	0	1	1993	65	1993	14
15	A	F	55	M	E	14	19	5	1	6	N	0	1	1994	45	1996	15
16	A	F	72	M	E	7	13	1	1	2	N	0	1	1977	47	1977	16
17	A	F	53	M	E	10	15	1	1	2	N	0	2	1992	44	1992	17
18	A	F	38	M	E	2	9	2	1	2	N	0	2	1993	29	1993	18
19	A	F	45	M	E	7	11	4	1	3	N	0	1	1993	37	1994	19
20	A	M	48	D	E	13	20	0	0	2	Y	0	3	1988	34	1988	20
21	A	F	53	D	E	4	12	1	0	3	N	0	1	1975	25	1975	21
22	A	F	39	M	B	11	16	3	1	2	N	1	3	1991	28	1991	22
23	A	F	46	M	A	14	21	4	1	6	N	0	3	1995	38	1995	23
24	A	F	60	M	E	9	13	4	1	3	N	0	3	1988	47	1991	24
25	A	F	41	M	E	14	18	2	1	2	N	0	3	2000	39	2000	25
26	A	F	48	M	E	5	14	4	1	4	N	1	4	1986	32	1986	26
27	A	F	41	D	E	11	16	1	0	1	N	1	4	1984	24	1984	27
28	A	F	55	M	E	14	17	2	1	3	N	0	3	1991	45	1997	28
29	A	F	67	M	G	7	13	2	1	5	N	0	2	1990	55	1990	29
30	A	F	55	M	E	10	15	1	1	1	N	2	4	1988	40	1989	30
31	A	F	44	M	A	11	16	3	1	10	Y	2	3	1991	29	1992	31
32	A	M	51	M	E	11	16	4	1	4	Y	0	2	2000	49	2000	32
33	A	F	42	M	A	11	16	3	1	1	N	0	2	1983	23	1984	33
34	A	F	60	M	E	12	19	1	1	2	N	0	3	1995	53	2002	34
35	A	F	65	M	E	7	14	2	1	5	N	0	1	1992	55	1993	35
36	A	F	54	M	E	12	17	1	1	1	N	0	3	1996	49	1998	36
37	A	F	64	M	E	5	12	2	1	1	N	0	1	1994	57	1995	37
38	A	F	53	M	E	12	17	1	1	3	N	0	1	1996	44	1997	38

Number	Ethnic Gp	Sex	Age	Marital	Employ	Yrs ed	Age end ed	Family at home	Partner	No who help	Smoker	EtOH /wk	Diet	Date onset	Age at onset	Diag made	Delay / mths
39	A	F	40	M	E	11	16	3	1	6	N	3	3	1999	38	2000	39
40	A	M	72	M	G	8	14	1	1	2	Y	1	2	1988	60	1997	40
41	A	F	40	S	A	14	18	1	0	1	N	0	3	1996	36	1999	36
42	A	F	45	D	E	11	16	2	0	4	Y	4	4	2000	43	2000	1
43	A	F	40	M	A	11	16	3	1	3	N	0	4	2001	39	2001	6
44	A	F	58	M	D	10	15	1	1	2	N	0	1	1991	48	1996	60
45	A	F	58	M	E	14	20	1	1	4	N	0	3	1975	31	1978	36
46	A	F	66	M	D	4	9	1	1	1	N	0	2	2000	65	2001	3
47	A	F	35	D	E	11	16	1	0	4	N	0	4	1999	33	1999	2
48	A	F	63	W	D	7	12	0	0	2	N	1	1	1995	57	1997	24
49	A	F	72	M	G	11	16	1	1	1	N	0	1	1992	63	1992	1
50	A	F	47	M	E	8	16	3	1	5	N	0	3	1989	37	1989	3
51	A	F	53	M	E	10	16	2	1	5	N	0	3	1998	50	1998	4
52	A	F	51	M	E	14	18	1	1	1	N	0	3	1984	33	1986	24
53	A	F	44	M	A	11	16	3	1	3	N	1	4	1997	39	1997	2
54	A	F	60	M	E	9	14	1	1	8	N	0	2	1982	40	1982	6
55	A	F	50	M	E	0	0	3	1	1	N	0	2	1995	45	1997	24
56	A	F	35	M	B	15	20	3	1	1	N	0	3	1996	30	1996	6
57	A	F	69	M	D	10	16	1	1	5	N	0	3	1996	63	2002	50
58	A	F	50	M	E	11	16	1	1	4	N	1	2	1982	31	1983	12
59	A	F	56	M	E	12	17	3	1	4	N	0	1	1991	46	1991	6
60	A	F	28	M	D	14	19	5	1	1	N	0	4	1998	23	1999	12
61	A	F	55	M	D	13	18	2	1	2	N	0	1	1992	45	2002	120
62	C	F	58	M	E	10	15	1	1	3	X	4	4	1978	35	1978	2
63	C	F	50	M	B	13	18	2	1	2	X	0	4	1998	47	1998	1
64	C	F	66	M	G	10	15	1	1	1	N	1	4	1997	62	1998	12
65	C	F	66	M	G	10	15	1	1	1	N	4	4	1978	44	1979	5
66	C	M	75	M	E	9	14	1	1	1	X	10	4	1970	45	2000	360
67	C	F	54	M	E	14	18	1	1	1	N	3	4	1986	40	1988	24
68	C	F	79	M	G	9	14	1	1	1	N	10	4	1997	76	1998	3
69	C	F	62	M	G	11	16	3	1	3	X	10	4	1989	50	1990	9
70	C	M	41	D	E	12	17	0	0	1	Y	4	4	1989	29	1990	12
71	C	F	59	W	E	11	15	0	0	0	X	1	4	1987	47	1987	5
72	C	F	76	M	G	9	14	1	1	2	N	0	4	1991	66	1993	24
73	C	F	48	M	A	17	22	3	1	3	N	1	4	1960	6	1965	60
74	C	F	79	W	E	9	14	0	0	5	N	2	4	1960	45	1962	18
75	C	F	67	M	G	12	16	1	1	1	X	0	4	1999	65	1999	9
76	C	F	51	D	E	11	15	1	1	3	X	0	4	1998	48	1998	3
77	C	M	55	M	G	15	20	3	1	0	X	33	4	1985	40	1986	12
78	C	M	58	M	A	11	15	1	1	1	N	0	4	1997	55	1997	6
79	C	F	65	M	G	10	15	1	1	0	N	1	4	1983	46	1987	48

Number	Ethnic Gp	Sex	Age	Marital	Employ	Yrs ed	Age end ed	Family at home	Partner	No who help	Smoker	EtOH /wk	Diet	Date onset	Age at onset	Diag made	Delay / mths
80	C	F	67	M	G	10	15	1	1	1	X	1	4	1972	38	1972	6
81	C	F	44	M	B	18	22	3	1	4	N	2	4	1990	32	1992	24
82	C	F	63	M	G	11	16	1	1	1	N	3	4	1991	53	1996	12
83	C	F	70	M	G	11	16	1	1	1	N	0	4	1991	60	1991	1
84	C	F	64	M	G	10	15	1	1	2	X	1	4	2001	63	2001	5
85	C	F	42	M	e	13	16	2	1	3	Y	1	4	1968	9	1968	1
86	C	F	64	M	G	10	15	1	1	1	N	1	4	1993	55	1993	3
87	C	M	80	M	G	10	14	2	1	2	X	0	4	1996	75	1996	2
88	C	M	67	M	G	10	15	2	1	1	Y	5	4	1996	75	1990	3
89	C	F	57	D	E	11	16	0	0	1	N	0	4	1990	61	1980	1
90	C	M	70	M	G	10	14	1	1	2	X	1	4	1980	48	1986	3
91	C	M	77	M	G	10	14	1	1	1	X	1	4	1986	50	1999	4
92	C	F	27	S	A	16	21	0	0	0	N	10	4	1999	60	1998	2
93	C	F	60	M	B	11	15	1	1	4	X	0	4	1998	24	1983	2
94	C	F	71	M	G	14	19	1	1	1	X	1	4	1983	58	1987	18
95	C	M	59	M	E	10	15	2	1	1	N	1	4	1985	50	2000	48
96	C	F	58	M	A	16	16	1	1	1	X	20	4	1996	45	1985	12
97	C	M	78	M	G	12	17	1	1	2	X	5	4	1984	54	1999	6
98	C	F	63	M	D	10	15	1	1	1	N	1	4	1999	62	1994	3
99	C	M	63	M	E	10	15	1	1	1	N	1	3	1994	60	1989	2
100	C	F	47	M	A	10	15	1	1	1	N	0	4	1989	58	1992	2
101	C	F	68	S	G	10	14	0	0	4	X	0	4	1992	36	1984	1
102	C	M	44	M	A	11	16	4	1	4	N	1	4	1984	59	1992	2
103	C	F	78	W	B	10	14	0	0	1	N	1	4	1994	27	1984	1
104	C	F	74	M	G	11	14	1	1	1	Y	1	4	1995	70	1994	6
105	C	f	66	m	G	10	15	1	1	1	X	3	4	1996	69	1996	1
106	C	F	57	M	E	10	15	1	1	1	N	18	4	1976	61	1996	6
107	C	F	47	M	E	10	15	1	1	3	N	0	4	1998	32	1976	6
108	C	M	64	M	E	10	15	1	1	1	X	0	4	1987	44	1999	12
109	C	F	46	M	A	10	15	1	1	2	Y	1	4	1996	50	1990	36
110	C	M	46	M	A	16	21	3	1	3	N	0	4	1997	41	1996	6
111	C	F	57	M	B	11	17	1	1	6	N	2	4	1964	41	1999	24
112	C	F	78	M	G	10	14	1	1	1	X	8	4	1995	20	1965	12
113	C	F	70	M	G	9	14	1	1	1	N	1	4	1993	72	1996	12
114	C	F	61	M	E	10	15	1	1	4	Y	1	4	1992	62	1993	2
115	C	F	45	D	B	10	15	1	0	3	N	2	4	1999	51	1992	4
116	C	F	42	D	E	13	17	1	0	3	Y	0	4	1992	42	2000	12
117	C	F	65	M	G	15	20	1	1	2	X	1	4	1989	33	1992	6
118	C	F	69	M	D	10	15	1	1	1	N	1	4	1983	52	1990	7
119	C	F	48	D	A	17	22	5	1	5	N	3	3	1992	50	1983	1
120	C	F	33	M	E	11	16	2	1	2	N	0	4	1995	39	1994	24

Number	Ethnic Gp	Sex	Age	Marital	Employ	Yrs ed	Age end ed	Family at home	Partner	No who help	Smoker	EtOH /wk	Diet	Date onset	Age at onset	Diag made	Delay / mths
121	C	F	50	M	A	16	11	2	1	3	N	6	4	1997	26	1998	36
122	C	M	55	M	E	10	15	1	1	1	Y	50	4	2001	45	1998	12
123	C	F	37	M	A	13	18	1	1	1	Y	12	4	2000	54	2001	2
124	C	F	71	D	G	9	14	0	0	4	Y	1	4	1997	36	2000	2
125	C	F	52	M	B	12	17	1	1	1	N	2	4	1998	68	1997	1
126	C	F	47	M	A	16	21	4	1	5	X	1	4	2001	49	1999	14
127	C	F	55	M	E	10	15	2	1	1	N	0	4	1999	47	2001	5
128	C	M	69	M	G	9	14	1	1	1	Y	10	4	1975	52	2000	18
129	C	F	72	W	G	12	17	0	0	0	N	0	4	1994	40	1970	60
130	C	F	60	M	G	11	16	1	1	1	N	8	4	1992	64	1995	12
131	C	F	74	M	G	12	17	1	1	2	N	2	4	1993	50	1996	48
132	C	M	64	D	E	10	15	2	1	1	X	0	4	1995	66	2000	84
133	C	F	56	M	E	28	33	1	1	1	X	2	4	2000	58	1995	0.5

Number	Duration /yrs	Date DMARD	Perc eff	Pain	Nodules	Adms	I-A Inj	Surg	Depr	Life events	SJC	Deform	HAQ	RF+	PV	HLA DRB1 (1)	HLA DRB1 (2)
1	17	1983	4	2	6.5	N	0	3	0	13	3	11	13	3	N	1.62	.
2	22	1982	2	0.25	8.5	N	6	4	0	14	2	6	8	3	Y	1.9	.
3	12	1989	3	2	4.8	N	1	3	0	10	2	10	9	1	N	1.81	15
4	13	1988	3	0.25	6.6	N	0	3	2	13	0	4	6	1	N	1.81	.
5	7	2001	4	1.5	4.9	N	0	0	0	8	0	4	1	0	Y	1.7	15
6	5	1997	4	1	4.8	N	0	0	0	4	0	21	0	1	Y	2.27	15
7	7	1996	4	0	6	N	0	4	0	10	1	8	0	2	N	1.61	10
8	5	1995	3	0.2	4.3	N	2	6	0	6	2	3	3	2	Y	1.65	4
9	19	1985	3	2	5.4	N	8	3	4	15	0	9	13	3	N	1.93	16
10	17	1989	3	0.5	6.4	Y	5	0	0	16	3	21	16	3	Y	1.78	.
11	6	1996	4	2	4.9	N	0	1	0	1	0	4	4	2	N	1.58	7
12	2	2002	2	3.5	6.1	N	0	0	0	3	0	8	0	2	Y	1.87	15
13	2	2001	4	0.25	1.8	N	0	0	0	7	0	1	0	0	N	1.48	.
14	9	1993	4	1	7.2	N	0	7	0	11	1	3	17	3	N	1.66	15
15	7	1996	4	3	7.9	N	0	12	0	6	0	10	8	2	N	1.72	15
16	25	1978	3	1	4.2	N	1	3	3	6	0	6	2	3	N	1.86	8
17	10	1994	3	3	6.9	N	4	0	2	12	0	19	21	3	Y	1.89	.
18	9	1993	3	0	5.2	N	0	4	0	10	4	12	9	1	N	1.67	.
19	8	1994	4	0.3	2.1	N	0	0	0	6	0	12	7	2	Y	1.86	11
20	14	1988	3	1.5	5.5	N	0	4	0	10	2	7	8	3	N	1.68	.
21	27	1984	3	1.5	7.4	Y	5	30	0	4	2	5	23	3	Y	1.58	15
22	10	1991	3	0.2	2	N	0	2	0	7	1	12	0	0	N	1.72	301
23	8	1996	4	0.5	2.1	Y	1	5	0	5	1	6	3	1	Y	1.75	4
24	14	1990	4	2	5.3	N	0	7	1	12	3	8	5	3	N	1.62	10

Number	Duration /yrs	Date DMARD	Perc eff	Pain	Nodules	Adms	I-A Inj	Surg	Depr	Life events	SJC	Deform	HAQ	RF+	PV	HLA DRB1 (1)	HLA DRB1 (2)
25	2	2001	3	0.5	5.1	N	0	0	0	2	0	5	4	2	Y	1.84	301
26	14	1986	3	7	8.6	N	10	20	2	17	6	12	5	3	N	1.49	301
27	18	1985	3	0.5	4.9	Y	1	6	0	11	4	6	18	1	Y	1.62	15
28	10	2000	3	3	6.4	N	0	1	0	12	2	5	0	1	N	1.66	.
29	12	1990	4	5	5.5	N	4	7	1	9	0	8	12	3	Y	1.9	14
30	15	1988	2	2	6.2	N	0	2	0	12	2	5	8	2	Y	1.84	4
31	10	1992	5	2.5	7.1	N	0	4	0	8	0	3	0	0	N	1.75	15
32	2	2001	3	0	3.9	N	0	1	0	11	3	5	5	1	Y	1.77	.
33	18	1984	3	1	5.6	N	0	3	0	13	0	10	8	2	N	1.89	.
34	7	2002	3	1	7.6	N	0	0	0	14	2	9	0	2	Y	1.76	15
35	10	1993	3	4.5	3.8	N	0	7	0	8	0	22	5	2	Y	1.96	.
36	8	1998	3	0.08	4.9	N	0	4	1	11	2	7	2	1	Y	1.78	4
37	6	1995	3	2.5	5.9	N	0	0	0	15	1	12	9	3	N	1.97	15
38	8	2000	4	0.5	7.2	Y	0	13	0	5	2	1	0	2	N	1.66	11
39	3	2000	3	2.5	6.9	N	0	0	0	15	0	12	0	1	Y	1.76	.
40	13	1997	4	0.25	5.3	Y	0	0	0	13	2	3	5	3	Y	1.87	11
41	4	2000	2	3.5	5	N	0	0	0	7	1	6	3	1	N	1.68	15
42	2	2000	3	0.5	6.3	N	0	0	0	14	4	6	5	2	N	1.76	11
43	2	2001	2	2	2.4	N	0	1	1	5	1	7	1	1	Y	2	4
44	11	1996	4	0.3	1.6	N	1	3	0	13	2	10	1	3	N	1.7	15
45	26	1978	3	2	6.8	N	1	9	3	9	1	5	5	3	Y	2.23	.
46	1	2001	4	0	2.5	N	0	2	0	5	1	8	0	1	Y	2.01	7
47	3	2001	4	1	5.3	N	0	0	0	16	1	3	0	3	N	1.81	.
48	6	1997	3	0.3	5.7	N	0	2	0	14	3	12	0	2	N	1.87	.
49	9	1992	4	0.2	1.6	N	0	4	2	6	0	5	0	2	N	1.72	4
50	12	1989	3	2	2.6	N	1	1	0	11	0	13	13	3	N	1.81	.
51	3	1998	3	2	7.1	N	1	4	0	15	1	5	3	2	Y	1.74	14
52	16	1989	3	2.5	4	Y	0	16	0	15	1	14	13	2	N	1.68	.
53	5	1997	2	0.5	5.6	Y	0	3	0	5	0	7	5	2	Y	1.83	.
54	20	1983	3	0.5	2.8	Y	3	7	0	13	3	17	17	3	N	1.72	10
55	6	1998	3	0.6	4.2	N	0	0	0	11	2	10	1	2	N	1.9	.
56	5	1998	4	0	1.6	N	0	2	0	2	0	1	3	0	N	1.63	10
57	6	2002	3	2	8.5	N	0	0	0	8	1	8	6	3	N	2	14
58	20	1984	4	0.3	5.8	N	3	10	0	6	0	8	20	3	N	1.54	.
59	10	1992	4	0.08	5.1	N	0	2	0	5	1	4	7	2	Y	1.78	15
60	4	1999	4	0.5	2.6	Y	10	1	0	8	2	2	9	1	N	1.45	.
61	10	2002	3	0	5	N	0	0	0	3	0	6	0	1	Y	1.96	15
62	23	1988	3	4.5	7.8	Y	2	5	0	7	0	19	9	3	Y	1.84	301
63	3	2000	4	0.5	4.9	Y	0	7	3	4	0	4	2	1	N	1.5	.
64	4	1999	4	1	2.1	N	0	9	0	1	1	15	5	1	Y	1.66	.
65	23	1979	4	0.5	3.6	Y	3	20	2	5	0	21	17	1	Y	1.63	.

Number	Duration /yrs	Date DMARD	Perc eff	Pain	Nodules	Adms	I-A Inj	Surg	Depr	Life events	SJC	Deform	HAQ	RF+	PV	HLA DRB1 (1)	HLA DRB1 (2)
66	31	2000	4	0.25	4.8	Y	0	0	0	4	1	26	16	3	Y	1.76	15
67	15	1989	5	0.5	1	N	0	9	0	1	0	22	9	0	Y	1.72	.
68	3	1998	3	2	5.2	N	0	7	2	9	1	8	13	2	N	1.5	.
69	12	1990	5	0	1.2	N	1	5	3	2	0	3	2	1	N	1.62	4
70	12	1990	2	3	8.4	Y	0	3	0	17	3	7	6	2	N	1.59	4
71	14	1987	3	3	6.4	Y	10	30	4	11	1	21	13	3	Y	1.71	4
72	10	1993	4	0	5.1	N	3	3	0	5	0	8	4	2	Y	1.64	7
73	40	1983	3	1	2.1	N	0	10	2	5	0	7	12	1	N	1.91	1
74	35	1970	3	0	5.7	Y	10	16	1	5	3	24	19	3	Y	1.76	301
75	2	2000	2	0	2.6	Y	0	0	0	2	1	15	10	1	Y	1.78	15
76	3	1998	3	1	7	Y	0	4	0	9	4	18	3	3	Y	1.6	1
77	15	1986	5	0	1.5	N	0	7	0	1	1	5	4	0	N	1.59	.
78	4	1997	3	1	6.4	N	0	0	0	11	2	17	2	2	Y	1.76	1
79	19	1987	4	3.5	5.6	Y	1	0	3	0	2	25	16	2	Y	1.65	4
80	28	1980	4	0.1	4.9	Y	1	10	8	2	0	12	14	1	Y	1.51	.
81	12	1992	5	0	0.1	N	0	1	2	4	1	6	11	0	Y	1.74	4
82	10	1996	4	0.1	0.7	Y	0	0	0	3	1	9	2	0	Y	1.67	1
83	10	1991	3	2	8.1	Y	4	15	3	12	2	14	7	3	N	1.7	15
84	1	2001	5	0.3	1.4	N	0	0	0	2	2	7	0	0	Y	1.88	7
85	33	1976	5	0.5	4.9	Y	10	10	4	10	2	32	18	3	Y	1.71	301
86	8	1993	4	0.5	5.6	Y	1	11	0	2	0	19	11	2	Y	1.84	15
87	5	1996	3	0.25	4.8	N	0	1	0	6	1	2	6	1	Y	1.6	1
88	7	1996	4	1	3.4	N	0	2	0	1	1	5	2	0	Y	1.53	3
89	11	1990	3	0.5	5.1	N	0	1	0	9	2	12	5	2	Y	1.67	.
90	20	1993	4	0.25	5.2	Y	0	1	1	1	0	9	6	1	Y	2.03	4
91	17	1986	3	0.5	0.2	N	1	2	0	7	2	5	4	1	Y	1.6	1
92	3	1999	4	0.5	2.8	N	0	0	0	6	0	2	0	0	Y	1.74	301
93	3	1998	5	1	5.1	N	2	4	0	2	0	10	0	1	Y	1.62	4
94	20	1985	3	1	5.1	Y	1	6	2	11	0	9	15	1	Y	2.07	103
95	15	1987	5	0.6	5	Y	0	1	3	3	0	11	4	1	Y	1.65	4
96	2	2000	4	0.75	1.4	N	0	0	0	5	0	6	0	0	Y	1.68	4
97	16	1985	4	0.5	1.9	N	0	1	0	0	0	4	4	1	N	1.67	4
98	3	1999	3	2.5	7.2	Y	3	0	0	9	0	21	7	3	Y	1.8	15
99	6	1994	5	0	0	N	0	0	0	0	0	0	3	0	Y	1.85	1
100	13	1989	5	0	7.3	N	2	3	2	4	2	6	2	1	N	1.61	4
101	9	1992	5	0	0	N	0	8	0	0	0	10	2	0	N	1.76	1
102	18	1985	3	0	1	N	1	6	1	2	1	9	6	1	Y	1.68	1
103	7	1994	4	2	3.2	N	0	2	0	5	2	5	4	1	N	1.6	4
104	5	1996	4	0	2.8	N	0	1	0	3	2	13	6	1	N	1.66	15
105	5	1996	4	0.8	0.4	N	0	4	0	6	2	6	11	1	Y	1.65	4
106	25	1976	4	2	3.3	Y	3	9	8	2	0	15	22	3	Y	1.62	1

Number	Duration /yrs	Date DMARD	Perc eff	Pain	Nodules	Adms	I-A Inj	Surg	Depr	Life events	SJC	Deform	HAQ	RF+	PV	HLA DRB1 (1)	HLA DRB1 (2)
107	3	1999	3	1	5.3	Y	1	4	0	11	1	14	3	3		1.94	4
108	18	1987	3	0	2.6	Y	0	1	0	6	0	4	5	0	Y	1.74	4
109	5	1996	5	0.5	1.5	N	0	1	0	4	0	4	0	0	N	1.58	1
110	4	1997	4	1	2.2	N	2	1	0	2	0	8	0	2	N	1.46	4
111	37	1965	4	0.1	2.9	Y	2	8	1	1	2	12	5	1	N	1.66	301
112	6	1996	3	0	0.9	N	0	1	0	2	2	6	7	1	Y	1.77	301
113	8	1993	4	0.3	6.1	Y	0	5	0	1	2	14	9	2	Y	1.66	15
114	10	1997	5	0	0.6	N	1	4	0	6	2	6	2	0	N	1.71	4
115	3	2000	2	1	7.5	N	0	0	0	11	1	10	4	1	N	1.59	1
116	8	1993	3	6	7	N	1	20	0	11	2	8	0	1	N	1.54	4
117	12	1990	3	0.25	6.1	Y	0	2	0	3	0	15	12	3	Y	1.75	.
118	19	1985	4	0.5	2.9	Y	0	11	1	10	1	11	17	1	Y	1.87	301
119	9	1995	3	0.1	2.5	N	0	2	0	9	3	7	10	1	N	1.59	103
120	6	1999	3	2	3	N	0	6	0	10	3	12	4	2	N	1.79	1
121	5	1998	4	1	3.8	N	0	2	0	3	0	3	0	1	Y	1.6	.
122	1	2001	4	0.25	1.9	Y	0	0	0	4	1	6	4	0	Y	1.63	15
123	1.5	2000	4	0.5	2.4	N	0	0	0	3	0	2	0	1	N	1.68	1
124	3	1998	3	1	4.7	N	0	0	0	12	0	12	6	2	N	1.84	15
125	3	1998	4	0.1	3.9	Y	1	7	0	12	1	17	6	1	Y	1.65	11
126	0.75	2001	5	1	1	N	0	0	0	0	0	1	0	0	N	1.7	.
127	3	2000	2	1	5.2	N	0	0	0	0	0	6	0	2	N	1.88	301
128	30	1997	4	0	3.2	Y	0	1	1	2	2	19	19	2	Y	1.56	1
129	8	1995	4	0.6	5.6	N	0	5	1	5	1	10	8	2	N	1.89	15
130	10	1996	5	0	1.5	N	0	8	0	0	1	2	2	0	Y	1.73	.
131	8	2000	5	0.3	0	N	0	11	1	0	1	6	11	0	N	1.63	15
132	7	1995	3	0.5	6.1	Y	1	6	0	4	2	6	5	2	Y	1.87	.
133	2.5	2000	4	0.5	1.4	N	0	1	0	12	5	4	2	0	Y	1.64	1

LIST OF ABSTRACTS

Neville, C. E. and W. Hassan (2002). "A Comparison Of Depression, Disability And Pain In Indian Asian And Caucasian Patients With Rheumatoid Arthritis." www.abstracts2view.com/eular: AB0067.

Neville, C. E. and W. Hassan (2002). "A Comparison Of Disease Severity In Indian Asian And Caucasian Patients With Rheumatoid Arthritis." www.abstracts2view.com/eular: AB0068.

Neville, C. E. and W. Hassan (2003). "Complimentary Therapy Use In Different Ethnic Groups With Rheumatoid Arthritis." Rheumatology **42**(Suppl 1): 94.

Neville, C. E. and W. Hassan (2003). "Varying Severity Of Depression In Different Ethnic Groups With Rheumatoid Arthritis." Rheumatology **42**(Suppl 1): 48.

Neville, C. E. and W. Hassan (2005). "Socioeconomic Differences In Rheumatoid Arthritis In Gujerati Asian And Caucasian Communities In Leicester: A Profound Effect On The Patient?" Rheumatology **44**(Supp 1): i96.

Neville, C. E., W. Hassan, et al. (2004). "A Comparative Study Of Disease Severity, Treatment Modalities And Depression In Australian And British Caucasian Patients With Rheumatoid Arthritis." Rheumatology **43**(Suppl 2): ii140.

Neville, C. E., D. Smillie, et al. (2007). "The Frequency Of The Shared Epitope In Rheumatoid Arthritis In Different Ethnic Populations." Rheumatology: (in print).

REFERENCES

Abdel-Nasser, A. M., S. Abd El-Azim, E. Taal, S. A. El-Badawy, J. J. Rasker, H. A. Valkenburg (1998). "Depression and depressive symptoms in rheumatoid arthritis patients: an analysis of their occurrence and determinants." British Journal of Rheumatology **37**(4): 391-397.

Agrawal, V., R. Gupta, R. Usha, S. V. Sharma (1996). "HLA Class I and Class II antigen association in rheumatoid arthritis at Varanasi, India." Indian Journal of Pathology and Microbiology **39**: 19-25.

Ahlmen, M., U. Nordenskiold, B. Archenholtz, I. Thyberg, R. Ronnqvist, L. Linden, A. K. Andersson and K. Mannerkorpi (2005). "Rheumatology outcomes: the patient's perspective. A multicentre focus group interview study of Swedish rheumatoid arthritis patients." Rheumatology **44**(1): 105-110.

Aho, K., M. Koskenvuo, J. Tuominen and J. Kaprio (1986). "Occurrence of rheumatoid arthritis in a nationwide series of twins." Journal of Rheumatology **13**: 899-902.

Albano, S. A., E. Santana-Sahagun and M. H. Weisman (2001). "Cigarette smoking and rheumatoid arthritis." Seminars in Arthritis and Rheumatism **31**: 146-159.

Albers, J. M. C., H. H. Kuper, P. L. C. M. van Riel, M. L. L. Prevoo, M. A. Van 't Hof, A. M. van Gestel and J. L. Severens (1999). "Socio-economice

consequences of rheumatoid arthritis in the first years of the disease." Rheumatology **38**: 423-430.

Alexander, D., M. J. Ball and J. Mann (1994). "Nutrient intake and haematological status of vegetarians and age-sex matched omnivores." European Journal of Clinical Nutrition **48**(8): 538-546.

Allison, T. R., D. P. M. Symmons, T. Brammah, P. Haynes, A. Rogers, M. Roxby and M. Urwin (2002). "Musculoskeletal pain is more generalised among people from ethnic minorities than among white people in Greater Manchester." Annals of Rheumatic Diseases **61**: 151-156.

Amit, M., D. Guedj and A. J. Wysenbeek (1996). "Expression of rheumatoid arthritis in two ethnic Jewish Israeli groups." Annals of Rheumatic Diseases **55**: 69-72.

Amos, D. B. (1965). Histocompatibility Testing: Report of a Conference and Workshop. First Histocompatibilty Conference, Duke University, North Carolina, USA, Washington DC: National Academy of Sciences - National Research Council, 1965.

Arnett, F. C., S. M. Edworthy, D. A. Bloch, D. J. McShane, J. F. Fries, N. S. Cooper, L. A. Healey, S. R. Kaplan, M. H. Liang, H. S. Luthra and e. al (1988). "The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis." Arthritis and Rheumatism **31**(3): 315-324.

Balarajan, R., P. Yuen and V. Soni Raleigh (1989). "Ethnic differences in general practitioner consultations." British Medical Journal **299**: 958-960.

Bellamy, N. (1993). Musculoskeletal Clinical Metrology. Netherlands, Kluwer Academic Publishers.

Benacerraf, B. (1981). "Role of MHC gene products in immune regulation." Science **212**(4500): 1229-1238.

Berglin, E., T. Johansson, U. Sundin, E. Jidell, G. Wadell, G. Hallmans, S. Rantapää-Dahlqvist (2006). "Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset." Annals of Rheumatic Diseases **65**(4): 453-458.

Bester, F. C., D. J. Weich, P. N. Badenhorst and J. I. de Wet (1993). "Erythrocyte sedimentation rate in elderly blacks." South African Medical Journal **83**(7): 498-500.

Beusenberg, M. and J. H. Orley (1994). A User's guide to the self-reporting questionnaire. Geneva, World Health Organization.

Bizzaro, N., G. Mazzanti, E. Tonutti, D. Villalta, R. Tozzoli (2001). "Diagnostic Accuracy of the Anti-Citrulline Antibody Assay for Rheumatoid Arthritis." Clinical Chemistry **47**(6): 1089-1093.

Boki, K. A., A. A. Drosos, A. G. Tzioufas, J. S. Lanchbury, G. S. Panayi and H. M. Moutsopoulos (1993). "Examination of HLA-DR4 as a severity marker for rheumatoid arthritis in Greek patients." Annals of Rheumatic Diseases **52**: 517-519.

Boyer, G. S., L. I. Benevolenskaya, D. Templin, S. Erdesz, A. Bowler, L. Alexeeva, W. P. Goring, M. Y. Krylov and N. M. Mylov (1997). "Prevelance

of rheumatoid arthritis in Circumpolar Native populations." Journal of Rheumatology **25**(1): 23-29.

Breuer, G. S., H. Orbach, O. Elkayam, Y. Berkun, D. Paran, M. Mates and G. Nesher (2005). "Perceived efficacy among patients of various methods of complementary alternative medicine for rheumatologic diseases." Clinical and Experimental Rheumatology **23**(5): 693-696.

Brugha, T., P. Bebbington, C. Tennant and J. Hurry (1985). "The List of Threatening Experiences: a subset of 12 life events categories with considerable long-term contextual threat." Psychological Medicine **15**(1): 189-194.

Buchbinder, R., M. Gingold, S. Hall and M. Cohen (2002). "Non-prescription complementary treatments used by rheumatoid arthritis patients attending a community-based rheumatology practice." Internal Medicine Journal **32**(5-6): 208-214.

Buckner, J. H., G. T. Nepom (2002). "Genetics of Rheumatoid Arthritis: is there a scientific explanation for the human leukocyte antigen association?" Current Opinion in Rheumatology **14**(3): 254-259.

Bukhari, M., M. Lunt, B. Harrison, D. G. Scott, D. Symmons and A. Silman (2002). "Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis: results from the Norfolk Arthritis Register Study, a large inception cohort." Arthritis and Rheumatism **46**: 906-912.

Bunce, M., C. M. O'Neill, M. C. N. M. Barnardo, P. Krausa, M. J. Browning, P. J. Morris, K. I. Welsh (1995). "Phototyping: comprehensive DNA typing for HLA-A, B, C, DRB1, DRB3, DRB4, DRB5 and DQB1 by PCR with 144 primer mixes utilizing sequence-specific primers (PCR-SSP) " Tissue Antigens **46**: 355-367.

Callahan, L. F., S. R. Kaplan and T. Pincus (1991). "The Beck Depression Inventory, Center for Epidemiological Studies Depression scale (CES-D) and general Well-Being Schedule Depression Subscale in rheumatoid arthritis." Arthritis Care Research **4**: 3-11.

Carr, I. and J. F. Mayberry (1999). "The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second-generation South Asians in Leicester (1991-1994)." American Journal of Gastroenterology **94**(10): 2918-2922.

Casey, P. R. D., G, B. D. Kelly, G. Birkbeck, O. S. Dalgard, V. Lehtinen, S. Britta, J. L. Ayuso-Mateos, C. Dowrick and O. Group (2006). "Factors associated with suicidal ideation in the general population: five-centre analysis from the ODIN study." British Journal of Psychiatry **189**: 410-415.

Casimiro, L., L. Barnsley, L. Brosseau, S. Milne, V. A. Robinson, P. Tugwell and G. Wells (2005). "Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis." Cochrane Database Systematic Reviews **19**(4): CD003788.

Cha, S., C. Choi, T. Han, C. Kang, C. Kang, S. Bae (2007). "Association of anti-cyclic citrullinated peptide antibody levels with PADI4 haplotypes in early

rheumatoid arthritis and with shared epitope alleles in very late rheumatoid arthritis." Arthritis and Rheumatism **56**(5): 1454-1463.

Chandrashekhara, S., T. Anilkumar and S. Jamuna (2002). "Complementary and alternative drug therapy in arthritis." Journal of the Association of Physicians in India **50**: 225-227.

Chapple, A. (1998). "Iron deficiency anaemia in women of South Asian descent: a qualitative study." Ethnicity and Health **3**(3): 199-212.

Cherkin, D. C., K. J. Sherman, R. A. Deyo and P. G. Shekelle (2003). "A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain." Annals of Internal Medicine **138**(11): 898-906.

Cimmino, M. A. (1998). "Prevalence of rheumatoid arthritis in Italy: the Chiavari study." Annals of Rheumatic Diseases **57**: 315-318.

Cohen, J. D., M. Dougados, P. Goupille, A. Cantagrel, O. Meyer, J. Sibilia, J. P. Daurès, B. Combe (2006). "Health assessment questionnaire score is the best predictor of 5-year quality of life in early rheumatoid arthritis." Journal of Rheumatology **33**(10): 1936-1941.

Cohen, J. W. (1988). Statistical power analysis for the Behavioural Sciences. Hillsdale, NJ, Lawrence Erlbaum Associates.

Combe, B. (2007). "Early rheumatoid arthritis: strategies for prevention and management." Best Practice and Research in Clinical Rheumatology **21**(1): 27-42.

Consortium, T. M. S. (1999). "Complete sequence and gene map of a human major histocompatibility complex." Nature **401**(6756): 921-923.

Cooper, H., C. Smaje and S. Arber (1998). "Use of health services by children and young people according to ethnicity and social class: secondary analysis of a national survey." British Medical Journal **317**: 1047-1051.

Cooper, J., N. Husain, R. Webb, W. Waheed, N. Kapur, E. Guthrie, L. Appleby (2006). "Self-harm in the UK: differences between South Asians and Whites in rates, characteristics, provision of service and repetition." Social Psychiatry and Psychiatric Epidemiology **41**(10): 782-788.

Costenbader, K. H., D. Feskanich, L. A. Mandl and E. W. Karlson (2006). "Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women." American Journal of Medicine **119**(6): 503e1-9.

Covic, T., B. Adamson, D. Spencer and G. Howe (2003). "A biopsychosocial model of pain and depression in rheumatoid arthritis: a 12 month longitudinal study." Rheumatology **42**: 1287-1294.

Covic, T., G. Tyson, D. Spencer and G. Howe (2006). "Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors." Journal of Psychosomatic Research **60**(5): 469-476.

Creed, F., M. Winterbottom, B. Tomenson, R. Britt, I. S. Anand, G. S. Wander and Y. Chandrashekhar (1999). "Preliminary study of non-psychotic disorders inpeople from the Indian subcontinent living in the UK and India." Acta Psychiatrica Scandinavica **99**(4): 257-260.

Dalgard, O. S., S. B. Thapa, E. Hauff, M. McCubbin and H. R. Syed (2006). "Immigration, lack of control and psychological distress: findings from the Oslo Health Study." Scandinavian Journal of Psychology **47**(6): 551-558.

Darmawan, J., H. S. Wirman, H. S. Soenarto, R. D. Wigley, K. D. Muirden and H. A. Valkenburg (1983). Population study of rheumatic disease in Sermarang and Bandungan. The Indonesian COPCORD. 5th SEAPAL Congress, Bangkok.

Deighton, C., L. A. Criswell, R. F. Lum and A. Silman (2007). "Ages of onset suggestive of genetic anticipation in rheumatoid arthritis multicase sibships can be explained by observational bias." Rheumatology **46**(1): 120-123.

Deighton, C. M. and D. J. Walker (1992). "What factors distinguish probands from multicase rheumatoid arthritis same sex sibships from sporadic disease?" Journal of Rheumatology **19**(2): 237-241.

Del Puente, A., W. C. Knowler, D. J. Pettitt and P. H. Bennett (1989). "High incidence and prevelance of rheumatoid arthritis in Pima Indians." American Journal of Epidemiology **129**: 1170-1178.

Del Rincon, I. and A. Escalante (1999). "H:A-DRB1 alleles associated with susceptibility or resistance to rheumatoid arthritis, articular deformities and disability in Mexican Americans." Arthritis and Rheumatism **42**(7): 1329-1338.

Deodar, S. D., R. Sethi and R. C. Srimal (1980). "Preliminary study on antirheumatic activity of curcumin (diferuloyl methane)." Indian Journal of Medical Research **71**: 632-634.

Deyo, R. A., A. K. Diehl, H. Hazuda and M. P. Stern (1985). "A simple language-based acculturation scale for Mexican Americans:Validation and application to health care research." American Journal of Public Health **75**: 51-55.

Dickens, C. and F. Creed (2001). "The burden of depression in patients with rheumatoid arthritis." Rheumatology **40**: 1327-1330.

Dickens, C., L. McGowan, D. Clark-Carter and F. Creed (2002). "Depression in rheumatoid arthritis: a systemic review of the literature with meta-analysis." Psychosomatic Medicine **64**: 52-60.

Dickens, C., J. Jackson, B. Tomenson, E. Hay and F. Creed (2003). "Association of Depression and Rheumatoid Arthritis." Psychosomatic Medicine **44**(3): 209-215.

DiMatteo, M. R., H. S. Lepper and T. W. Croghan (2000). "Depression is a risk factor for non-compliance with medical treatment:meta-analysis of the effects of the anxiety and depression on patient adherence." Archives of Internal Medicine **160**: 2101-2107.

Doherty, D. G., R. Vaughan, P. Donaldson and A. Mowat (1992). "HLA DQA, DQB and DRB genotyping by oligonucleotide analysis: distribution of alleles and haplotypes in British Caucasoids." Human Immunology **34**(1): 53 - 63.

Doran, M. F., G. R. Pond, C. S. Crowson, W. M. O'Fallon and S. E. Gabriel (2002). "Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty year period." Arthritis and Rheumatism **46**: 625-631.

Drosos, A. A., J. S. Lanchbury, G. S. Panayi and H. M. Moutsopoulos (1992). "Rheumatoid arthritis in Greek and British patients: a comparitive clinical, radiologic and serologic study." Arthritis and Rheumatism **35**: 745-748.

du Montcel, S. T., L. Michou, E. Petit-Teixeira, J. Osorio, I. Lemaire, S. Lasbleiz, C. Pierlot, P. Quillet, T. Bardin, B. Prum, F. Cornelis, F. Clerget-Darpoux (2005). "New classification of HLA-DRB1 alleles supports the shared epitope hypothesis of rheumatoid arthritis susceptibility." Arthritis and Rheumatism **52**(4): 1063-1068.

Eberhardt, K., B. M. Larsson, K. Nived, E. Lindqvist (2007). "Work disability in rheumatoid arthritis--development over 15 years and evaluation of predictive factors over time." Journal of Rheumatology **34**(3): 481-487.

Escalante, A. and I. del Rincon (1999). "How much disability in rheumatoid arthritis is explained by rheumatoid arthritis?" Arthritis and Rheumatism **42**: 1712-1721.

Evers, A. W., F. W. Kraaimaat, R. Geenen, J. W. Jacobs and J. W. Bijlsma (2002). "Longterm predictors of anxiety and depressed mood in early rheumatoid arthritis: a 3 and 5 year followup." Journal of Rheumatology **29**(11): 2327-2336.

Evers, A. W., F. W. Kraaimaat, R. Geenen, J. W. Jacobs and J. W. Bijlsma (2003). "Stress-vulnerability factors as long-term predictors of disease activity in early rheumatoid arthritis." Journal of Psychosomatic Research **55**(4): 293-302.

Farragher, T. M., M. Lunt, D. K. Bunn, A. J. Silman, D. P. Symmons (2007). "Early functional disability predicts both all-cause and cardiovascular mortality in people with inflammatory polyarthritis: results from the Norfolk Arthritis Register." Annals of Rheumatic Diseases **66**(4): 486-492.

Feder, G., A. M. Crook, P. Magee, S. Banerjee, A. D. Timmis and H. Hemingway (2002). "Ethnic differences in invasive management of coronary disease: prospective cohort study of patients undergoing angiography." British Medical Journal **324**: 511-516.

Felson, D. T., J. J. Anderson, M. Boers, C. Bombardier, M. Chernoff, B. Fried, D. Furst, C. Goldsmith, S. Kieszak, R. Lightfoot, et al (1993). "The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials." Arthritis and Rheumatism **36**(6): 729-740.

Fisher, P. and D. L. Scott (2001). "A randomised controlled trial of homeopathy in rheumatoid arthritis." Rheumatology **40**(9): 1052-1055.

Ford, J. A., E. M. Colhoun, W. B. McIntosh and M. G. Dunnigan (1972). "Biochemical response of late rickets and osteomalacia to a chupatty-free diet." British Medical Journal **3**: 446-447.

Frank, R. G., N. C. Beck, J. C. Parker, J. H. Kashani, T. R. Elliott, A. E. Haut, E. Smith, C. Atwood, M. Brownlee-Duffeck and D. R. Kay (1988). "Depression in rheumatoid arthritis." Journal of Rheumatology **15**(6): 920-925.

Fries, J. F., P. W. Spitz, R. G. Kraines and H. R. Holman (1980). "Measurement of patient outcome in arthritis." Arthritis and Rheumatism **23**: 137-145.

Funch, D. P. and J. Marshall (1983). "The role of stress, social support and age in survival from breast cancer." Journal of Psychosomatic Research **27**(1): 77-83.

Funk, J. L., J. B. Frye, J. N. Oyarzo, N. Kuscuoglu, J. Wilson, G. McCaffrey, G. Stafford, G. Chen, R. C. Lantz, S. D. Jolad, A. M. Solyom, P. R. Kiela and B. N. Timmermann (2006). "Efficacy and mechanism of action of turmeric supplements in the treatment of experimental arthritis." Arthritis and Rheumatism **54**(11): 3452-3464.

Furuya, T., M. Hakoda , N. Ichikawa, K. Higami, Y. Nanke, T. Yago, T. Kobashigawa, K. Tokunaga, N. Tsuchiya, N. Kamatani, S. Kotake (2007). "Differential association of HLA-DRB1 alleles in Japanese patients with early rheumatoid arthritis in relationship to autoantibodies to cyclic citrullinated peptide." Clinical and Experimental Rheumatology **25**(2): 219-224.

Gallo, J. J., D. R. Royall and J. C. Anthony (1993). "Risk factors for the onset of depression in middle and later life." Social Psychiatry and Psychiatric Epidemiology **28**(3): 101-108.

Garrod, A. B. (1859). The Nature and Treatment of Gout and Rheumatic Gout London, Walton and Maberly.

Gazerani, P. and L. Arendt-Nielsen (2005). "The impact of ethnic differences in response to capsaicin-induced trigeminal sensitization." Pain **117**(1-2): 223-229.

Gillam, S. J., B. Jarman, P. White and R. Law (1989). "Ethnic differences in consultation rates in general practice." British Medical Journal **299**: 953-957.

Gillum, R. F. (1993). "A racial difference in erythrocyte sedimentation." Journal of the National Medical Association **85**(1): 47-50.

Gold, D. T., W. Safi and H. Trinh (2006). "Patient preference and adherence: comparative US studies between two bisphosphonates, weekly risedronate and monthly ibandronate." Current Medical Research and Opinion **22**(12): 2383-2891.

Goldberg, R. J., J. Katz (2007). "A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain." Pain **129**(1-2): 210-223.

Goodenow, C., S. T. Reisine and K. E. Grady (1990). "Quality of social support and associated social and psychological functioning in women with rheumatoid arthritis." Health and Psychology **9**(3): 266-284.

Gorman, J. D., R. F. Lum, J. J. Chen, M. E. Suarez-Almazor, G. Thomson and L. A. Criswell (2004). "Impact of the shared epitope genotype and ethnicity on erosive disease." Arthritis and Rheumatism **50**(2): 400-412.

Gregersen, P. K. (2004). Genetic Determinants. Rheumatoid Arthritis. E. W. St. Clair, D. S. Pisetsky, B. F. Haynes, Lippincott, Williams and Wilkins: 107-117.

Gregersen, P. K., J. Silver and R. J. Winchester (1987). "The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis." Arthritis and Rheumatism **30**: 1205-1213.

Griffiths, B., R. D. Situnayake, B. Clark, A. Tennant, M. Salmon and P. Emery (2000). "Racial origin and its effect on disease expression and HLA-DRB1 types in patients with rheumatoid arthritis: a matched cross-sectional study." Rheumatology **39**: 857-864.

Griffiths, C., G. Kaur, M. Gantley, G. Feder, S. Hillier, J. Goddard, G. Packe (2001). "Influences on hospital admission for asthma in south Asian and white adults: qualitative interview study." British Medical Journal **323**(7319): 962-966.

Hafstrom I., B. R., A. Spanberg, L. von Zweigbergk, S. Brannemark, I. Nylander, J. Ronnelid, L. Laarsonen, L. Klareskog (2001). "A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlates with a reduction in antibodies to food antigens." Rheumatology **40**: 1175-1179.

Hameed, K. and T. Gibson (1997). "A comparison of the prevalence of rheumatoid arthritis and other rheumatic diseases amongst Pakistanis

living in England and Pakistan." British Journal of Rheumatology **36**: 781-785.

Hameed, K., T. Gibson, M. Kadir, S. Sultana, Z. Fatima and A. Syed (1995). "The Prevalence of rheumatoid arthritis in affluent and poor urban communities of Pakistan." British Journal of Rheumatology **34**: 252-256.

Hamson, C., L. Goh, P. Sheldon and A. Samanta (2003). "Comparative study of bone mineral density, calcium, and vitamin D status in the Gujarati and white populations of Leicester." **79**(931): 279-283.

Harrison, B. and D. Symmons (2000). "Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature." Rheumatology **39**: 939-949.

Helliwell, P. S. and G. Ibrahim (2003). "Ethnic differences in responses to disease modifying drugs." Rheumatology **42**: 1197-1201.

Herman, C. J., P. Allen, W. C. Hunt, A. Prasad and T. J. Brady (2004). "Use of complementary therapies among Primary Care clinic patients with arthritis." Preventing Chronic Disease: Public Health Research, Practice and Policy **1**(4): 1-15.

Hsu, R. T., M. E. Ardron, W. Brooks, D. Cherry, N. A. Taub and J. L. Botha (1999). "The 1996 Leicestershire Community Stroke & Ethnicity Study: differences and similarities between South Asian and white strokes." International Journal of Epidemiology **28**(5): 853-858.

Irigoyen, P., A. Lee, M. Wener, W. Li, M. Kern, F. Batliwalla, R. Lum, E. Massarotti, M. Weisman, C. Bombardier, E. Remmers, D. Kastner, M.

Seldin, L. Criswell, P. Gregersen (2005). "Regulation of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis: contrasting effects of HLA-DR3 and the shared epitope alleles." Arthritis and Rheumatism **52**(12): 3813-3818.

Jacobsson, L. T. H., R. L. Hanson, W. C. Knowler, S. Pillemer, D. J. Pettitt, D. R. McCance and P. H. Bennett (1994). "Decreasing incidence and prevelance of rheumatoid arthritis in Pima Indians over a twenty-five year period." Arthritis and Rheumatism **37**: 1158-1165.

Jaraquemada, D., W. Ollier, J. Awad, A. Young, A. Silman, I. M. Roitt, M. Corbett, F. Hay, J. A. Cosh, R. N. Maini, P. J. Venables, B. Ansell, J. Holborow, J. S. Reeback, H. L. F. Currey and H. Festenstein (1986). "HLA and rheumatoid arthritis: a combined analysis of 440 British patients." Annals of Rheumatic Diseases **45**: 627-636.

Jenkins, J. K., P. J. Seligman and S. Galson (2005). Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk. C. f. D. E. a. Research, Food and Drug Administration: 1-19.

Johnson, M. T., L. R. Waite and G. Nindl (2004). "Noninvasive treatment of inflammation using electromagnetic fields: current and emerging therapeutic potential." Biomedical Sciences Instrumentation **40**: 469-474.

Kaltenhäuser, S., M. Pierer, S. Arnold, M. Kamprad, C. Baerwald, H. Häntzschel, U. Wagner (2007). "Antibodies against cyclic citrullinated peptide are

associated with the DRB1 shared epitope and predict joint erosion in rheumatoid arthritis." Rheumatology **46**(1): 100-104.

Katbamna, S., W. Ahmad, P. Bhakta, R. Baker and G. Parker (2004). "Do they look after their own? Informal support for South Asian carers." Health and Social Care in the Community **12**(5): 398-406.

Katz, P. and E. H. Yelin (1993). "Prevalence and correlates of depressive symtpoms among persons with rheumatoid arthritis." Journal of Rheumatology **20**: 790-796.

Katz, P. P. and E. H. Yelin (1993). "Prevalence and correlates of depressive symptoms among persons with rheumatoid arthritis." Journal of Rheumatology **20**(5): 790-796.

Kellgren, J., J. S. Lawrence and J. Aitken-Swan (1953). "Rheumatic complaints in an urban population." Annals of Rheumatic Diseases **12**: 5-15.

Kent, P. D. and E. L. Matteson (2004). Clinical features and differential diagnosis. Rheumatoid Arthritis. E. W. St Clair, D. S. Pisetsky and B. F. Haynes, Lippincott, Williams & Wilkins: 11-25.

Kievit, W., P. M. Welsing, E. M. Adang, A. M. Eijsbouts, P. F. Krabbe and P. L. van Riel (2006). "Comment on the use of self-reporting instruments to assess patients with rheumatoid arthritis: the longitudinal association between the DAS28 and the VAS general health." Arthritis and Rheumatism **55**(5): 745-750.

Kim, H., J. K. Neubert, A. San Miguel, K. Xu, R. K. Krishnaraju, M. J. Iadarola, D. Goldman and R. A. Dionne (2004). "Genetic influence on variability in

human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament." Pain **109**(3): 488-496.

King, H. and M. Rewers (1993). "Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group." Diabetes Care **16**(1): 157-177.

Kirwan, J. R. (2001). "Links between radiological change, disability, and pathology in rheumatoid arthritis." Journal of Rheumatology **28**: 881-886.

Kirwan, J. R. and J. S. Reeback (1986). "Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis." British Journal of Rheumatology **25**: 206-209.

Kjeldsen-Kragh, J., M. Haugen, O. Førre, H. Laache, U. F. Malt (1994). "Vegetarian diet for patients with rheumatoid arthritis: can the clinical effects be explained by the psychological characteristics of the patients?" British Journal of Rheumatology **33**(6): 569-575.

Kjeldsen-Kragh J., M. H., C. F. Borchgrevink (1991). "Controlled trial of fasting and one year vegetarian diet in Rheumatoid arthritis " Lancet **338**: 899-902.

Kop, W. J., J. S. Gottdiener, C. M. Tangen, L. P. Fried, M. A. McBurnie, J. Walston, A. Newman, C. Hirsch and R. P. Tracy (2002). "Inflammation and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia." American Journal of Cardiology **89**: 275-283.

Krishnan, E., P. Tugwell, J. F. Fries (2004). "Percentile benchmarks in patients with rheumatoid arthritis: Health Assessment Questionnaire as a quality indicator " Arthritis Research and Therapies **6**: R505-R513.

Kroenke, C. H., L. D. Kubzansky, E. S. Schernhammer, M. D. Holmes and I. Kawachi (2006). "Social networks, social support, and survival after breast cancer diagnosis." Journal of Clinical Oncology **24**(7): 1105-1111.

Kroot, E.-J. J. A., B. A. W. De Jong, M. A. van Leeuwen, H. Swinkels, F. H. J. van den Hoogen, M. van 't Hof, L. B. A. van de Putte, M. H. van Rijswijk, W. J. van Venrooij, P. L. C. M. van Riel (2000). "The Prognostic Value of Anti-Citrullinated Peptide Antibody in Patients with Recent-Onset Rheumatoid Arthritis." Arthritis and Rheumatism **43**(8): 1831-1835.

Kumar, A., A. N. Malaviya, A. Pandhi and R. Singh (2002). "Validation of an Indian version of the Health Assessment Questionnaire in patients with rheumatoid arthritis " Rheumatology **41**: 1457-1459.

Lau, E., D. P. Symmons, C. R. Bankhead, A. J. MacGregor, S. Donnan and A. J. Silman (1993). "Low prevalence of rheumatoid arthritis in the urbanized Chinese of Hong Kong." Journal of Rheumatology **20**(7): 1133-1137.

Lightstone, L., A. J. Rees, C. Tomson, J. Walls, C. G. Winearls and J. Feehally (1995). "High incidence of end-stage renal disease in Indo-Asians in the UK." Quaterly Journal of Medicine **88**(3): 191-195.

Lindesay, J., C. Jagger, M. J. Hibbert, S. M. Peet and F. Moledina (1997). "Knowledge, uptake and availability of health and social services among

Asian Gujarati and white elderly persons." Ethnicity and Health **2**(1-2): 59-69.

Linn-Rasker, S. P., A. H. van der Helm-van Mil, F. A. van Gaalen, M. Kloppenburg, R. R. de Vries, S. Le Cessie, F. C. Breedveld, R. E. Toes, T. W. Huizinga (2006). "Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles." Annals of Rheumatic Diseases **65**(3): 366-371.

Linos, A., V. Kaklamani, E. Kaklamani, Y. Koumantaki, E. Giziaki, S. Papazoglou and C. S. Mantzoros (1999). "Dietary factors in relation to rheumatoid arthritis: a role for olive oil and cooked vegetables?" American Journal of Clinical Nutrition **70**: 1077-1082.

Linos, A., E. Kaklamanis, A. Kontomerkos, Y. Koumantaki, S. Gazi, G. Vaiopoulos, G. C. Tsokos and P. Kaklamanis (1991). "The effect of olive oil and fish consumption on rheumatoid arthritis - a case control study." Scandinavian Journal of Rheumatology **20**: 419-426.

Lorant, V., D. Deliege, W. Eaton, A. Robert, P. Philippot and M. Ansseau (2003). "Socioeconomic inequalities in depression: a meta-analysis." American Journal of Epidemiology **157**(2): 98-112.

Lukassen J, B. M. (2005). "Alcohol dependence and depression among heavy drinkers in Canada." Social Science and Medicine **61**(8): 1658-1667.

Macfarlane, G., B. Palmer, D. Roy, C. Afzal, A. Silman and T. O'Neill (2005). "An excess of widespread pain among South Asians: are low levels of vitamin D implicated? ." Annals of Rheumatic Diseases **64**: 1217-1219.

MacGregor, A. J., L. K. Riste, J. M. W. Hazes and A. J. Silman (1994). "Low prevalence of rheumatoid arthritis in Black-Caribbeans compared with Whites in inner city Manchester." Annals of Rheumatic Diseases **53**: 293-297.

Magni, G., C. Moreschi, S. Rigatti Luchini and H. Merskey (1994). "Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain." Pain **56**: 289-297.

Malaviya, A. N., S. K. Kapoor, R. R. Singh, A. Kumar and I. Pande (1993). "Prevalence of rheumatoid arthritis in the adult Indian population." Rheumatology International **13**: 131-134.

Malaviya, A. N., N. K. Mehra, B. Dasgupta, K. M. Khan, U. R. K. Rao, A. Agarwal and S. C. Tiwari (1983). "Clinical and Immunogenetic studies in rheumatoid arthritis from Northern India." Rheumatology International **3**: 105-108.

Manahan, L., R. Caragay, K. D. Muirden, E. Allander, H. A. Valkenburg and R. D. Wigley (1985). "Rheumatic pain in a Philippine village: a WHO-ILAR COPCORD study." Rheumatology International **5**: 149-154.

Manfredsdottir, V. F., T. Vikingsdottir, T. Jonsson, A. J. Geirsson, O. Kjartansson, M. Heimisdottir, S. L. Sigurdardottir, H. Valdimarsson and A. Vikingsson (2006). "The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis." Rheumatology **45**(6): 734-740.

Matsuda, Y., H. Yamanaka, K. Higami and S. Kashiwazaki (1998). "Time lag between active joint inflammation and radiological progression in patients with early rheumatoid arthritis." Journal of Rheumatology **25**: 427-432.

Matsuzaki, T., A. Nakajima, S. Ishigami, M. Tanno and S. Yoshino (2006). "Mirthful laughter differentially affects serum pro- and anti-inflammatory cytokine levels depending on the level of disease activity in patients with rheuamtoid arthritis." Rheumatology **45**: 182-186.

Mavreas, V., P. Bebbington and G. Der (1989). "The structure and validity of acculturation - analysis of an acculturation scale." Social Psychiatry and Psychiatric Epidemiology **24**: 233-240.

McDermott, E., M. A. Khan and C. Deighton (1996). "Further evidence for genetic anticipation in familial rheumatoid arthritis." Annals of Rheumatic Diseases **55**(7): 475-477.

McKellar, G., E. Morrison, A. McEntegart, R. Hampson, A. Tierney, G. Mackle, J. Scoular, J. A. Scott, H. A. Capell (2007). "A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow." Annals of Rheumatic Diseases **66**(9): 1239-1243.

Mehra, N. K., M. C. Vaidya, V. Taneja, A. Agarwal and A. N. Malaviya (1982). "HLA-DR antigens in rheumatoid arthritis in North India." Tissue Antigens **20**: 300-302.

Mewar, D., A. Coote, D. J. Moore, I. Marinou, J. Keyworth, M. C. Dickson, D. S. Montgomery, M. H. Binks, A. G. Wilson (2006). "Independent associations

of anti-cyclic citrullinated peptide antibodies and rheumatoid factor with radiographic severity of rheumatoid arthritis." Arthritis Research and Therapies **8**(4): R128.

Mindham, R. H. S., A. Bagshaw, S. A. James and A. J. Swannell (1981). "Factors associated with the appearence of psychiatric symptoms in rheumatoid arthritis." Journal of Psychosomatic Research **25**: 429-435.

Mittendorf, T., B. Dietz, R. Sterz, H. Kupper, M. A. Cifaldi, J-M. von der Schulenburg (2007). "Improvement and Longterm Maintenance of Quality of Life During Treatment with Adalimumab in Severe Rheumatoid Arthritis " Journal of Rheumatology **34**(2345-2350): 2345.

Mody, G. M. and O. L. Meyers (1989). "Rheumatoid arthritis in blacks in South Africa." Annals of Rheumatic Diseases **48**: 69-72.

Mody, G. M. and M. Hammond (1994). "Differences in HLA-DR association with rheumatoid arthritis among migrant Indian communities in South Africa." British Journal of Rheumatology **33**: 425-427.

Moolenburg, J. D., S. Moore and H. A. Valkenburg (1984). "Rheumatoid arthritis in Lesotho." Annals of Rheumatic Diseases **43**: 40-43.

Murphy, H., C. Dickens, F. Creed and R. Bernstein (1999). "Depression, illness perception and coping in rheumatoid arthritis." Journal of Psychosomatic Research **46**: 155-164.

Murphy, S., F. H. Creed and M. I. V. Jayson (1988). "Psychiatric disorders and illness behaviour in rheumatoid arthritis." British Journal of Rheumatology **27**: 357-363.

Myllykangas-Luosujarvi, R., K. Aho, H. Kautiainen and M. Hakala (2000). "Reduced incidence of alcohol related deaths in subjects with rheumatoid arthritis." Annals of Rheumatic Diseases **59**(1): 75-76.

Nazroo, J. Y. (2001). "South Asian people and heart disease: an assessment of the importance of socioeconomic position." Ethnic diseases **11**(3): 401-411.

Neame, R. and A. Hammond (2005). "Beliefs about medications: a questionnaire survey of people with rheumatoid arthritis." Rheumatology **44**: 762-767.

Nelson, J. L., G. Boyer, D. Templin, A. Lanier, R. Berrington, B. Nisperos, A. Smith, E. Mickelson and J. A. Hansen (1992). "HLA antigens in Tlingit Indians with rheumatoid arthritis." Tissue Antigens **40**: 57-63.

Newman, S. P., R. Fitzpatrick, R. Lamb and M. Shipley (1989). "The origins of depressed mood in rheumatoid arthritis." Journal of Rheumatology **16**: 740-744.

Nishimura, K., D. Sugiyama, Y. Kogata, G. Tsuji, T. Nakazawa, S. Kawano, K. Saigo, A. Morinobu, M. Koshiba, K. M. Kuntz, I. Kamae, S. Kumagai (2007). "Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis." Annals of Internal Medicine **146**(11): 797-808.

O'Brien, W. M., P. H. Bennett, T. A. Burch and J. J. Bunim (1967). "A genetic study of rheumatoid arthritis and rheumatoid factor in Blackfeet and Pima Indians." Arthritis and Rheumatism **10**: 163-179.

Olerup, O., H. Zetterquist (1992). "HLA-DR typing by PCR ampification with sequence-specific primers (PCR-SSP) in 2 hours: An alternative to serological DR typing in clinical practice including donor-recipient matching in cadavaric transplantation." Tissue Antigens **39**: 225-235.

Ollier, W., C. Stephens, J. Awad, D. Carthy, A. Gupta, D. Perry, A. Jawad and H. Festenstein (1991). "Is rheumatoid arthritis in Indians associated with HLA antigens sharing a DRB1 epitope?" Annals of Rheumatic Diseases **50**: 295-297.

Onder, G., B. W. Penninx, P. Lapuerta, L. P. Fried, G. V. Ostir, J. M. Guralnik, M. Pahor (2002). "Change in physical performance over time in older women: the Women's Health and Aging Study." The Journals of Gerontology: Series A, Biological Sciences And Medical Sciences **57**(5): M289-293.

OPCS (1991). Ethnicity: Leicestershire Districts, Census Crown copyright.

Palanichamy, M., C. Sun, S. Agrawal, H. J. Bandelt, Q.-P. Kong, F. Khan, C.-Y. Wang, T. K. Chaudhuri, V. Palla and Y.-P. Zhang (2004). "Phylogeny of Mitochondrial DNA Macrohaplogroup N in India, Based on Complete Sequencing: Implications for the Peopling of South Asia." American Journal of Human Genetics **75**: 966-978.

Palmer, B., G. Macfarlane, C. Afzal, A. Esmail, A. Silman and M. Lunt (2007). "Acculturation and the prevalence of pain amongst South Asian minority ethnic groups in the UK." Rheumatology **46**(6): 1009-1014.

Park, J. and E. Ernst (2005). "Ayurvedic medicine for rheumatoid arthritis: a systematic review." Seminars in Arthritis and Rheumatism **34**(5): 705-713.

Patten, S. B., C. A. Beck, A. Kassam, J. V. Williams, C. Barbui and L. M. Metz (2005). "Long-term medical conditions and major depression: strength of association for specific conditions in the general population." Canadian Journal of Psychiatry **50**: 195-202.

Pattison, D. J., A. Silman, N. J. Goodson, M. Lunt, D. Bunn, R. Luben, A. Welch, S. Bingham, K. T. Khaw, N. Day and D. P. Symmons (2004). "Vitamin C and the risk of developing inflammatory polyarthritis: prospective nested case-control study." Annals of Rheumatic Diseases **63**: 843-847.

Paykel, E. S. (2001). "Stress and affective disorders in humans." Seminars in Clinical Neuropsychiatry **6**(1): 4-11.

Pease, C. T., B. B. Bhakta, J. Devlin and P. Emery (1999). "Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors." Rheumatology **38**(3): 228-234.

Penzottia, J. E., D. Doherty, T. P. Lybranda, G. T. Nepomb (1996). "A Structural Model for TCR Recognition of the HLA Class II Shared Epitope Sequence Implicated in Susceptibility to Rheumatoid Arthritis " Journal of Autoimmunity **9**(2): 287-293.

Pincus, T., L. F. Callahan, L. Bradley, W. K. Vaughan and F. Wolfe (1986). "Elevated MMPI scores for hypochondriasis, depression and hysteria in patients with rheumatoid arthritis reflect disease rather than psychosocial status." Arthritis and Rheumatism **29**: 1456-1466.

Pincus, T., M. J. Bergman, Y. Yazici, P. Hines, K. Raghupathi, R. Maclean. (2008). "An index of only patient-reported outcome measures, routine

assessment of patient index data 3 (RAPID3), in two abatacept clinical trials: similar results to disease activity score (DAS28) and other RAPID indices that include physician-reported measures." Rheumatology **47**(3): 345-349.

Pincus, T., V. Strand, G. Koch, I. Amara, B. Crawford, F. Wolfe, S. Cohen, D. Felson. (2003). "An index of the three core data set patient questionnaire measures distinguishes efficacy of active treatment from that of placebo as effectively as the American College of Rheumatology 20% response criteria (ACR20) or the Disease Activity Score (DAS) in a rheumatoid arthritis clinical trial." Arthritis and Rheumatism **48**(3): 625-630.

Ploghaus, A., I. Tracey, J. S. Gati, S. Clare, R. S. Menon, P. M. Matthews and J. N. Rawlins (1999). "Dissociating pain from its anticipation in the human brain." Science **284**(5422): 1979-1981.

Podas, T., J. M. Nightingale, R. Oldham, S. Roy, N. J. Sheehan, J. F. Mayberry (2007). "Is rheumatoid arthritis a disease that starts in the intestine? A pilot study comparing an elemental diet with oral prednisolone." Postgraduate Medicial Journal **83**(976): 128-131.

Poór, G., Z. Nagy, Z. Schmidt, M. Brózik, K. Merétey, P. Gergely (2007). "Genetic background of anticyclic citrullinated peptide autoantibody production in Hungarian patients with rheumatoid arthritis." Annals of New York Academy of Science **1110**: 23-32.

Prevoo, M. L., M. A. van 't Hof, H. H. Kuper, M. A. van Leeuwen, L. B. van de Putte and P. L. van Riel (1995). "Modified disease activity scores that

include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis." Arthritis and Rheumatism **38**(1): 44-48.

Radstake, T. R., P. Barrera, J. M. Albers, H. L. Swinkels, L. B. van de Putte and P. L. van Riel (2000). "Familial vs sporadic rheumatoid arthritis (RA). A prospective study in an early RA inception cohort." Rheumatology **39**(3): 267-273.

Radstake, T. R., P. Barrera, M. J. Albers, H. L. Swinkels, L. B. van de Putte, P. L. van Riel and E. C. o. R. A. Families (2001). "Genetic anticipation in rheumatoid arthritis in Europe. European Consortium on Rheumatoid Arthritis Families." Journal of Rheumatology **28**(5): 962-967.

Rajalingam, R., P. Krausa, H. Shilling, J. B. Stein, A. Balamurugan, M. McGinnis, N. Cheng, N. Mehra and P. Parham (2002). "Distinctive KIR and HLA diversity in a panel of north Indian Hindus." Immunogenetics **53**(12): 1009-1019.

Ramjeet, J., M. Koutantji, E. M. Barrett and D. G. Scott (2005). "Coping and psychological adjustment in recent onset inflammatory polyarthritis: the role of gender and age." Rheumatology **44**: 1166-1168.

Rao, J. N., K. Mihaliak, K. Kroenke, J. Bradley, W. Tierney and M. Weinberger (1999). "Use of complementary therapies for arthritis among patients of rheumatologists." Annals of Internal Medicine **131**: 409-416.

Registries, A. I. o. H. a. W. a. A. A. o. C. (2004). Cancer in Australia 2001. Canberra.

Reilly, P. A. (1999). "The differential diagnosis of generalised pain." Ballieres Clinical Rheumatology **13**: 391-401.

Reveille, J. D. (1998). "The genetic contribution to the pathogenesis of rheumatoid arthritis." Current Opinion in Rheumatology **10**: 187-200.

Ritchie, D., M. Ahmad, J. Atkinson, W. Azmi, C. Dutton, Z. Haque and J. Sharples (2001). Oldham Independent Review: 1-102.

Rothschild, B. M., K. R. Turner and M. A. DeLuca (1988). "Symmetrical erosive peripheral polyarthritis in the Late Archaic Period of Alabama." Science **241**(4872): 1498-1501.

Roudier, J., J. Peterson, G. H. Rhodes, J. Luka, D. A. Carson (1989). "Susceptibility to rheumatoid arthritis maps to a T-cell epitope shared by the HLA-Dw4 DR Beta-1 chain and the Epstein-Barr virus glycoprotein gp110." Proceedings of the National Academy of Sciences of United States of America **6**(13): 5104-5108.

Royal College of Physicians and R. C. o. Psychiatrists (2003). The psychological care of medical patients. London, RCP, RCPsych.

Rupp, I., H. C. Boshuizen, H. J. Dinant, C. E. Jacobi, G. A. van den Bos (2006). "Disability and health-related quality of life among patients with rheumatoid arthritis: association with radiographic joint damage, disease activity, pain, and depressive symptoms." Scandinavian Journal of Rheumatology **35**(3): 175-181.

Samanta, A., S. Roy, J. Feehally, D. P. Symmons (1992). "The prevalence of diagnosed systemic lupus erythematosus in whites and Indian Asian

immigrants in Leicester city, UK." British Journal of Rheumatology **31**(10): 679-682.

Schellekens, G. A., H. Visser, B. de Jong, F. H. J. van den Hoogen, J. M. W. Hazes, F. C. Breedveld, W. J. van Venrooij (2000). "The Diagnostic Properties of Rheumatoid Arthritis Antibodies Recognizing a Cyclic Citullinated Peptide." Arthritis and Rheumatism **43**(1): 155-163.

Seldin, M. F., R. Shigeta, P. Villoslada, C. Selmi, J. Tuomilehto, G. Silva, J. W. Belmont, L. Klareskog and P. K. Gregersen (2006). "European Population Substructure: Clustering of Northern and Southern Populations." PLoS Genetics **2**(9): 1339-1351.

Sen, B. and P. Williams (1987). "The extent and nature of depressive phenomena in primary care; a study in Calcutta, India " British Journal of Psychiatry **151**: 486-493.

Serhan, E., P. Newton, H. A. Ali, S. Walford and B. M. Singh (1999). "Prevalence of hypovitaminosis D in Indo-Asian patients attending a rheumatology clinic." Bone **25**(5): 609-611.

Shankar, S., R. Grover, R. Handa (2006). "Role of anti cyclic citrullinated peptide antibodies in erosive disease in patients with rheumatoid arthritis." Indian Journal of Medical Research **124**(6): 689-696.

Silman, A., P. Davies, H. L. Currey and S. J. Evans (1983). "Is rheumatoid arthritis becoming less severe?" Journal of Chronic Diseases **36**: 891-897.

Silman, A. J. (1988). "Has the incidence of rheumatoid arthritis declined in the United Kingdom?" British Journal of Rheumatology **27**: 77-79.

Silman, A. J., A. J. MacGregor, W. Thomson, S. Holligan, D. Carthy, A. Farhan and W. E. Ollier (1993). "Twin concordance rates for rheumatoid arthritis: results from a nationwide study." British Journal of Rheumatology **1993**(32): 903-907.

Silman, A. J., W. Ollier, S. Holligan, F. Birrell, A. Adebajo, M. C. Asuzu, W. Thomson and L. Pepper (1993). "Absence of rheumatoid arthritis in a rural Nigerian population." The Journal of Rheumatology **20**(4): 618-622.

Simmonds, M. J., S. C. Gough (2005). "Genetic insights into disease mechanisms of autoimmunity." British Medical Bulletins **71**: 93-113.

Sin, C. H. (2006). "Expectations of support among White British and Asian-Indian older people in Britain: the interdependence of formal and informal spheres." Health Society Care in the Community **14**(3): 215-224.

Smedstad, L. M., P. Vaglum, T. Moun and T. K. Kvien (1997). "The relationship between psychological distress and traditional clinical variables: a 2 year prospective study of 216 patients with early arthritis." British Journal of Rheumatology **36**: 1304-1311.

Snorrason, E. (1952). "Landre-Beauvais and his 'goutte asthenique primitive'." Acta Medica Scandinavica Supplement **266**: 115-118.

Sokka, T., A. Häkkinen, E. Krishnan, P. Hannonen (2004). "Similar prediction of mortality by the health assessment questionnaire in patients with rheumatoid arthritis and the general population." Annals of Rheumatic Diseases **63**(5): 494-497.

Sokka, T., H. Kautiainen, P. Hannonen, T. Pincus (2006). "Changes in Health Assessment Questionnaire disability scores over five years in patients with rheumatoid arthritis compared with the general population." Arthritis and Rheumatism **54**(10): 3113-3118.

Solomon, L., G. Robin and H. A. Valkenburg (1975). "Rheumatoid arthritis in an urban South African Negro population." Annals of Rheumatic Diseases **34**: 128-135.

Soni Raleigh, V. and R. Balarajan (1992). "Suicide and self-burning among Indians and West Indians in England and Wales." British Journal of Psychiatry **161**: 365-368.

Stastny, P. (1978). "Association of the B-cell alloantigen DRw4 with rheumatoid arthritis." New England Journal of Medicine **298**: 869-871.

Statistics (2005). Neighbourhood statistics, www.neighbourhood.statistics.gov.uk.

Stavropoulos, C., M. Spyopoulou, Y. Koumantaki, I. Kappou, V. Kaklamani, A. Linos, E. Giziaki and E. Kaklamani (1997). "HLA-DRB1 alleles in Greek rheumatoid arthritis patients and their association with clinical characteristics." European Journal of Immunogenetics **24**: 265-274.

Stewart, A. and J. N. Rao (2002). "Asian patients may receive inferior care." British Medical Journal **325**: 659.

Strating, M. M., W. H. Van Schuur, T. P. Suurmeijer (2007). "Predictors of functional disability in rheumatoid arthritis: results from a 13-year prospective study." Disability and Rehabilitation **29**(10): 805-815.

Symmons, D., G. Turner, R. Webb, P. Asten, E. Barrett, M. Lunt, D. Scott and A. Silman (2002). "The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century." Rheumatology **41**: 793-800.

Symmons, D. P., E. M. Barrett, C. R. Bankhead, D. G. Scott and A. J. Silman (1994). "The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register." British Journal of Rheumatology **33**: 735-739.

Symmons, D. P., C. R. Bankhead, B. J. Harrison, P. Brennan, E. M. Barrett, D. G. Scott and A. J. Silman (1997). "Blood transfusion, smoking and obesity as risk factors for the development of rheumatoid arthritis: results from a a primary care-based incident case control study in Norfolk, England." Arthritis and Rheumatism **40**: 1955-1961.

Thomson, W., B. Harrison, B. Ollier, N. Willes, T. Payton, J. Barrett, D. Symmons and A. Silman (1999). "Quantifying the exact role of HLA-DRB1 alleles in susceptibility to inflammatory polyarthritis: results from a large, population based study." Arthritis and Rheumatism **42**: 757-762.

Timonen, M., K. Viilo, H. Hakko, T. Sarkioja, M. Ylikulju, V. B. Meyer-Rochow, E. Vaisanen and P. Rasanen (2003). "Suicides in persons suffering from rheumatoid arthritis." Rheumatology **42**: 287-291.

Turesson, C., W. M. O'Fallon, C. S. Crowson and e. al (2000). "Incidence of extra-articular disease manifestations in a population based cohort of patients with rheumatoid arthritis." Arthritis and Rheumatism **43**(9S): S152.

Turesson, C., W. M. O'Fallon, C. S. Crowson, S. E. Gabriel and E. L. Matteson (2003). "Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years." Annals of Rheumatic Diseases **62**(8): 722-727.

Upadhyaya, A., F. Creed and M. Upadhyaya (1009). "Psychiatric morbidity among mothers attending a well-baby clinic: a cross-cultural comparison." Acta Psychiatrica Scandinavica **81**(2): 148-151.

Urwin, M., D. Symmons, T. Allison, T. Brammah, H. Busby, M. Roxby, A. Simmons and G. Williamse (1998). "Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation " Annals of Rheumatic Diseases **57**: 649-655.

van der Heijde, D., R. Landewé, R. van Vollenhoven, S. Fatenejad, L. Klareskog (2008). "Level of radiographic damage and radiographic progression are determinants of physical function: a longitudinal analysis of the TEMPO trial." Annals of Rheumatic Diseases **epub ahead of print**.

van der Heijde, D. M., M. van't Hof, P. L. van Riel and L. B. van de Putte (1993). "Development of a disease activity score based on judgment in clinical practice by rheumatologists." Journal of Rheumatology **20**: 579-581.

van der Helm-van Mil, A., K. Verpoort, F. Breedveld, T. Huizinga, R. Toes, R. de Vries (2006). "The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an

independent risk factor for development of rheumatoid arthritis." Arthritis and Rheumatism **54**(4): 1117-1121.

van der Helm-van Mil AH, V. K., le Cessie S, Huizinga TW, de Vries RR, Toes RE. (2007). "The HLA-DRB1 shared epitope alleles differ in the interaction with smoking and predisposition to antibodies to cyclic citrullinated peptide." Arthritis and Rheumatism **56**(2): 425-432.

van Gaalen, F., J. van Aken, T. Huizinga, G. Schreuder, F. Breedveld, E. Zanelli, W. van Venrooij, C. Verweij, R. Toes, R. de Vries (2004). "Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis." Arthritis and Rheumatism **50**(7): 2113-2121.

Viller, F., F. Guillemin, S. Briancon, T. Moum, T. Suurmeijer and W. van den Heuvel (1999). "Compliance to drug treatment of patients with rheumatoid arthritis: a 3 year longitudinal study." Journal of Rheumatology **26**(10): 2114-2122.

Voight, L. F., T. D. Koepsell, J. L. Nelson, C. E. Dugowson and J. R. Daling (1994). "Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis." Epidemiology **5**: 525-532.

Walser-Kuntz, D. R., C. M. Weyand, A. J. Weaver, W. M. O'Fallon, J. J. Gorozny (1995). "Mechanisms underlying the formation of the T cell receptor repetoire in rheumatoid arthritis." Immunity **2**(6): 597-605.

Watson, P. J., R. K. Latif and D. J. Rowbotham (2005). "Ethnic differences in thermal pain responses: a comparison of South Asian and White British healthy males." Pain **118**(1-2): 194-200.

Watts, R. A., J. Mooney, S. E. Lane and D. G. Scott (2004). "Rheumatoid vasculitis: becoming extinct?" Rheumatology **43**: 920-923.

Webster, R. A., D. R. Thompson, R. A. Mayou (2002). "The experiences and needs of Gujarati Hindu patients and partners in the first month after a myocardial infarction." European Journal of Cardiovascular Nursing **1**(1): 69-76.

Wener, M. (2004). Autoantibodies and Other Laboratory Tests. Rheumatoid Arthritis. E. W. St Clair, D. S. Pisetsky, B. F. Haynes, Lippincott, Williams and Wilkins: 64-79.

Williams, R. C. and J. E. McAuley (1991). "HLA class II variation in the Gila River Indian community of Arizona: alleles, haplotypes, and a high frequency epitope at the HLA-DR locus." Human Immunology **33**: 29-38.

Willkens, R. F., G. T. Nepom, C. R. Marks, J. W. Nettles and B. S. Nepom (1991). "Association of HLA-Dw16 with rheumatoid arthritis in Yakima Indians." Arthritis and Rheumatism **34**: 43-47.

Wolfe, F. (2000). "A reappraisal of HAQ disability in rheumatoid arthritis " Arthritis and Rheumatism **43**: 2751-2761.

Wolfe, F. and J. T. Sharpe (1998). "Radiographic outcome of recent onset rheumatoid arthritis: a 19 year study of radiographic progression." Arthritis and Rheumatism **41**: 1571-1582.

Wolfe, F. and K. Michaud (2004). "Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize ra patients with fibromyalgia." Journal of Rheumatology **31**(4): 695-700.

Wolfe, F., S. M. Kleinheksel and M. A. Khan (1988). "Familial vs. Sporadic rheumatoid arthritis: A comparison of the demographic and clinical characteristics of 956 patients." Journal of Rheumatology **15**(3): 400-404.

Wolfe, F., S. M. Kleinheksel and M. A. Khan (1988). "Prevalence of familial occurrence in patients with rheumatoid arthritis." British Journal of Rheumatology **27**(Suppl 2): 150-152.

Wolfe, F., K. Michaud, O. Gefeller, H. K. Choi (2003). "Predicting mortality in patients with rheumatoid arthritis." Arthritis and Rheumatism **48**(6): 1530-1542.

Woodrow, J. C., F. E. Nichol and G. Zaphiropoulos (1981). "DR antigens and rheumatoid arthritis: a study of two populations." British Medical Journal **283**: 1287-1288.

Wright, G. E., J. C. Parker, K. L. Smarr, J. C. Johnson, J. E. Hewett and S. E. Walker (1998). "Age, depressive symptoms, and rheumatoid arthritis." Arthritis and Rheumatism **41**: 298-305.

Yazici, Y., H. Kautiainen and T. Sokka (2007). "Differences in clinical status measures in different ethnic/racial groups with early rheumatoid arthritis: implications for interpretation of clinical trial data." Journal of Rheumatology **34**(2): 311-315.

Yazici, Y., T. Pincus, H. Kautiainen and T. Sokka (2004). "Morning stiffness in patients with early rheumatoid arthritis is associated more strongly with functional disability than with joint swelling and erythrocyte sedimentation rate." Journal of Rheumatology **31**(9): 1723-1726.

Yazici, Y., T. Pincus, H. Kautiainen, T. Sokka (2004). "Morning stiffness in patients with early rheumatoid arthritis is associated more strongly with functional disability than with joint swelling and erythrocyte sedimentation rate." Journal of Rheumatology **31**(9): 1723-1726.

Young, A. and E. s. group (2001). "Socioeconomic deprivation and rheumatoid disease: what lessons for the health service?" Annals of Rheumatic Diseases.

Young, A., J. Dixey, E. Kulinskaya, N. Cox, P. Davies, J. Devlin, P. Emery, A. Gough, D. James, P. Prouse, P. Williams and J. Winfield (2000). "Socioeconomic deprivation and rheumatoid disease: What lessons for the health service?" Annals of Rheumatic Diseases **59**: 794-799.

Young, A., J. Dixey, E. Kulinskaya, N. Cox, P. Davies, J. Devlin, P. Emery, A. Gough, D. James, P. Prouse, P. Williams and J. Winfield (2002). "Which patients stop working because of rheumatoid arthritis? Results of five years' follow up in 732 patients from the Early RA Study (ERAS)." Annals of Rheumatic Diseases **61**: 335-340.

Zyrianova, Y., B. D. Kelly, C. Gallagher, C. McCarthy, M. G. Molloy, J. Sheehan and T. G. Dinan (2006). "Depression and anxiety in rheumatoid arthritis:

the role of perceived social support." Irish Journal of Medical Science **175**(2): 32-36.