UNIVERSITY OF SOUTHAMPTON

Health status of adults with chronic arthritis since childhood: a clinical, functional and psychosocial assessment

Dr Jonathan Charles Packham

This thesis is submitted for the qualification of Medical Doctorate.

The research for this thesis was performed in Wexham Park Hospital, Slough

The research is entirely based on work performed whilst in registered postgraduate candidature. It does not include work performed on a joint basis or submitted for another degree.

Consultant in Rheumatology, Department of Rheumatology
Staffordshire Rheumatology Centre
Haywood Hospital, High Lane, Burslem, Stoke on Trent ST6 7AG

April 2004

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE

MEDICINE

Medical Doctorate

Health status of adults with chronic arthritis since childhood:
a clinical, functional and psychosocial assessment.

by Jonathan Charles Packham

This research assessed the health status of patients with juvenile idiopathic arthritis (JIA) who continue to require rheumatological support into adulthood. Features of JIA such as onset in childhood, chronicity, disability and pain suggest a possible increased risk of psychological problems.

259 adults with JIA were traced, 246 (95%) agreed to participate in the study, whilst 13 (5%) declined. Patients' clinical, functional and psychological status was documented using interview, examination, complete notes review and psychological questionnaires.

The mean disease duration was 28.3 years, the mean patient age was 35.4 years and the mean age at onset was 7.1 years. 43.3% of all patients had active arthritis clinically and 54.4% on laboratory measures (CRP). Clinical inflammation was less common in systemic onset JIA. 42.9% of all patients had severe disability (HAQ score > 1.5). 40% of all patients used mobility aids, and 48% lived in houses with no stairs or a stair lift/rail. 60% of the study group had difficulty using public transport.

29.9% of patients were unemployed as a direct result of their JIA, despite a high proportion (34.8%) of patients who went onto tertiary education. These results raise important questions regarding the provision of career guidance for adolescents with JIA and the return to work of disabled patients. 25.1% of patients had encountered discrimination in the workplace.

Fewer patients (42.8%) were in stable relationships compared to their siblings (55.3%). 27.5% of patients had children. 23% of all known pregnancies ended in miscarriage. 78.9% of all women having a caesarean had either reduced hip mobility or short stature. JIA had a detrimental effect on body image in 50.7% of patients but relationships were affected in only 28.2%. 83.3% of patients were sexually active or had previous sexual experience. 58.3% of these had disease related sexual problems.

31.6% of patients were anxious, but only 5.2% were depressed. 21.1% of patients had previously suffered from depression and 37.9% felt their disease had a negative influence on mood. 78.8% of anxiety variance and 54.5% of depression variance could be predicted by other variables, but there was only small influence from physical disease related factors.

32.9% of patients had severe/very severe pain on pain visual analogue scale. 22.8% of patients had poor/very poor perceived control of their pain. 39.6% of the variance in pain could be predicted using function (HAQ), coping strategies, pain self-efficacy, clinical inflammation and previous depression. Comparing adults with children, although disease activity and control over pain remain predictors of pain they become less important than disability and coping strategies.

The incidence of non-iatrogenic premature ovarian failure was significantly increased below the ages of both 40 and 30.

LIST OF CONTENTS

List of Figures

List of Tables

Acknowledgements

I would like to thank the following for their help and support in producing this thesis:

Arthritis Research Campaign who funded the work by a clinical research fellowship

Dr Ann Hall, Wexham Park Hospital, Slough for her constant enthusiasm, support, ideas and access to her patients

Nursing and medical staff at Wexham Park Hospital for their collaboration

Dr Richard Hull, Queen Alexandra Hospital, Portsmouth for his support and guidance and access to his patients

Professor Paul Wordsworth for allowing access to his laboratory at the Wellcome Centre For Musculoskeletal Genetics, Oxford and his help with the genetic tests performed on the study group

Scientists at the Wellcome Centre For Musculoskeletal Genetics for their tuition and patience

The late Barbara Ansell for access to her files whilst tracing patients for the study

Dr John Pimm, Oxford Regional Rheumatic Diseases Research Centre, Stoke Mandeville Hospital, Aylesbury for his advice on the psychological aspects of the study

Professor Peter Jones, Department of Mathematics, Keele University for his help with statistical support

All of the patients who gave their time and interest to participate in the study

My wife Jayne for her support, patience and thorough proof reading

Peer reviewed papers published as a result of this research

Association of HLA-DRB1*13 with Susceptibility to Uveitis in Juvenile Idiopathic Arthritis in Two Independent Cohorts
Zeggini E, Packham JC, Wordsworth BP, Hall MA and Thomson W
Submitted 'Rheumatology' April 2004

Psychosocial concerns of young adults with juvenile arthritis
Packham JC
Musculoskeletal Care 2004; 2 (1): 6-16

Premature ovarian failure in adults with JIA
Packham JC, Hall MA
Clinical and Experimental Rheumatology 2003; 21 (3): 347-350

Functional outcome in adults with JIA
Packham JC, Hall MA
Rheumatology 2002;41:1428-1435

Predictive factors for mood and pain in adults with JIA
Packham JC, Hall MA, Pimm J
Rheumatology 2002;41:1444-1449

Education and employment in adults with JIA
Packham JC, Hall MA
Rheumatology 2002;41:1436-1439

Social function, relationships and sexual activity in JIA adults
Packham JC, Hall MA
Rheumatology 2002;41:1440-1443

Presentations

Long term outcome of juvenile arthritis
British Health Professionals Group invited lecturer 2000

Predictive factors for mood and pain
British Paediatric Rheumatology Group presentation 2000

Education and employment status
Royal College of Paediatrics and Child Health *Plenary presentation* 1999

Measuring outcome in disability
National Association of Podiatrists invited lecturer 1999

Clinical research overview
ARC fellows meeting invited presentation 1999

Sexual activity related to social outcome
Royal Society Medicine annual meeting presentation 1999

Abbreviations

AIMS	arthritis impact measurement scale
ANA	antinuclear antibody
ARA	American Rheumatism Association
ARAra	American Rheumatism Association rheumatoid arthritis classification
BDI	Beck depression inventory
CES-D	Center for Epidemiologic Studies Depression Scale
CHAQ	childhood health assessment questionnaire
CPR	C-reactive protein
DEXA	dual energy x-ray absorptiometry
DMARD's	disease modifying anti-rheumatic drugs
DRP	disease repercussion scale
EAOA	early adult onset arthritis
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAPA	fever, apthous ulceration, pharyngitis and adenopathy
GnRH-a	gonadotrophin-releasing hormone agonistic analogue
GCSE	general certificate in education
GHQ	general health questionnaire
GWB-D	general well-being schedule depression subscale
HAD	Hospital Anxiety and Depression Scale
HAQ	health assessment questionnaire
HSCL	Hopkins symptom checklist
IBDJA	inflammatory bowel disease related juvenile arthritis
IgG	immunoglobulin G
ILAR	International League Against Rheumatism
JA	juvenile arthritis
JAS	juvenile ankylosing spondylitis
JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JPsA	juvenile psoriatic arthritis

JRA	juvenile rheumatoid arthritis
JspA	juvenile spondyloarthropathy
LCAS	London coping with arthritis scale
LUF syndrome	luteinised unruptured follicle syndrome
MAA	mental adjustment to arthritis score
MCTD	mixed connective tissue disease
MTHFR	Methylentetrahydrofolate reductase
NSAID's	non-steroidal anti-inflammatory drugs
OCP	oral contraceptive pill
p	probability
PC	pre-classification
QOLS	quality of life scale
RA	rheumatoid arthritis
RAQOL	rheumatoid arthritis quality of life scale
RhF	rheumatoid factor
S.D.	standard deviation
SEA	seronegative enthesopathy and arthropathy
SAP	serum amyloid protein
SF-36	short form 36
SLE	systemic lupus erythematosus
TK	Thompson Kirwan
TMJ	temporomandibular joint
UK	United Kingdom
VAS	visual analogue score
-ve	negative
+ve	positive
vs.	versus
WHO	World Health Organisation

1 CHAPTER I - Introduction

1.1 Introduction

Chronic inflammatory arthritis is the most common form of rheumatic disease to affect children. With an annual incidence in the UK of 10 per 100,000[1] it is the fifth most common chronic disease of childhood behind asthma, congenital heart disease, diabetes and cleft lip/palate. Juvenile idiopathic arthritis (JIA) is often self-limiting with around 60% of patients reaching adulthood with no active synovitis or functional incapacity[2]. However, many patients experience the detrimental effects of chronic arthritis, including joint deformities and destruction, osteoporosis and growth abnormalities, which may result in pain, impairment of psychological health or difficulty with daily activities. The course of disease is unpredictable in all forms of JIA, but commonly follows a fluctuating course. Exacerbations are characterised by increased synovitis in previously involved joints and/or by an increased number of joints being involved. It is particularly during these exacerbations that joint damage occurs. The cumulative effect of continuing active arthritis into adulthood increases the degree of functional limitation and joint destruction, giving JIA the potential to cause significant disability.

It is therefore important to suppress joint inflammation while the arthropathy is in its active phase. This can usually be accomplished by the use of NSAIDs and intra-articular corticosteroids (which are often administered under general anaesthesia). In general, there is a good response, but second-line disease modifying drugs e.g. methotrexate, are usually needed for those who develop more severe polyarticular disease. Physical methods of treatment to prevent joint and soft tissue contractures (such as nocturnal splints and prone lying) and regular exercise regimes are used to maintain optimum joint function. Surgical intervention is occasionally required for those who develop severe contractures (soft tissue release or tenotomy) or abnormalities of bone growth occurring secondary to epiphyseal involvement (epiphyseal stapling). Joint replacement surgery is used in those patients with severe destructive arthritis.

The goals of arthritis treatment include the control of active disease, pain relief, maintenance of quality of life, minimizing treatment side effects and cost effectiveness.

The long-term follow up of patients with such chronic disease is an important tool for understanding the impact of chronic arthritis starting in childhood.

1.2 Long-term outcome studies

1.2.1. Factors affecting long-term outcome studies

Long-term outcome studies of JIA show that between 2-48% of patients will have severe functional limitation (Steinbrocker classes III & IV).[3] The length of follow-up is extremely important in identifying long-term outcome. Scott[4] prospectively followed 112 adult patients with RA at 5, 10 and 20 years that were treated aggressively with disease-modifying drugs. Although function initially improved, it deteriorated considerably between 10 and 20 years. These findings are mirrored in JIA, with Laaksonen[5] demonstrating that the number of patients in functional classes III & IV increased from 12% at 3 - 7 years after onset, to 48% after 16 or more years.

The majority of previous studies have not separated the disease subsets, which are known to affect prognosis and outcome. This study is one of the first to apply the recently introduced ILAR criteria[6] for juvenile arthritis, rather than the EULAR criteria[7] or ARA criteria[8, 9] to patients with longstanding disease. The main differences between these classifications are an expansion in the recognised subsets as discussed in 1.3.1.

All papers with a follow-up duration of over 10 years with 25 or more patients are reviewed in **Table 1.1.** Only those studies with data on disease activity, functional ability or psychosocial outcomes are included. Those papers with specific orientation to radiological changes, osteoporosis or uveitis outcomes have been excluded.

There have been major changes in disease classification over the time. 10 papers were published before EULAR[7] (1978) and the ARA[8, 9] (1977) had agreed classifications, although some papers used identical classification criteria to those later adopted by the ARA[10] and EULAR[11-13]. Between 1978 and 2002 the majority of studies in the USA/Canada used the ARA criteria[9] for juvenile rheumatoid arthritis and most European studies used the EULAR criteria[7] for juvenile chronic arthritis. Since 2002

the majority of studies are now using the ILAR criteria[6] for juvenile idiopathic arthritis.

When considering long-term outcome, duration of disease is not the only important factor. Case recruitment can have a major effect on study results. If patients are recruited prospectively into a cohort, then the study theoretically includes those patients who do well and require no ongoing follow-up. This group of patients are lost in retrospective studies. However, some prospective studies are adversely affected if the proportion of prospective patients recruited from the cohort is low, (such as Miller[14] 67%, Ruperto[15] 66% and Oen[16] 60%), as those not recruited tend to be less severely affected by their arthritis.

There is also potential bias from where patients are recruited from, with hospital inpatient recruits more likely to have severe disease than their outpatient clinic counterparts. In retrospective studies, it is also relevant as to whether the patients are current clinic attendees, as this group are more likely to have severe active disease than those recruited from a database of previous clinic attendees.

There are differences in the variation of definitions for active disease between studies; these can include raised inflammatory markers, clinically apparent synovitis, physician global scales or a combination of these. Few studies have compared the level of disease activity indicated by these different measures in the same study group.

Historically, many studies have used the Steinbrocker functional classes III/IV[3] as a primary measure of physical disability. There has been a move towards using the well-validated HAQ score[17] to describe physical ability. Unfortunately, in reality this has led to less uniformity between papers. The underlying cause of this is that different authors use differing cut off scores on the HAQ score to indicate physical disability, varying from HAQ>0[18] to HAQ>1.5[16]. This makes drawing conclusions from the different outcomes in physical ability between some of the more recent studies difficult.

1.2.2. Review of long-term outcome studies

Table 1.1 Long-term outcome studies in juvenile arthritis

Author Year Reference	Country	Mean disease length (years)	Case recruitment	Class	No. of cases	Questionnaires	Active disease %	Functional class III/IV %
Ansell 1959[19]	UK	10	Subgroup of 216 prospective hospital admissions	(JCA)	35	_	_	24
Sury 1961[20]	Denmark	23	-	PC	100	-	27	31
Lindbjerg 1964[21]	Denmark	10.6	Prospective serial hospital admissions	ARAra	75	_	_	24
Laaksonen 1966[5]	Finland	>16	Prospective paediatric clinic referrals + patients retrospectively from adult clinic onset < 15	PC	505	_	42	30
Jeremy 1968[10]	USA	18 (5-20)	Current clinic attendees	(JRA)	46	_	51	24
Ansell 1969[22]	UK	>15	Prospective hospital referrals within 5 years of onset	(JCA)	168	_	24	18
Goel 1974[13]	UK	10.1 (1-20)	Retrospective hospital admissions	(JCA)	100	_	11	18
Ansell 1976[11]	UK	>15	Prospective serial hospital admissions	(JCA) JAS	243	_	_	20
Hill 1976[12]	Canada	14.5	Retrospective clinic attendees over age 19	JCA	58	Interview	_	33
Hanson 1977[23]	USA	10 (5-25)	Current clinic attendees	?	123	_	55	28
Meyer 1978[24]	France	16	Retrospective clinic attendees over age 18 with pre-pubertal onset	JCA	30	-	-	17
Stoeber 1981[25]	Germany	15 (10-22)	Retrospective clinic attendees with disease duration over 10 years	JCA	433	-	-	41
Dequeker 1982[26]	Belgium	13.8 (2-50)	Prospective serial clinic referrals	JCA others	96	_	27	24
Miller 1982[14]	USA	>16	Prospective clinic attendees	JRA JAS	121	HAQ	49	*16% HAQ>1*
Svantesson 1983[27]	Sweden	10 (4-24)	Retrospective hospital admission systemic onset	JCA	33	_	17	31
Rennebohn 1984[28]	USA	14.7	Prospective clinic attendees	JRA	115	_	33	9
Prieur 1984[29]	France	17.5	Retrospective clinic attendees systemic onset only	JCA	26	-	54	-
Pedersen 1987[30]	Denmark	10 (3-30)	Retrospective hospital admissions	JCA	93	-	pauci 47 poly 29	6
Doherty 1988[31]	Ireland	13	Retrospective functionally independent current clinic attendees	JCA	25	AIMS	76	0
Calabro 1989[2]	USA	25	Prospective cohort of clinic referrals	JRA	100	-	9	15
Levinson	USA	15-20	Prospective clinic	JRA	101	-	45	17

1991[32]			attendees					
Cabral 1992[33]	Canada	11	Prospective initially presenting with SEA syndrome	SEA	36	-	-	-
David 1994[34]	UK	19.7	Retrospective clinic attendees with polyarticular involvement	JCA	43	BDI GHQ MAA	49	14
Ruperto 1997[15]	USA Italy	15 (5-36)	Retrospective clinic attendees within 6 months of onset of symptoms	JRA	227	HAQ CHAQ QOLS Pain VAS	_	*4%* *HAQ>1.5* *15%* *HAQ>0.5*
Peterson 1997[18]	USA	24.7	Controlled, population based cohort	JRA	44	HAQ SF-36	?? 65.9	*38.6%* *HAQ>0*
Musiej-Nowakoska 1999[35]	Poland	28	Retrospective female clinic attendees early onset pauciarticular only	JRA	39	-	38	-
Zak 2000[36]	Denmark	26.4	Retrospective hospital admissions previously studied by Pedersen 1987	JCA	65	HAQ pain VAS cope VAS	37	11
Lomater 2000[37]	Italy	10.7	Prospective clinic referrals with systemic onset JCA	JCA	80	_	_	29
Speigel 2000[38]	Canada	>10	Subgroup of inception cohort of systemic onset JRA referrals to hospital	JRA	33	HAQ CHAQ	-	-
Archenholtz 2001[39]	Sweden	13	Retrospective	JRA	32	QOLS	-	-
Narayanan 2002[40]	India	11.4 (6-22)	Retrospective current clinic attendees	JRA	26		83	23
Minden 2002[41]	Germany	16.5 (10-30)	All patients in referral cohort to hospital between 1978-1988	JIA	215	HAQ RAQOL CES-D pain VAS	55	10 *6.5%* *HAQ>1.0*
Packham 2003[42-45]	UK	28.5	Retrospective current clinic attendees	JIA	246	HAQ HAD pain VAS LCAS Sarason SES/DPR	43.3	37.1 *42.9%* *HAQ>1.5*
Foster 2003[46]	UK	21	Retrospective current clinic attendees	JIA	82	HAQ SF36 pain VAS	39	*Median HAQ=1.1 25*
Flato 2002[47, 48]	Norway	14.9 (12-25)	Cohort of hospital admissions	JRA JAS SEA JPsA IBDJA	268	HAQ SF-36 HSCL	-	36% HAQ>0
Bruinooge 2003[49]	Holland	19.2	Prospective clinic attendees between 18-40	JIA	104	AIMS2	_	_
Oen 2003[16]	Canada	10.5 (5-23)	Prospective multi-centre clinic attendees	JRA	392	CHAQ Pain VAS	41	2 *5.6%* *HAQ>1.5*
Fantini 2003[50]	Italy	10.2 (0.6-37)	Prospective clinic attendees	JCA JSpA	550	_	42	_

HAQ = Health Assessment Questionnaire; AIMS = Arthritis Impact Measurement Scale: BDI = Beck Depression Inventory; GHQ = General Health Questionnaire; MAA = Mental Adjustment to Arthritis score; CHAQ = Childhood Health Assessment Questionnaire; QOLS = Quality of Life Scale; pain VAS = Pain Visual Analogue Scale; SF-36 = Short Form 36; cope VAS = Coping Visual Analogue Scale; RAQOL = Rheumatoid Arthritis Quality of Life Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; HAD = Hospital Anxiety and Depression Score; LCAS = London Coping with Arthritis Scale; Sarason = Sarason Short Form Social Scale; DPR = Disease Repercussion Scale.PC = pre-classification; JCA = juvenile chronic arthritis; ARAra = American Rheumatism Association rheumatoid arthritis classification; JRA = juvenile rheumatoid arthritis; JIA = juvenile idiopathic arthritis; JAS = juvenile ankylosing spondylitis; SEA = seronegative enthesopathy and arthropathy; JpsA = juvenile psoriatic arthritis; IBDJA = inflammatory bowel disease related juvenile arthritis; JSpA = juvenile spondyloarthropathy; HSCL = Hopkins Symptom Checklist

Ansell 1959[19]. This was the first publication to consider the long-term follow-up of juvenile arthritis (JA). The definition used for JA was subsequently taken up as the EULAR classification. In a study of 216 hospital admissions with juvenile arthritis, disease duration was over 10 years in 35 cases. 9/35 of these cases were in Steinbrocker class III/IV. No additional data on this subgroup was published. (There is some confusion in the literature with some articles erroneously crediting the journal editor JJ. Bunim with the authorship of this publication.)

Sury 1961[20]. This study described 100 patients with JA from Copenhagen. 31% were severely disabled and there was a mortality rate of 13.2%. 4/32 (12.5%) of men and 14/68 (20.6%) of women were in Steinbrocker functional class IV.

Lingberg 1964[21]. 75 prospective serial hospital admissions with JA were followed-up for 10.6 years. Patients were included in the study if they met the American Rheumatoid Arthritis classification (1959). There was a broad range in the duration of follow-up from 5-30 years. 36% were monoarticular, 64% were polyarticular and 47% had a fever at presentation. The mortality rate related to disease was 4/74 (5%). All 4 disease related deaths were in the 'systemic/fever' group. 24% were in Steinbrocker functional class III/IV. 12/75 (16%) had active disease, but this fell to 7/63 (11%) when patients with disease duration of less than 5 years were excluded.

Laaksonen 1966[5]. This remains one of the largest studies in JA in the literature. Overall 544 patients were included in the study. They were a mix of all patients with JA treated between 1951-61 (prospective) and other adult patients with arthritis onset in childhood (retrospective). The mean duration of disease was 16 years (range 3-50), with 368 having a duration greater than 9 years. Of the 544, 14 were either untraceable or

declined participating in the study and 25 (4.6%) had died. 29.7% of patients were in Steinbrocker class III/IV, which worsened with disease duration; the percentage at 3-7 years was 12%, at 8-15 years 24% and at over 16 years 48%. 42% of patients were clinically active with 34% in remission. ESR values were available for 226 patients who had been admitted to hospital in the preceding 3 years. 111/226 (49%) had an ESR>30mm/hr.

26% were married. Patients were better educated than their peers. At 15 years of age 29.4% had completed either 'middle' or trade school compared to 16.7% of the general population. Those patients in employment tended to be in 'lower class' jobs with 84% in class III/IV jobs compared with 52.7% in the general population. 33% were in employment, 32% in education and 35% incapacitated and unable to participate in either.

Jeremy 1968[10]. This study included 46 current clinic attendees with JA, with a mean disease duration of 16 years. They were described prior to the ACR classification, but the criteria used had almost identical parameters. 30% of patients had a mono/pauciarticular onset, 61% a polyarticular onset, 4% had systemic features and 4% were unknown. 24% were in Steinbrocker class III/IV. 51% had a raised ESR (level not described) suggesting continued disease activity.

Ansell 1969[22]. This published abridged lecture described 168 patients with over 15 years disease duration (84 patients with over 20 years of disease). 17/168 (10%) had died and 2 were lost to follow-up, leaving 149 patients. Of these 18% were in Steinbrocker class III/IV and 24% had both an ESR > 20 mm/hr and soft tissue swelling of the joints.

Goel 1974[13]. This Scottish study described 100 patients with a mean disease duration of 10.1 years. Patients had all previously been admitted to hospital with JA and were recruited retrospectively. The mortality rate was 9%. In the remaining 91 patients, 18% were in Steinbrocker class III/IV and 11% had clinically evident active disease. Patients were split into the same classification as Ansell 1959,[19] with 52% systemic onset, 48% polyarticular onset and 10% pauciarticular. This patient group appeared to be heavily

biased to the systemic onset group. Patients were assessed according to their disease duration; of the 37 patients with a duration over 10 years, 19% were in Steinbrocker class III/IV and 8% had active disease. For those with over 20 years duration (10 patients) 30% were in Steinbrocker class III/IV and 10% had active disease.

Ansell 1976[11]. 243 prospective hospital admissions were described after at least 15 years of disease. Overall there was a mortality rate of 7% and 20% of all patients were classified as Steinbrocker class III/IV. 68/243 (28%) of patients had systemic onset, with 15% mortality and 37% were in functional class III/IV. 26/243 (11%) of patients had rheumatoid factor positive polyarthritis, with 12% mortality. 32/243 (13%) had juvenile ankylosing spondylitis with no associated mortality. Other subgroups included: chronic uveitis 5%, monoarticular 17% (probably including some psoriatic patients as 16% subsequently developed poor hand function), and 26% 'residual forms' left unclassified, although 87% of these had a polyarticular rheumatoid factor negative onset.

The study group was split into 3 groups: employable (defined as men and unmarried women), married women and those remaining in education. In the employable group, 87% of the 156 patients were pursuing normal employment, 10% were unemployed and 4% had died. Of the 52 married women, 85% were able to 'run a home', 2% could not and 13% had died. Of the 35 patients in education, 66% were in 'normal' education, 20% were not and 14% had died.

Hill 1976[12]. This was a retrospective study of clinic attendees with a mean disease duration of 14.5 years. Of the 88 patients identified, 58 were included in the study (22 patients lived out of reach of the investigation). The patients all met the EULAR classification and included 19% systemic onset, 34.5% monoarticular onset and 46.5% polyarticular onset. 6/20 monoarticular onset patients were HLA-B27 positive and had late onset disease. 33% of patients were in functional class III/IV.

This is the first study where a sexual activity interview was included. Of the 19 males in the study, 37% were married (all sexually active) and 67% were single (33% sexually active). Of the 33 women, 42% were married (all sexually active) and 58%

single (68% sexually active). Comparing the groups with published data on sexual activity in single young adults, the women have similar levels of activity 68% vs. 73%, but single men with JA appeared to be much less sexually active 33% vs. 73%.

JA also affected schooling in this group. 31% of the patients in functional class III/IV had 'prolonged absence from school' and 7/19 dropped out of school due to disease. However, more of the study group attended university (31.1%) compared to 15.8% of the general population. 7% of patients were unemployed and 17% were still in education.

Hanson 1977[23]. This was a retrospective study of 123 patients under current review in clinic with a median disease duration of 10 years (range 5-25). 28% of patients were in functional class III/IV and 55% continued to have clinically active disease. The paper did not state which classification was used, but the subtypes described were systemic onset 49%, polyarticular onset 22% and pauciarticular 23%. The paper noted that the patients included were 'those patients most accessible to review', which was likely to bias the study towards more severe disease, with over representation of the systemic subgroup.

Meyer 1978[24]. This was a retrospective study of 30 current clinic attendees over the age of 18 years with pre-pubertal onset of JA. The average disease duration was 16 years and 17% were in functional class III/IV. There were 13% systemic, 37% pauciarticular and 50% polyarticular onset patients. 27% of the pauciarticular group had progressed to polyarticular disease.

63% were employed, 20% students, 3% homemakers and 13% were unemployed. 47% of all patients had 'psychological difficulties'. None of the 4 males in the study group were sexually active. 62% of the women were sexually active.

Stoeber 1981[25]. This was a large retrospective study of 433 previous clinic attendees with a disease duration over 10 years. The subgroups included 48% systemic onset, 42% polyarticular onset and 9% pauciarticular onset. The overall mortality rate was 6.9%, but within the large systemic subset there was a 13.8% mortality rate

predominantly from renal failure secondary to amyloidosis. Overall, 41.3% of patients were in functional class III/IV, of which 43.2% were systemic, 45% polyarticular onset and 17% pauciarticular onset.

Dequeker 1982[26]. This study of 96 prospective serial clinic attendees with a mean disease duration of 13.8 years (range 2-50) had a broad definition of JA. It included widely accepted subsets such as systemic onset, rheumatoid factor positive polyarticular, and monoarticular onset, but also included subgroups not present in the EULAR classification such as psoriatic arthritis and ankylosing spondylitis without peripheral arthritis. In addition it included subsets outside all the definitions such as inflammatory bowel disease related arthritis, SLE/MCTD related arthritis and Reiter's disease. Within this heterogeneous population 24% of patients were in functional class III/IV and 27% had an ESR > 30mm/hr.

Miller 1982[14]. A large group of 394 prospective serial clinic attendees were seen between 1955 and 1978. A relatively low proportion, 265/394 (67%) of patients identified entered the study, with 121 of these being over 18 years of age. The subgroups included those within the ACR criteria: systemic 25%, polyarticular 30% and pauciarticular onset 38% and additionally juvenile ankylosing spondylitis 6%. This was the first study to use a validated questionnaire (HAQ), but it did not include a clinical review of the patients. 16% of patients had a HAQ score over 1.0. 49% of patients reported joint swelling.

77% of patients were working or in education, 11.5% were homeworkers and 11.5% were unemployed. There were no significant differences in either education or employment between the study group and their siblings, apart from polyarticular onset females receiving a lower salary.

Svantesson 1983[27]. This study only considered systemic onset JA patients. It retrospectively reviewed 33 patients with an average disease duration of 10 years (range 4-24). 18 patients had a disease duration over 10 years. 31% were in functional class III/IV, rising to 45% in the over 10 year group. 17% had continued active disease with ESR >20mm/hr; 50% of patients were felt to be in full remission. 42% of patients had

cardiac involvement (30% pericarditis and 12% myocarditis/perimyocarditis). 20% of patients developing pericarditis had their first episode after more than 10 years of disease duration.

Rennebohm 1984[28]. 115/250 prospective clinic attendees had a disease duration over 10 years, with a mean of 14.7 years. Subsets were systemic onset 19%, rheumatoid factor negative polyarticular 26%, rheumatoid factor positive polyarticular 10% and 44% pauciarticular onset. 33% of patients had continuing active disease, rising to 42% if the pauciarticular subset was excluded. 9% of patients were in functional class III/IV. The pauciarticular group probably included a number of spondyloarthropathy patients, as 43% were HLA-B27 positive and 80% were over 10 years of age at onset.

Prieur 1984[29]. This study only considered systemic onset JA patients. It retrospectively reviewed 100 patients, 26 of whom had a disease duration over 12 years, with average duration of 17.5 years. 54% of patients were either active clinically or had a raised ESR. There was little additional data separate from the 100 patients in the main study.

Pedersen 1987[30]. This was a retrospective study of 93 JA hospital admissions with an average disease duration of 10 years (range 3-30). A significant number of patients were aged 3-9 years. The subsets were pauciarticular 67% (3% in functional class III/IV), polyarticular 27% (12% in functional class III/IV) and systemic onset 6%. 40% of the pauciarticular onset group had become polyarticular, correlating with continued disease activity. The study suggested that disease activity in the pauciarticular subset reduced by around 5% per annum, from 65% active at 5 years to 24% active at 15 years.

Doherty 1988[31]. This study looked at 25 functionally independent JA adults. As severely affected individuals were excluded, no patients fell within functional class III/IV. 76% of patients had soft tissue swelling of joints. Subsets were systemic onset 24%, polyarticular 20%, and pauciarticular 44% (12% developed ankylosing spondylitis in adulthood). The AIMS questionnaire was used and showed significant disability compared to controls, despite the group being biased to those with a good outcome. Specific areas highlighted by AIMS included: mobility, physical activity,

household activity, pain, depression and health perceptions. The systemic onset group generally had poorer outcomes than the poly/pauciarticular subsets.

Calabro 1989[2]. 100 patients consecutively referred to a paediatric rheumatology clinic were followed as a cohort for 25 years. Subsets included pauciarticular 32%, 8 of whom (25%) developed extended pauciarticular disease, polyarticular 48% and systemic 20%. 3 patients had died, 15% were in functional class III/IV and 9% had continuing active disease. An increasing proportion of patients achieved remission through the study with 60% at 10 years, 67% at 15 years, 77% at 20 years and 88% at 25 years.

Levinson 1991[32]. The patients in this study were those remaining under review from the Rennebohm study 1984. 101/115 patients were included with a disease duration of 15-20 years. 45% of patients continued to have disease. The percentage of patients in Steinbrocker class III/IV increased from 9 to 17%.

Cabral 1992[33]. This study followed-up 36/39 patients having SEA seronegative enthesopathy and arthropathy, with a mean disease duration of 11 years. This diagnosis has now been superseded by enthesitis related arthritis in the JIA classification. Of the 13 patients described as definite seronegative spondyloarthropathy, 69% developed ankylosing spondylitis, 7% polyarticular JRA and 23% were in remission. Of the 26 patients described as not having definite spondyloarthropathy, 46% developed probable/definite ankylosing spondylitis, 15% had JRA, 8% were fibromyalgic, 8% were in remission and 12% had an alterative musculoskeletal diagnosis.

David 1994[34]. In this study 43 retrospective clinic attendees with polyarticular disease, had an average disease duration of 19.7 years. They included polyarticular onset rheumatoid factor positive and negative, extended oligoarticular onset and systemic onset patients. 57% of patients had active disease (85% of rheumatoid factor positive patients and 14% of systemic patients). 14% were in Steinbrocker class III/IV, with a high level of disability in the extended pauciarticular group from uveitis related blindness.

Health perceptions were measured with the GHQ general health questionnaire, which showed no significant difference between the study group and the general population. Psychological state was measured with the Beck Depression Inventory, which indicated 21% of patients with moderate to severe depression, and the Mental Adjustment to Arthritis scale which showed an increase in anxious preoccupation. 42% of patients had passed school exams at 16 years of age and 21% had a university education. 66% were employed and 30% unemployed.

Ruperto 1997[15]. This was a retrospective study of 227/346 clinic attendees identified in USA and Italy. They were seen initially within 6 months of symptom onset, with a disease duration of at least 5 years. The mean disease duration was 15 years (range 5-36). The HAQ score was over 1.5 in 4% of patients and over 0.5 in 11%. Subsets at onset were pauciarticular 56%, polyarticular 24% and systemic 20%, with mean HAQ scores in the 3 groups of 0.2, 0.4, and 0.4 respectively. Quality of life scale indicated that 77% of patients were either delighted or pleased with their quality of life. Pain VAS (scale 0-3) showed a mean score of 0.5.

Peterson 1997[18]. This is the only published population based cohort of 44/50 JA patients. The average disease duration was 24.7 years. Subsets at onset were pauciarticular 73%, polyarticular 16% and systemic 11%. There was no clinical review; assessment was made on notes review and questionnaire. 65.9% of patients reported joint swelling or pain, but it is difficult ascertain whether this was related to ongoing disease activity. 15.9% remained under medical review for their arthritis. 38.6% of patients had a raised HAQ score, but no data on the degree on functional disability was published.

Musiej-Nowakowska 1999[35]. This was a retrospective study of 39/54 females with the onset of pauciarticular disease before the age of 6, and with a disease duration of at least 15 years. The mean disease duration was 28.1 years. 49% of patients had progressed to polyarticular disease. Prior to pregnancy, 38% of patients had active disease. 94% of those patients with active disease improved during pregnancy. 52% of all women experienced a post-partum flare, (39% if previously in remission and 75% if previously active).

Zak 2000[36]. This was a study of 65/93 patients in the study by Pedersen 1987. The mean disease duration was 26.4 years. 37% of patients had active disease (raised ESR) compared to 41% at 10 years follow up. 11% of patients were in functional class III/IV. 90% of pauciarticular patients were functionally normal (HAQ score=0), whereas 47% of the other disease subsets had a HAQ score of zero. The study showed that functional ability declined between the 10 and 26 year follow-up. The number of patients in functional class I fell from 86% to 68%, class II rose from 6% to 22%, and class III/IV rose from 8% to 11%. No reduction in the proportion of patients with active arthritis was noted between the two studies.

Lomater 2000[37]. This study only considered systemic onset JA patients. It retrospectively reviewed 80 patients with average duration of 10.7 years. There was no indication of the number of patients lost to follow-up. 15% of patients had active disease and 36% were felt to be in remission. 29% of patients were in functional class III/IV. The paper evaluated clinical response to DMARD therapy, but this was based on a retrospective global physician assessment of response, with no published information on inflammatory mediator or active joint count response.

Speigel 2000[38]. As part of an inception cohort of 122 patients with systemic onset JA, there was a subgroup of 33 patients with a disease duration over 10 years. After 6 months of disease, patients were predicted as high risk by the presence of active systemic features (persistent fever or corticosteroid requirement) and a platelet count over 600 $x10^9$/L. At a 10-year review, those with a predicted high risk had a mean HAQ of 1.8 (0.8-2.0) and those at low risk had a mean HAQ of 0.2 (0-0.6). Although data on disease activity was published, the over 10-year group were not evaluated separately.

Archenholtz 2001[39]. This study compared the educational achievements of 32 patients with JA (age range 18-30 years, average disease duration 13.0 years), with 47 patients with early adult onset arthritis (EAOA) (mean age 26.7 years, mean disease duration 6.3 years) and an age / sex matched general population reference group (n=95). 46% of the reference group had attended university vs. 19% of JA patients and 21% of EAOA patients. The EAOA patients were significantly less likely to attend university ($p<0.01$)

than the reference group. However, the JA group did not reach statistical significance because they had a lower mean age than the reference group; the authors failed to include the mean age of the JA group in the paper. Predictive factors for university attendance in the JA group included age and satisfaction with studies on QOLS.

Narayanan 2002[40]. This was a small retrospective study of 26 JA patients who were current clinic attendees over 18 years of age. The subsets included oligoarticular onset (38%), polyarticular onset (50%) and systemic onset (12%). 81% of all patients had active disease and 23% were in functional class III/IV.

Minden 2002[41]. This was a study of 215/260 (83%) patients with JA in a cohort of hospital referrals over 10 years. Mean disease duration was 16.5 years. 17% of patients were lost to follow-up. 74% had oligoarticular or enthesitis related arthritis and tended to have a better functional outcome. Subtypes of JIA included oligoarthritis 40%, polyarthritis 14%, systemic onset 14%, psoriatic 1%, enthesitis related 15% and unclassified 16%. No deaths occurred in the cohort. Reviewing the oligoarticular onset patients: 31% had extended to polyarticular, 7% had psoriasis, 8% developed definite/probable AS and 1% developed inflammatory bowel disease.

55% of patients had active disease (based on clinical and inflammatory assessment), with no correlation between disease activity and subset. The mean HAQ score was 0.22, with 61% of all patients reporting no disability (HAQ = 0). 6.5% of patients had a HAQ score over 1. 39% of patients graduated from high school compared to 33% of the age matched general population. Employment was lower (55% vs. 69% of the general population) and more patients remained in education/vocational training (35% vs. 16% respectively).

Foster 2003[46]. This was a retrospective study of 82/101 adult patients with JA, with a median disease duration of 21 (3-61) years. 39% of patients had active disease on a physicians' global assessment, 72% in the polyarticular onset subset. Subsets included oligoarticular 26% (38% becoming polyarticular), polyarticular 39% (47% rheumatoid factor positive), systemic 15%, psoriatic 9% and enthesitis related 12%. There was an overall median HAQ score of 1.125. This varied with subset from 1.6 in systemic, 1.5

in polyarticular to 0.25 in persistent oligoarticular disease. The HAQ and SF-36 physical summation scores (PSS) worsened with age. Below the age of 30 HAQ = 0.9, PSS = 40, between 30-45 years HAQ = 1.3, PSS = 34 and over 45 years HAQ = 2.2 and PSS = 33. The SF-36 mental summation score did not change with age.

Education was comparable or better than a local control population. 46% of patients obtained qualifications aged 16 compared to 37% of controls and 15% went to university compared to 10% controls. Unemployment was significantly higher (24.6%) than the control population (7.4%).

Flato 2003[47]. A cohort of 268/316 JA hospital admissions over a 5-year period with median disease duration of 14.9 (11.7-25.1) years was assessed for disease variables and patient characteristics present within the first 6 months of disease, that predicted persistent disease, joint erosions and physical disability. 50% of patients were in remission and 36% had impaired physical functioning (HAQ>0). Comparable levels of education, social function and mental health were found compared to the general population. Patients had consistently higher rates of unemployment compared to controls.

Bruinooge 2003[49]. This study prospectively collected data on 104/142 JA patients aged between 18-40 years (average disease duration of 19.2 years, mean age 27). They compared it to a group of 34 adult rheumatoid arthritis patients below the age of 40 (mean age 35). 38% of the JA patients compared to 79% of RA patients were living with a partner, however, the 8-year age difference between the groups made this difficult to interpret. JA subsets included systemic onset 11%, oligoarticular 36%, enthesitis related 12%, polyarticular rheumatoid negative 30% and polyarticular rheumatoid positive 12%. 23% of JA patients reported severe pain.

Comparing AIMS2 outcome for the JA and RA groups, polyarticular JA had worse mobility (1.29 vs. 2.2 respectively), but the duration of disease in the RA group was 7.8 years less than the JA group. Oligoarticular JA patients had better family/friend support than polyarticular JA patients (1.37 vs. 2.25) and less pain (3.35 vs. 4.51).

Oen 2003[16]. This was a study of 393/652 (60%) patients in a multi-centre cohort of patients with JRA, excluding those with spondyloarthropathy (psoriatic arthritis, enthesitis related arthritis, ankylosing spondylitis and inflammatory bowel disease associated arthritis). The 40% of patients lost to follow-up or declining participation tended to be older and more likely to be male. Subsets included systemic onset 12%, pauciarticular onset 57%, polyarticular rheumatoid negative 20% and polyarticular rheumatoid positive 10%. 2% of patients were in functional class III/IV (7% systemic, 0.5% pauciarticular, 3% polyarticular rheumatoid negative and 5% polyarticular rheumatoid positive) and 5.6% had a HAQ score over 1.5 (7, 2, 6 and 7% respectively). 20% of pauciarticular onset patients became polyarticular after a median duration of 4 years. 15% of these extended after 10 years of disease duration. 41% of patients had active disease, 38% were inactive off all medication over 2 years (in remission). The probability of remission at 10 years for patients with systemic, pauciarticular, polyarticular rheumatoid negative and positive was 37, 47, 23 and 6% respectively.

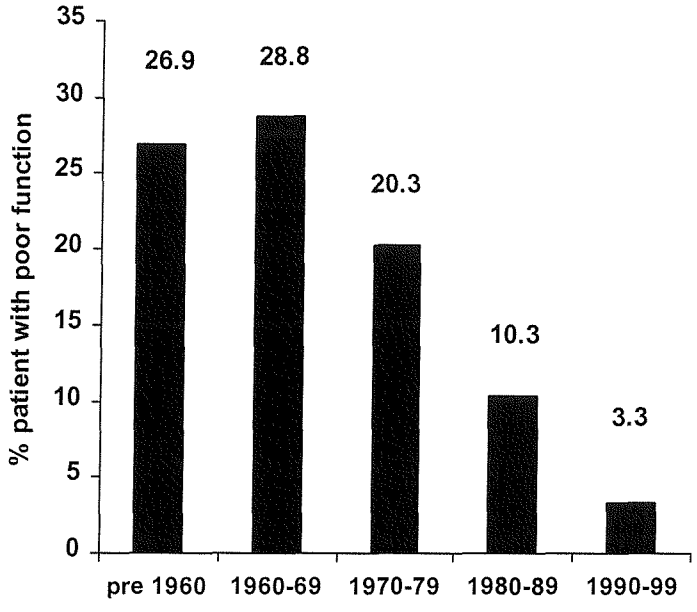
In education 95.8% of patients were at an age appropriate stage of education - 3% fell behind and 1.5% accelerated. Similar levels of high school graduation (85% men, 89% women) were found compared to the general population (79% men, 84% women). However, women were significantly less likely to complete post secondary education (55% men, 55% women) compared to the general population (64% men, 71% women).

Fantini 2003[50]. This was a study of 550/683 (81%) prospective clinic attendees with a mean disease duration of 10.2 years (0.6-36.6). The 153 patients who were lost to follow up tended to have shorter disease duration and higher remission rates. Subsets included oligoarticular onset 61%, polyarticular rheumatoid negative 12%, polyarticular rheumatoid positive 3%, systemic 13% and juvenile spondyloarthropathy 10% (3% psoriatic, 1% ankylosing spondylitis and 5% undifferentiated). 42% of patients had active disease, 25% were inactive and 33% in remission. Remission occurred in the subsets at the following rates: polyarticular onset 18%, extended oligoarticular 13%, persistent oligoarticular 43%, systemic onset 32% and spondyloarthropathy 36%.

1.2.3 The effect of publication date on outcome studies

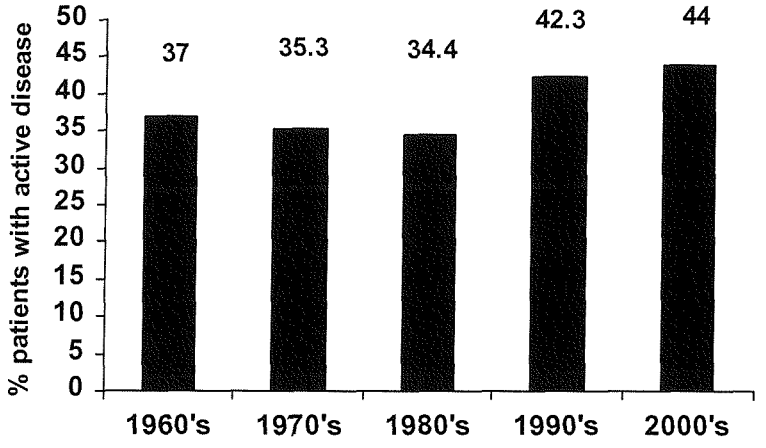
The mean year of disease onset was estimated for each of the long-term follow-up papers by taking the mean years of disease duration from the year of paper publication. Publications were then grouped together into those with a disease onset prior to 1960, 1960-69, 1970-79, 1980-89 and 1990-99. For each of these groups, the mean percentage of patients with poor functional outcome (either Steinbrocker functional class III/IV or HAQ score > 1.5) Figure 1.1.

Figure 1.1 Percentage of patients with poor functional outcome related to mean year of disease onset.



If the mean percentage of patients with active disease at review is determined by grouping articles into the decades in which they were published, disease activity does not seem to have fallen, in contrast to the improvement in functional outcome. **Figure 1.2.**

Figure 1.2 Percentage of patients with active disease related to the decade of article publication



With the introduction and use of disease modifying agents such as sulphasalazine in the 1980's, methotrexate in the 1990's and etanercept in the 2000's, which in randomised trials are more efficacious than placebo[51-54] and produce radiological improvement[55], the improvement in functional outcome from this time is to be expected. The fact that functional outcome started to improve from the 1970's may be an indication of the benefits of earlier diagnosis and treatment of juvenile arthritis, improving rehabilitation techniques or some subtle beneficial effects from disease modifying agents used at the time (gold, chloroquine and d-penicillamine) not borne out in controlled studies.

The unchanged levels of disease activity over the decades are hard to explain in the context of an increasing use of disease modifying agents over the decades. The definitions for disease activity may have become more exacting over time, with patients previously described as inactive who would now be classed as having active disease. Active disease described in these studies tends to be either present or absent and the level of activity is often not recorded. It may be that although the number of patients with active disease is unchanged, the degree of that activity on DMARDs is reduced enough to reduce joint damage and subsequent functional deterioration. Functional outcome is reliant upon both physical and psychosocial effects; the level of disease activity might remain unchanged, with functional improvement occurring from better psychosocial support of patients (although this would be in contrast to the studies showing that disease activity drops with the new generation disease modifying agents).

1.2.4. The effect of prospective and retrospective patient recruitment

Reviewing the overall effect of retrospective and prospective collection of patients with regards to functional outcome, 26.3% of patients collected retrospectively had poor functional outcome (Steinbrocker III/IV or HAQ>1.5) compared to 18.4% of patients collected prospectively. The poorer functional outcome in the retrospective group is likely to be related to those patients with less severe disease being less likely to have continuing long-term follow-up.

1.2.5. The effect of population and hospital based recruitment

The only study to look at long-term outcome for a population based cohort, was in an American population by Peterson[18]. The paper reviewed physical outcome using the HAQ score and the Health Status Questionnaire. Although patients had a worse physical outcome compared to controls and similar mental and social functioning outcomes on the HSQ, it is difficult to compare the HSQ to other measures of functional outcome. 38.6% of patients had a HAQ score above 0, but there is no comment upon the number of patients with significant functional disability using either a higher cut off for the HAQ score or a Steinbrocker functional class. Unfortunately, this makes it difficult to compare the single population-based trial with the majority of hospital-based trials. The only trial to have comparable HAQ score data in a hospital-based study is from Flato[47]. Comparing the two studies, similar proportions of patients had impaired physical functioning (HAQ>0) with 36% in the hospital study[47] and 38.6% in the population study[18]. However, the Peterson study is from an earlier era when a worse functional outcome might have been expected.

Although Peterson does comment on the degree of disease activity within their study group, physical examination and measurement of inflammatory markers were not part of this study. Disease activity was measured on patients' self report of joint swelling or pain on movement of a joint. As might be expected, the percentage of patients reporting swelling or pain (65.9%) was much higher than expected compared to studies using a more robust measure of activity. It is likely that a number of patients reporting pain in a

joint, and therefore counted as active, were reporting joint damage rather than disease activity.

1.2.6 The effect of differing disease classifications

The effects of disease classifications are biased by different populations (Europe vs. USA) and different time periods of introduction and use of EULAR[7] (JCA) and ARA[9] (JRA) classifications in the 1970's-1990's vs. ILAR (JIA)[6] in the 1990's-2000's. When comparing the significant impact of these two factors with the relatively small differences between the classifications, it is difficult to draw conclusions on the effect of classification. No studies have directly compared the long-term outcome of the same group of patients, classified by more than one classification model. This is further complicated by studies combining other disease states such as JSpA[50] and JAS[47, 56] not included in the JCA or JRA classifications.

There are no North American publications that have used the ILAR[6] criteria, so comparing the ARA criteria[9] with the ILAR criteria[6] is not possible. The study by Zak[36] using EULAR criteria[7] in 2000 was similar in many respects to that of Minden using ILAR criteria[6] in 2002 in an adjacent European country. Comparing the Zak and Minden studies, similar levels of disease activity (37% and 55%) and functional outcome (functional class III/IV 11% and 10%) respectively are seen.

1.3 Classification of diseases

1.3.1 Classification of juvenile idiopathic arthritis

In 1897, Sir George Frederic Still distinguished childhood arthritis from adult rheumatoid arthritis (RA).[57] Significantly, he noted that they were a heterogeneous group and commented on the fever found in the systemic form. The first classification of 'Still's disease' was by Ansell and Bywaters[19] in 1959, according to mode of onset. Subsequently, mode of onset formed the basis for classifications proposed by both the American Rheumatism Association in 1977,[8, 9] and the European League Against Rheumatism (EULAR) and the World Health Organisation (WHO) in 1978.[7]

A WHO / International League Against Rheumatism (ILAR) report in 1995[6] proposed the now widely accepted classification based on clinical patterns, including seven different subtypes of juvenile idiopathic arthritis (JIA). These subtypes include: systemic onset arthritis, oligoarthritis and extended oligoarthritis, rheumatoid factor positive polyarthritis, rheumatoid factor negative polyarthritis, enthesitis related arthritis and psoriatic arthritis. An eighth category 'other' is also included in the classification. The criteria that exclude an individual from one of the subtypes above and place them in the 'other' category have been the cause of some debate (see 1.3.1). Exclusion criteria include specific disease states causing joint inflammation, such as systemic lupus erythematosus (SLE), rheumatic fever, septic arthritis and neoplasia.

Table 1.2 The frequencies of JIA subsets observed in the UK[1].

	JIA subset
	Frequency %
Systemic onset JIA	11
Oligoarticular JIA	50
Extended Oligoarticular JIA	
Polyarticular (RhF –ve) JIA	17
Polyarticular (RhF +ve) JIA	3
Enthesitis related JIA	10
Psoriatic JIA	7

The main differences between the EULAR and WHO/ILAR classifications are noted in **Table 1.3.** Individuals may change their classification with time after the initial diagnosis at 6 months **Table 1.4.** This is particularly true for the oligoarticular onset group who often develop disease involving 5 or more joints and enter the extended oligoarticular subset. The systemic onset subset does not change with time, as this subset is entirely dependant on the clinical features at onset rather than subsequent disease progression.

Oligoarticular onset patients without dactylitis/psoriatic nail changes, in whom a family member develops psoriasis, are at present reclassified as 'other'. This exclusion from the oligoarticular onset subsets has been identified as a difficulty in the classification,[58]

and it has been suggested that 'second degree heredity for psoriasis be withdrawn as an exclusion criteria from the ILAR criteria'.[59]

Table 1.3 Differences between the EULAR/WHO 1977 and ILAR 1995 criteria for the diagnosis of juvenile arthritis

Disease name	Juvenile chronic arthritis	Juvenile idiopathic arthritis
Classifying body (date)	EULAR/WHO (1977)[8]	ILAR (1995)[6]
Age at onset	< 16 years	< 16 years
Minimum duration of arthritis	3 months	6 weeks
Classification by onset in the first 6 months of the disease	Systemic onset JCA	Systemic arthritis
	Pauciarticular JCA	Oligoarthritis – persistent extended
	Polyarticular JCA	Polyarthritis RF negative
	Juvenile rheumatoid arthritis	Polyarthritis RF positive
	Juvenile spondyloarthropathy (juvenile ankylosing spondylitis, juvenile psoriatic arthritis, inflammatory bowel disease related arthritis and Reiter's syndrome)	Enthesitis related arthritis
		Psoriatic arthritis
		Unclassifiable (other)

Table 1.4 Changes in subset of JIA after 6 months (excluding systemic onset JIA)

Initial subset	Factor influencing change	Subsequent subset
Oligoarthritis	More than 4 joints affected after 6 months	Extended oligoarthritis
Polyarthritis RF negative	Patient becomes RF positive	Polyarthritis RF positive
Other subsets		Unclassified
RF positive	Patient develops enthesitis or 2 of the following: - painful anterior uveitis - inflammatory spinal pain - sacroiliac tenderness - family history of uveitis, spondyloarthropathy or colitis	Unclassified
ANA positive		Unclassified
Other subsets		Enthesitis related arthritis
Enthesitis related arthritis	Patient becomes ANA positive	Unclassified
RF positive polyarthritis	Patient develops psoriasis	Unclassified
Other subsets		Psoriatic arthritis
RF positive polyarthritis	Family member develops psoriasis	Unclassified
Other subsets with dactylitis/nail change		Psoriatic arthritis
Other subsets without dactylitis/nail change		Unclassified

1.3.2 Systemic onset juvenile idiopathic arthritis

Previously known as Still's disease this form of childhood arthropathy carries the most adverse prognosis, with a significant mortality (up to10% in studies prior to aggressive immuno-modulatory therapies).[27] It is characterised by a quotidian fever for at least 2 weeks, an evanescent non-fixed macular erythematous rash and arthritis. If arthritis is not present (as may be the case in early disease), the diagnosis may still be made in the presence of organ involvement, such as serositis (pericarditis or pleurisy), generalised lymphadenopathy, splenomegaly or hepatomegaly. These features, coupled with a neutrophilia (greater than 13 x 10^9/L in 75% or more of patients) and elevated acute

phase reactants, may suggest infection, particularly if the arthropathy is not evident at disease onset with systemic features. Specific exclusions include neonatal onset multi-system inflammatory diseases, hyper IgD, FAPA (fever, apthous ulceration, pharyngitis and adenopathy), other periodic syndromes such as familial Mediterranean fever and drug hypersensitivity.

Systemic features of the disease frequently pre-date the arthropathy by several months. Some patients exhibit complete remission within 2 years of onset, whereas others have repeated cycles of activity. The mean duration of active disease is 5 years, but some patients have persistent disease into adult life. In some patients the systemic features, including the fever and malaise, respond well to non-steroidal anti-inflammatory drugs (NSAIDs). In most patients, particularly those with persistent polyarticular arthritis and severe systemic features (such as serositis), corticosteroids and disease modifying drugs may be necessary. The established practice has become the use of low-dose methotrexate administered weekly, since most other disease modifying anti-rheumatic drugs (DMARDs) (gold, sulphasalazine, etc.) have not been shown to be of proven benefit. AA amyloidosis is relatively common (7-11%)[60] in this subtype. The use of chlorambucil has dramatically improved the outcome of amyloidosis, but is used with caution in view of its potential toxicity, particularly neoplasia in the longer term. The recent introduction of soluble tumour necrosis factor-alpha p75 fusion protein (Etanercept: Embrel; Wyeth) may signal more specific and effective therapy[61, 62]. Although the systemic onset subset of juvenile arthritis appears to be the least responsive subset to treatment with Etanercept. Systemic features, rather than joint inflammation appear to be particularly unresponsive. In systemic JIA there also appears to be a progressive loss of effectiveness with long term use[61].

1.3.3 Oligoarticular and extended oligoarticular JIA

Oligoarticular JIA affects young girls at least six times more frequently than boys, with a peak incidence below 3 years of age. The prevalence is between 20 and 30 per 100,000, and most ethnic groups are affected.[63] Children with this form of JIA have four or less joints affected within the first 6 months of disease, although as many as one-third may subsequently progress to polyarticular involvement.[64] Those that

subsequently have a cumulative involvement of 5 or more joints are reclassified into the extended oligoarticular subtype. Specific exclusions include a positive family history of psoriasis or spondyloarthropathy and a positive rheumatoid factor.

Although joint pain may be an obvious feature in a disease involving such a young population, the initial presentation is sometimes less obvious. Commonly a parent notices a swollen joint in the absence of symptoms, or observes non-specific features such as poor behaviour or cessation from walking. Almost two-thirds of patients have only one joint involved, and more than 90% have no more than two joints involved in the first 6 months. Children who remain oligoarticular for 5 years are unlikely to progress to extended oligoarticular arthritis.

This group of patients is classically associated with antinuclear factor in the serum (40 to 75%), usually in low titre (less than 1 in 640) with a homogeneous or sometimes speckled pattern. A positive antinuclear antibody (ANA) is very important in identifying those children at highest risk of developing chronic anterior uveitis, which is the most serious potential consequence of oligoarticular JIA[65]. Prior to the use of routine topical steroid treatment in uveitis, over half of those with uveitis became blind or partially sighted.[66] If the ANA is positive regular ophthalmologic screening with slit-lamp examination must be carried out regularly for many years,[67] because the onset of uveitis is often delayed and is initially asymptomatic. Ocular disease affects 20% of those with pauciarticular JIA, usually as anterior uveitis, although rarely isolated posterior disease may be present. The uveitis can persist for between 2 and 15 years and most commonly affects both eyes. Topical corticosteroids and mydriatics are effective in 40% of patients, but intra-ocular injections or systemic corticosteroids are frequently required to prevent the formation of posterior synechiae between the lens and the iris. In some cases, immunosuppressive drugs such as methotrexate, cyclosporin or azathioprine may be necessary to control the uveitis. Overall, 80 to 90% of patients with uveitis are positive for ANA. Girls younger than 2 years of age, presenting with oligoarticular disease have a 95% likelihood of developing chronic anterior uveitis.

1.3.4 Rheumatoid factor positive polyarticular JIA

This is classified as an arthritis involving 5 or more joints during the first 6 months of disease associated with a rheumatoid factor positive test on at least 2 occasions at least 3 months apart. This subtype is generally considered to be the juvenile form of erosive adult rheumatoid arthritis. Rheumatoid nodules and classical vasculitis are seen only in this group, in which all extra articular manifestations found in adult rheumatoid arthritis may occur, including ocular, cardiac and pulmonary involvement.

1.3.5 Rheumatoid factor negative polyarticular JIA

This subtype is classified as a polyarthritis affecting 5 or more joints during the first 6 months of disease in the absence of a consistently raised rheumatoid factor. It tends to occur in young girls below the age of 7. There is a much lower risk and severity of erosive changes on x-ray than in rheumatoid factor positive JIA and prognosis is less severe. There is a lower incidence of chronic asymptomatic anterior uveitis than in the oligoarticular JIA subset, but there is a similar association with ANA positivity.

1.3.6 Enthesitis related arthritis

This subset was previously referred to as either juvenile ankylosing spondylitis or type II pauciarticular arthritis. It is a spondyloarthropathy usually manifesting as a predominantly lower limb arthritis and enthesitis (inflammation of the insertions of tendon, ligament, joint capsule into bone). It is the only form of JIA to show a male preponderance,[68] usually occurring in the early teens. There is a reduced incidence of sacroiliitis compared to adult ankylosing spondylitis. If enthesitis is absent, then the diagnosis can still be made if arthritis and two other spondyloarthropathy related features are present as shown in **Table 1.5.** Acute uveitis is a prominent extra articular feature, usually occurring as an acute unilateral anterior uveitis with a high frequency of recurrence, sometimes in the contra-lateral eye. Anterior uveitis in these cases is likely to be extremely painful and therefore not liable to go undetected, in contrast to the uveitis associated with oligoarticular JIA, which is often asymptomatic and requires slit lamp examination for detection.

Table 1.5 ILAR task force criteria for juvenile enthesitis-related arthritis

Arthritis **AND** Enthesitis **OR** Arthritis **AND** at least one of the following: • sacroiliac joint tenderness • inflammatory spinal pain • HLA-B27 • positive family history of at least one of the following: (a) anterior uveitis (b) spondyloarthropathy confirmed by a rheumatologist (c) inflammatory bowel disease

1.3.7 Psoriatic JIA

This is classified as arthritis associated with psoriasis either in the patient or in a first-degree relative. Arthritis may predate the onset of psoriasis by many years. Even if psoriasis is present, it may be limited in its extent (e.g. natal cleft or scalp). Indicators of psoriatic arthritis in the absence of a psoriatic rash include a positive family history, pitting or onycholysis of the nails and dactylitis, when the whole digit (toe or finger) is swollen as a result of inflammation in the digital joints and associated tendon sheaths. The prognosis of psoriatic arthritis is poorer than that of persistent oligoarthritis.

1.4 Aims

The long-term outcome of adults with juvenile arthritis in the UK, related to the subsets in the new classification of JIA[6] has not previously been described. The impact of JIA across all aspects of adult life needs to be understood.

This is the largest and longest follow-up study to give detailed clinical and functional information on adult patients with long-standing JIA, from all subsets of the disease. They do not represent a true cohort, but are patients who have more severe JIA, and are

those most likely to be encountered in an adult rheumatologists clinical practice. Therefore the aim of this research was not to undertake cohort based epidemiological research, but to document patients' functional, psychological and social support needs, highlighting areas that commonly affect patients' function and independence.

This may improve the ability of health workers to anticipate patients' requirements to keep them independent and assist a more appropriate distribution of health resources in this disabling disease.

The accurate and efficient assessment of disability is an important parameter for measuring outcome in JIA. However, it cannot be considered separately from other aspects of outcome, such as mortality, pain, iatrogenic problems and economic impact. The WHO states that health is 'not merely the absence of disease, but complete physical, mental and social well being'. It is therefore apparent that a full assessment of health outcome is not just physical and should include measures to assess all of the above areas.

1.5 Objectives

- To explore the health status and overall outcome of JIA persisting into adulthood.

Disability is intrinsically linked to ability. Although physical function is often thought of as analogous to ability, it is only one area of an individuals' ability. Ability encompasses a much broader range of skills, many such as social functioning, education, skills within the workplace and coping strategies. These are all to some degree measurable. But there are many areas of ability that are altogether more subjective or ephemeral. These include many of the personality traits such as confidence, determination, assertiveness, strength of conviction, empathy, openness and the ability to show tenderness or love. These are all important abilities that affect an individuals' life and may be influenced by previous experiences, including that of a chronic disease in childhood. The difficulties inherent in describing these subjective qualities objectively mean that they have not been assessed formally in this study. It

does not follow that they are any less important in influencing 'outcome' in its broadest sense, than other more measurable qualities.

- To evaluate the effects on physical function, mobility and requirements for medical intervention.

Functional ability can be measured by self-administered patient questionnaires, interview or physical assessment. This study used the Health Assessment Questionnaire (the benefits/limitations of which are discussed in 2.3.1.). Measurements of mobility were restricted to the use of mobility aids, use of public transport and car adaptations. More thorough evaluation of mobility, such as direct observation of mobility at home and in the workplace fell outside the scope of this study.

- To describe levels of pain and predictive factors for pain.

There are numerous potential measurements of pain as discussed in 2.3.2. Pain varies in its intensity and nature with time. This study did not record pain in any longitudinal fashion. Therefore an individual's experience of pain over time was not addressed. However, with the relatively large numbers of patients involved in the study, the pain levels for the group as a whole are likely to be representative of the overall pain experience. The impact and severity of pain is dependant upon the individual experiencing that pain. Patients may under report pain and their effectiveness in controlling it as part of a coping mechanism (such as denial) to deal with the pain.

- To assess educational achievement and employment status.

Measurement of employment and education tends to be reasonably straightforward. However, unemployment is caused by many different factors such: as being unable to find a job, being unable to retain a job, motherhood, doing voluntary work, being a housewife and deciding not to work, as a life choice.

- To assess social function and satisfaction.

There are objective end points of social functioning such as having children and living with a long-term partner. There are validated questionnaires (discussed in 2.3.2.) that can be used to reflect the breadth of an individuals' social spectrum and their satisfaction with the support that they derive from their social environment. With crude end points such as marital state and offspring, individuals can be reasonably compared to their siblings (who will be of similar age and originate from the same social background). The extent of social interaction is dependant upon both internal (degrees of extraversion and introversion, self-confidence, personal choice of sociability) and external (social environments being amenable to those with physical disability, discrimination by others) determinants. In many respects it is the satisfaction an individual feels they have with their social environment and support which has more impact, rather than the number of individuals involved within their social network.

- To explore sexual activity including age of first sexual experience and disease related sexual problems.

This area can have a major impact on the individual, but is an area where both investigator and patient can encounter difficulty. Assessment can be made by either interview or questionnaire (2.3.2). With either form of assessment there are concerns that a patients may not be as frank as in other areas, particularly if the interviews are carried out in the presence of relatives, or if the patient and interviewer have not built up a rapport.

- To describe the impact of depression and anxiety in adults with JIA.

There are a number of questionnaires to measure depression and anxiety (described in 2.3.2.) However, describing the impact of mood abnormality on an individual differs from the simpler task of measuring mood dysfunction. There also needs to be an attempt to link any mood dysfunction detected to the other areas of an individual's life, and to try and begin to describe how these areas overlap and affect each other.

In this study although pain and iatrogenic problems are addressed to a degree, there are areas that are not fully examined. Economic impact of chronic disease is touched upon in terms of looking at employment. The additional time for interview and questionnaires involved in thoroughly investigating the socio-economic effects of JIA was felt to place too many demands on the study group. Because the study group is not a cohort it is not possible to make any realistic estimate of mortality.

2 CHAPTER II - Methods

2.1 Patient recruitment

I studied 261 patients with JIA over the age of 18 years, who were either still attending hospital clinics or who had continuing contact with Wexham Park Hospital, a paediatric rheumatology tertiary referral centre. Patients were identified through searching a computerised database, by manually searching patient lists and reviewing patient notes. Local ethics committee approval was obtained.

2.1.1 Patient enrolment

Patients eligible for study entry were sent a letter (Appendix 1.1) describing the aims and requirements of the study and were asked to return a signed consent form (Appendix 1.2). Non-responders were sent a second study letter and subsequently contacted by telephone to ensure that their contact address was correct. Because of the close proximity with the now closed national centre for juvenile arthritis at the Canadian Red Cross Memorial Hospital, Taplow, there were a high number of JIA adult patients both living in the locality and travelling in from outside the region.

2.2 Patient assessment

Patients were assessed individually by interview and clinical examination. Subsequently a full review of the patient's clinical notes was performed. A self-report psychological, functional and handicap questionnaire was given to each patient at interview and the methods for completing the questionnaire were discussed. Patients completed the self-report questionnaires later and returned them by post 93.9% (231/246). If patients could not attend Wexham Park Hospital for review, they were reviewed in local research clinics or in their homes. The interview and examination was performed by the primary examiner in the majority 245/246 of cases.

2.2.1 Interview and clinical assessment

During the interview, clinical examination and notes review, information was gathered on height, weight, marital status, offspring, education, employment, discrimination in the workplace, social activities, sexual function, housing, transport and social service support (Appendix 1.3.).

There are a large number of articular indices that can be used to assess the amount of synovitis. They vary in terms of joints assessed from 28[69] to 68[70]. Some, such as the Ritchie index[71] only assess tenderness. Most others record tenderness and swelling. Some are joint counts, i.e. the results equates to the number of abnormal joints[69, 70]. Others, such as the Ritchie index, are joint scores in which the abnormality of each joint is graded. Joint counts are more reproducible than joint scores. The Thompson-Kirwan index[72] weights the score according to the size of the joint involved and has been shown to correlate strongly with the CRP. Joint inflammation was therefore measured using the Thompson-Kirwan index,[72] a 38 joint scale identifying joints that were both tender and swollen with a score for each individual joint (Appendix 1.4.). The range of movement in all joints and leg length discrepancy and other growth abnormalities were recorded (Appendix 1.5.).

A modified Steinbrocker functional class[3] (Appendix 1.6.) was allocated to allow comparison with older studies with class II (functional ability to conduct normal activities), split into IIa (despite discomfort) and IIb (despite limited mobility or fixed flexion deformity).[34] This assigned patients to one of four functional classes, based on the physician's assessment.

Sexual function/dysfunction can be assessed by interview or validated questionnaires. The questionnaires are universally long and complex and many patients find that they enquire into their sexual lives in too much depth for patient comfort. Research performed by the investigator (JP) on a population of rheumatoid arthritis patients, had to be altered during the course of the study because of the poor acceptance and completion (below 30%) of a sexual function questionnaire. Sexual function was therefore assessed by interview, in a private setting, with relatives excluded at request.

Questions on sexuality were placed towards the end of a structured interview on health and social functioning, so that a reasonable rapport could be established with each patient.

2.2.2 Notes review

The mode of onset, duration of disease, family history of psoriasis and subsequent pattern of disease were extracted from the patients' notes. Each patient was assigned to a disease subtype using the World Health Organisation/International League Against Rheumatism (ILAR) classification[6] (Appendix 1.7.). The history of any concurrent disease, both JIA related (e.g. amyloidosis, uveitis and osteoporosis) or otherwise was noted. A history of pharmacological interventions, adverse reactions, surgical procedures and subsequent complications were recorded using a structured questionnaire (Appendix 1.8.).

2.3 Self-report questionnaires

2.3.1 Functional Status

The oldest and simplest way of measuring functional disability is by the Steinbrocker functional class[3], which has subsequently been revised[73]. The revised version assigns patients to one of four functional classes based on the physician's opinion. It is insensitive to short-term change, but has been used successfully in following-up cohorts of patients over long periods of time. Using the Steinbrocker functional class has the benefit of allowing the function of the present study group to be compared directly with other patient groups, which have been studied in the past.

Patients' perceived functional ability was assessed, with the most widely used validated self-report functional questionnaire in musculoskeletal disorders, the Health Assessment Questionnaire (HAQ)[17] (English version)[74] (Appendix 1.9.). There is now extensive literature showing the value of the HAQ in assessing the short-term response to treatment, and as a strong predictor of future disability and premature death[75].

The HAQ score assesses function through 20 questions covering 8 functional areas: dressing and grooming, rising, eating, walking, hygiene, reach, grip and activities.

Three components were evaluated for each area:

a) the degree to which daily functions were difficult to perform
b) use of special aids or devices
c) activities for which the assistance of another person was required.

Each question was scored 0 to 3 (0 = no difficulty, 1 = some difficulty, 2 = much difficulty and 3 = unable to do). The question with the highest score determined the score for that functional area. If aids or help were required then a minimum score of 2 was recorded for the corresponding functional area.

An alternative measure of functional ability is the Arthritis Impact Measurement Scale (AIMS)[76]. This takes longer than the HAQ to complete and has been less widely used in published studies. It does have the benefit of being disease specific to arthritis, but this specificity restricts the comparison of the study group to other long-term disabled patient groups. For these reasons the AIMS was not used in this study.

2.3.2 Psychological Status

Although there is a wealth of literature showing that pain is a sensitive measure in short and medium trials in arthritis, there is little data on the use of pain as an outcome measure over long periods of time. The little data available suggests that pain may plateau rather than worsen with disease duration[77].

A number of self-administered questionnaires have been developed to measure **pain**, the best known of which is the McGill Pain Questionnaire[78]. In a study design, which includes a number of self-administered questionnaires, it was felt that a simple visual analogue scale would be less time consuming. As part of the arthritis self-efficacy scale[79], the patients' perception of control over their pain was measured.

Pain was therefore assessed using a 100mm horizontal visual analogue score (VAS) (Appendix 1.10.). The end points of the scale were 'no pain' (zero) and 'most severe pain' (100). Patients were asked how much pain they had because of their illness over the past week. The VAS is a reliable and valid method for assessing pain. Straight, horizontal and ungraded lines have been shown to be the most sensitive[80].

Emotional state can be determined by a number of self-report questionnaires. Three of the most widely used measures of depression are the Beck Depression Inventory (BDI)[81], the Center for Epidemiological Studies Depression Scale (CES-D)[82] and the General Well-Being Schedule depression subscale (GWB-D)[83]. These were studied in rheumatoid arthritis[84]. 19/45 items within the three questionnaires were felt to be likely to differ in patients with RA and control subjects because of the presence of RA, regardless of psychological status. These items were generally those questions that could be affected by somatic disease as well as by depression, such as 'I am too tired or fatigued to do a lot of the things I used to do'. Adults with JIA experience similar symptoms to adults with rheumatoid arthritis, in view of this it was felt that using the depression scales noted above would be likely to bias (increase) the amount of depression seen in the study group.

Emotional state was therefore determined using the 'Hospital Anxiety and Depression Scale[85] (HAD) (Appendix 1.11.). This was a specifically designed measure of emotional disturbance in patients with physical illness. It consists of 14 items, 7 specific for depression and 7 measuring anxiety. Those items measuring depression have been selected so that somatic items on fatigue or sleep disturbance (often caused by physical illness) are mostly excluded. Anhedonia (a lack of enjoyment in life) is emphasised. This reduces the risk of falsely indicating depression in patients with arthritis due to their illness, rather than mood, increasing the specificity of the scale for genuine depression.

Behavioural strategies that were adopted to limit the impact of arthritis were assessed by using two scales. The 'London Coping with Rheumatoid Arthritis Scale[86] (Appendix 1.12.), is a specific 36 item scale developed specifically for inflammatory joint disease. It assesses specific coping characteristics and identifies four broad

patterns of coping strategy, which have been shown to impact in different ways on levels of pain and stiffness. The catastrophising subset of the 'Coping Strategies Questionnaire[87] (Appendix 1.13.) is a 6-item subset assessing the cognitive strategy of catastrophising, which highlights passivity during periods of extreme pain. Outcome in arthritis and other chronic pain conditions is adversely affected in passive responders.

Cognition was reviewed using two of the three subscales from the Arthritis Self Efficacy Scale[79] (Appendix 1.14.). This is an arthritis specific scale measuring a patient's belief that they can control certain symptoms or perform certain tasks. This scale has three subsets assessing the areas of pain, function and 'other symptoms'; the function subset was not included in the extensive measurements of function used in this study.

Social support refers to the social, emotional and other supports which are provided by an individual's social contacts. There are a variety of social support measures that have been used in health-related research[88]. Many of these suffer by failing to distinguish between either social support and social network, or between different categories of support such as practical and emotional. Measures such as the Significant Others Scale[89], have the advantage of providing measures of practical and emotional support across a range of key individuals. Unfortunately, scales that are able to fully assess social interactions and support are universally long and time consuming to complete, and in the context of a study with numerous self-assessment questionnaires, a shorter questionnaire was felt to be more appropriate.

Social support that included both the perceived satisfaction of support and the level of support was therefore measured using the Sarason 'Short Form Social Support Questionnaire[90] (Appendix 1.15.). This provides a short and reliable measure of two aspects of social support, but does not attempt to distinguish between types of social support such as practical and emotional. The Sarason scale, a 6-item version of the original 27-item social support questionnaire, was used to assess the number of contacts providing various forms of support and the patient's satisfaction with that support. Studies on social support have shown that it isn't the *actual* support that exists that benefits patients, but the *perceived* level of social support.

2.3.3 Handicap Status

The ***patients' perception of the handicap*** due to the effects of JIA was the final part of the questionnaire. The WHO expresses the impact of chronic disease in terms of impairment, disability and handicap.[91] Impairment is defined as 'any loss or abnormality of psychological or anatomical structure or function'. Disability is defined as 'any restriction or lack (resulting from impairment) of ability to perform an activity in the manner or within the range considered normal for a human being'. Handicap is defined as 'a disadvantage for an individual resulting from an impairment or disability that limits or prevents the fulfilment of a role that is normal (depending on age, sex and cultural factors) for that individual'. Handicap not only relates to the degree of functional disability, but also the effect of the disease on an individual's present life role, their needs and future aspirations in life. It tends to reflect the sociological and economical affects of a chronic disease on the individual.

The Disease Repercussion Profile[92, 93] (Appendix 1.16.) is a 6-part assessment of the perceived impact of arthritis on a patient's lifestyle including: physical activity, social activity, employment and finances, relationships with family, friends and partners, appearance or body image and emotional state. It is often possible to alleviate handicap, even when impairment and disability seem insurmountable. For example, the inability to walk out of doors unaided (disability) may not be amenable to change, but the resultant handicap (being housebound) may be alleviated by the use of a wheelchair.

2.4 Piloting the study

Before the study was started, 3 patients were asked to enter a pilot of the study by having a structured interview and physical examination and then filling in the questionnaire in the presence of the primary investigator.

After the interview, each patient was asked about the clarity of questions, the flow and length of the interview, any areas that they felt they were uncomfortable with and any suggestions to improve the interview. Responding to the feedback, changes were made to the interview proforma, placing the questions on sexual function and health later into

the interview to allow more of a rapport to build up between patient and interviewer before broaching these sensitive areas. No changes were felt to be required to the examination process.

The questionnaire completion was in the presence of the primary investigator, but without assistance. After the questionnaire had been completed, each patient was asked about the length of time required for completion, the clarity of the questionnaires and the perceived relevance of each questionnaire. The average time for completion was 35 minutes. Patients felt that as the questionnaire only had to be filled in on a single occasion, the length of time required was acceptable. In general, the clarity and relevance of the questionnaires was felt to be reasonable. This was subsequently borne out, with a 93.9 % completion rate of the questionnaire within the study.

2.5 Laboratory tests

All patients that were in agreement 231/246 had phlebotomy performed. This was performed at interview and blood was sent for a laboratory-based score of disease activity. Laboratory tests included haemoglobin, white cell count, platelets, erythrocyte sedimentation rate (ESR) (Westergren method), C-reactive protein (CRP), ANA and immunoglobulin levels.

2.6 Statistical Analysis

Statistical support was given initially from the Centre for Statistics in Medicine, Oxford University and later from Professor Peter Jones, Professor of Statistics, Keele University, Staffordshire. Before the study was started, extensive discussions were undertaken to ensure that the patient database would be compatible with the statistical software package. Steps were taken to ensure that the database complied with the Data Protection Act.

Data from the study proforma was initially entered into Microsoft Access and Excel. All calculations were performed using the statistics package SPSS 10.0 for Windows.

Throughout the thesis, for assessment of differences between groups, Mann Whitney U tests and chi-squared tests were used. Univariate associations were expressed as Spearman correlation coefficients (two-tailed) due to the non-normal distribution of disease variables. In all analyses the p value ≤ 0.05 was considered to be statistically significant.

Multiple regression analysis was performed using candidate predictive factors, which were initially assessed using a matrix of Spearman's correlation coefficients. Those factors with significant correlation coefficients ($p<0.05$) were entered into a forward stepwise multiple linear regression analysis, testing for predictive variables. As each variable is entered into the model, the remaining variables that are no longer significant predictors are removed from the pool of potential predictive variables being assessed. In all multiple regression analysis tables in the thesis, F is the ratio of the regression mean square to the residual mean square (test of the null hypothesis).

3 CHAPTER III - Patient Demographics

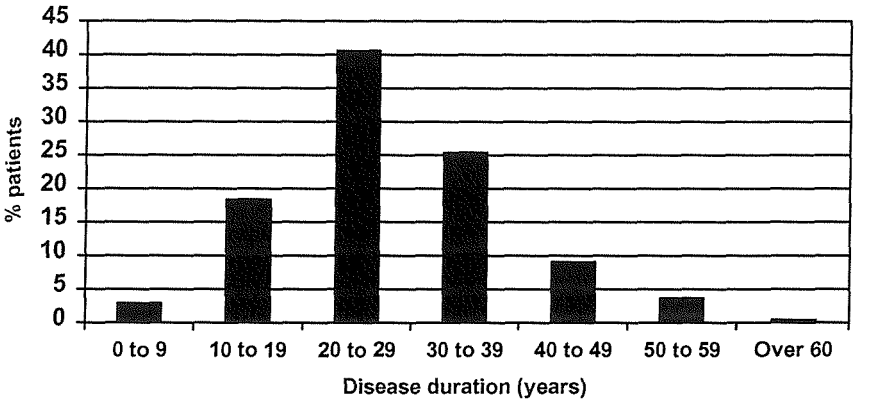
3.1 Study patients

Of the 261 patients with a putative diagnosis of JIA over the age of 18 years, two were not included in the study because they did not meet the ILAR criteria for JIA, (1 with juvenile dermatomyositis, 1 with adult onset systemic arthritis). Of the remaining 259 patients, 246 (95%) participated in the study. Self-report questionnaires were completed and returned by post by 231 (93.9%) of the patients interviewed. 52 patients (21%) were reviewed either in local clinics or at home. The same investigator (JP) performed the interview and examination in 245 (99.6%) of cases. Phlebotomy was performed on 238 (96%) of patients.

3.2 Patient demographics

A total of 246 patients were included in the study (176 females and 70 males), with a gender ratio of 2.5:1. This was consistent with other comparable studies.[18, 34, 36] The mean patient age was 35.4 years (range 19-78, S.D. = 11.1). The mean age at disease onset was 7.1 years (range 0.5-17.5, S.D. = 4.5). The mean disease duration was 28.3 years (range 8-73, S.D. = 10.8). **Figure 3.1.** Less than 3% of patients had a disease duration below 10 years and 9% below 15 years.

Figure 3.1 Duration of disease on review



3.2.1 JIA Subsets

The frequency of each JIA subset is shown in **Table 3.1.** This is contrasted with the overall frequencies of each subset based on data from the British Paediatric Rheumatology Group database.[1] Since this is a long-term follow-up study, but not cohort based, the frequencies found in the study group varied from those seen in a paediatric population. Those subsets with a good outcome such as persistent oligoarticular arthritis were underrepresented in the study group as smaller numbers required long-term follow-up. In cohort studies one-third of oligoarticular patients progress to polyarticular involvement,[64] but in this study almost 80% of the oligoarticular subset had progressed to polyarticular disease. This is related to the need for long-term medical review of polyarticular arthritis. Similarly, the most severe forms of JIA (systemic and rheumatoid factor positive polyarthritis) comprised just 14% of a paediatric population, but 36.3% of the adult study group.

Table 3.1 Frequency of JIA subsets in adult and paediatric populations

	BPRG paediatric subset[1]	Study subset	
	Frequency %	Frequency %	Number
Systemic onset JIA	11	21.2	52
Oligoarticular JIA	50	6.1 28.5	15 70
Extended Oligoarticular JIA		22.4	55
Polyarticular (RhF –ve) JIA	17	16.7	41
Polyarticular (RhF +ve) JIA	3	15.1	37
Enthesitis related JIA	10	13.1	32
Psoriatic JIA	7	5.3	13

Table 3.2 shows that, as expected, the age at disease onset was significantly lower in the oligoarticular, extended oligoarticular and polyarticular (rheumatoid factor negative) JIA subsets and significantly higher in the polyarticular (rheumatoid factor positive), enthesopathy related and psoriatic JIA subsets. Patients in the oligoarticular subset were also significantly younger and had shorter disease duration. The lower disease duration may suggest that either soon after reaching adulthood a number of

patients no longer require continuing rheumatological review, or that patients continue to extend the number of joints involved in adulthood.

Table 3.2 Age at onset, duration of disease and age at review of each JIA subset

	Age at onset	Duration disease	Age at review
Systemic onset JIA	6.5 (S.D. 3.8)	29.3 (S.D. 10.4)	35.8 (S.D. 10.4)
Oligoarticular JIA	5.0 (S.D. 4.5)**	19.5 (S.D. 6.3)*	24.4 (S.D. 5.4)*
Extended Oligoarticular JIA	4.9 (S.D. 3.8)*	29.2 (S.D. 10.1)	34.9 (S.D. 9.7)
Polyarticular (RhF –ve) JIA	5.8 (S.D. 4.3)**	29.7 (S.D. 10.0)	35.5 (S.D. 10.4)
Polyarticular (RhF +ve) JIA	10.2 (S.D. 3.8)***	29.0 (S.D. 12.8)	39.1 (S.D. 13.0)
Enthesopathy related JIA	10.0 (S.D. 3.3)***	27.0 (S.D. 12.1)	37.0 (S.D. 12.4)
Psoriatic JIA	9.9 (S.D. 3.3)****	27.4 (S.D. 10.2)	37.3 (S.D. 10.5)

* lower compared to other subsets ($p < 0.001$)

** lower compared to other subsets ($p < 0.05$)

*** higher compared to other subsets ($p < 0.001$)

**** higher compared to other subsets ($p < 0.05$)

3.2.2 Clinical inflammation and raised inflammatory markers

In previous studies the proportion of patients with active disease has ranged between 31-55%,[2, 5, 11, 23, 34, 36] dependant upon the selection and severity of the population studied. **Table 3.3.** In the current study disease activity was separated into clinical inflammation determined by the Thompson Kirwan scale[94] and the presence of raised inflammatory markers measured with C reactive protein and ESR. **Table 3.4.**

Table 3.3 Hospital based studies of functional outcome in JIA

Author (Year)	Length of follow up (years)	Active disease %
Laaksonen (1966)[5]	>15	41
Ansell (1976)[11]	>15	31
Hanson (1977)[23]	>10	55
Calabro (1989)[2]	>25	35
Levinson (1991)	>15	45
David (1994)[34]	>10	48
Zak (2000)[36]	>20	37

Table 3.4 Degrees of clinical and laboratory inflammation

Degree of inflammation	Clinical activity TK index	Laboratory activity	
		CRP	ESR
None	(0) 56.7%	(0-6) 45.6%	(0-25) 43.3%
Moderate	(1-99) 24.5%	(7-49) 45.2%	(26-60) 43.4%
Severe	(>100) 18.8%	(>50) 9.2%	(>60) 13.3%

As disease duration increased, there was no significant change in clinical or laboratory evaluation of disease activity. Physical function (HAQ) is strongly related to laboratory measures for inflammation CRP and ESR ($p<0.001$), but there was no significant relationship with clinical inflammation. Although there was no correlation between laboratory measured inflammation (ESR/CRP) and individual JIA subsets, high levels of clinical inflammation (TK index) were most commonly found in the extended oligoarticular subset ($p = 0.001$).

Systemic onset JIA is associated with the highest levels of inflammation in the paediatric population and the worst long-term functional outcome. However, in adulthood the levels of clinical inflammation are significantly lower than any other subset ($p<0.02$). This effect was also described by David et al[34] and suggests that the concept of arthritis 'burning out' may hold true in this specific group.

3.2.3 Growth

A generalised growth failure is seen in JIA secondary to either severe inflammation (previously described as occurring most commonly in systemic JIA)[95] or treatment with corticosteroids.[5, 96, 97] If normal function is maintained, growth will be relatively normal. Without use, muscles, joints and bones fail to fully develop. Active disease in puberty may cause premature epiphyseal closure and lead to stunting from this mechanism alone.

The mean male and female heights were 170.8cm and 158.2cm respectively, 3.8cm shorter and 4.2cm shorter than the general population. The standard deviations were also increased indicating a greater variation in height than the general population. **Table 3.5.** 145 patients out of 246 had been prescribed oral steroids in the past. There was a significant association between the length of time on oral steroids and both final male ($p = 0.001$) and final female height ($p < 0.01$), implicating steroids in growth retardation. However, steroids are usually reserved for use in severe inflammatory arthritis, the latter also having a negative effect on growth. Growth defects were strongly associated with physical disability (HAQ) ($p < 0.001$ for men and women). Perhaps surprisingly, there was no link between growth defects and height.

Table 3.5 Patient height compared to the general population

	Male patient mean height	Male population mean height	Female patient mean height	Female population mean height
Height (cm)	170.8	175	158.2	162
S.D.	13.2	6.5	9.6	3.5

The mean male and female weights were 67.6kg and 58.5kg respectively, which were similar to the predicted mean weight of the general population (64kg and 57kg). The standard deviation was increased indicating a greater variation of weight than the general population. **Table 3.6**

Table 3.6 Patient weight compared to the general population

	Male patient mean weight	Male population mean weight	Female patient mean weight	Female population mean weight
Weight (kg)	67.6	64	58.5	57
S.D.	15.9	9	14.6	9

Growth defects are commonly due to active arthritis affecting the growth of certain joints during childhood. These growth defects can be related to premature fusion of epiphyses including: a small mandible (micrognathia), reduction in the size of fingers, hands, forearms, toes or feet. The defects may also be due to localized overgrowth; classically this causes leg length discrepancy, which it is postulated may be secondary to hyperaemic knee synovitis. However, in this adult group of JIA patients with a high incidence of lower limb major joint replacement, leg length discrepancy may be iatrogenic. **Table 3.7.** Leg length discrepancy predisposes to a scoliosis, which although is initially compensatory, may become permanent.

Table 3.7 Incidence of disease related growth defects in adults with JIA

Specific growth defect	**Incidence of defect % (number of patients)**
None	62.7 (154)
Micrognathia (chin)	24.0 (59)
Fingers	2.0 (5)
Hands	2.0 (5)
Forearms	9.7 (24)
Toes	4.0 (10)
Feet	1.6 (4)
Leg length discrepancy $\geq$ 2 cm	11.5 (28)

There was a significant association between leg length discrepancy $\geq$2 cm and systemic JIA ($p < 0.001$). In the systemic subset 16/52 patients (30.8%) had leg length discrepancy, but all of them had previously undergone total hip replacements, 11/16 (68.8%) having had revision of a hip prosthesis. Across all subsets 23/28 (82.1%) with

leg length discrepancy had a hip prosthesis. This indicated that in adults with JIA the main cause of leg length discrepancy was surgical.

Micrognathia was more commonly seen in systemic JIA (32.7%) than in other subsets ($p < 0.05$). Only 2 of these patients had had major jaw surgery in the past, indicating that the main cause for micrognathia was growth restriction due to temporomandibular joint (TMJ) inflammation in childhood. The long term TMJ damage related to this inflammation was shown in the range of TMJ movement measured as mouth aperture between the teeth. 40.2% of patients had restricted TMJ movement (mouth opening less than 3.0cm). In the systemic subset, this was more common involving 53.8% of individuals ($p < 0.05$).

3.2.4 Physical disability

The disability of patients was measured with the modified Steinbrocker score (Appendix 1.6.) and the Health Assessment Questionnaire (Appendix 1.9.) and related to JIA subset **Table 3.8.**

Long-term outcome studies of JIA show that between 23-48% of patients will have severe functional limitation (Steinbrocker classes III & IV).[5, 10-12, 19, 23, 25, 34, 36] This study group mirrored these findings, with severe functional limitation shown to be present in 37.1% (91/246) of all patients (Steinbrocker III or IV) and 42.9% (99/231) of all patients using HAQ score (1.5 or higher to indicate severe disease). Systemic JIA was strongly related and rheumatoid factor negative polyarticular JIA weakly related to poor functional outcome. Conversely, both oligoarticular and enthesitis related JIA tended to have relatively few functional problems. The level of disability (HAQ score) significantly deteriorated as the duration of disease increased ($p < 0.001$).

Table 3.8 Disability related to JIA subset

	Health Assessment Questionnaire % of individuals (number of patients)		Modified Steinbrocker Scale % of individuals (number of patients)	
	0 – 1.49	1.5 – 3.0	I, IIa and IIb	III and IV
	Mild	Severe	Mild	Severe
Systemic onset JIA	37.5 (18)	62.5** (31)	34.6 (18)	65.4** (34)
Oligoarticular JIA	100 (14)	0* (0)	93.3 (14)	6.7* (1)
Extended Oligoarticular	58 (30)	42 (22)	63.6 (35)	36.4 (20)
Polyarticular (RhF –ve)	50 (19)	50*** (19)	58.6 (24)	41.4 (17)
Polyarticular (RhF +ve)	47.2 (17)	52.8 (18)	62.2 (23)	37.8 (14)
Enthesopathy related	83.9 (25)	16.1* (5)	93.7 (30)	6.3* (2)
Psoriatic JIA	75 (9)	25 (3)	77.2 (10)	22.8 (3)
All subsets	57.1 (132)	42.9 (99)	62.9 (155)	37.1 (91)

* Subset negatively correlates with poor functional outcome ($p < 0.001$)

** Subset positively correlates with poor functional outcome ($p < 0.001$)

*** Subset positively correlates with poor functional outcome ($p < 0.05$)

3.2.5 Mobility

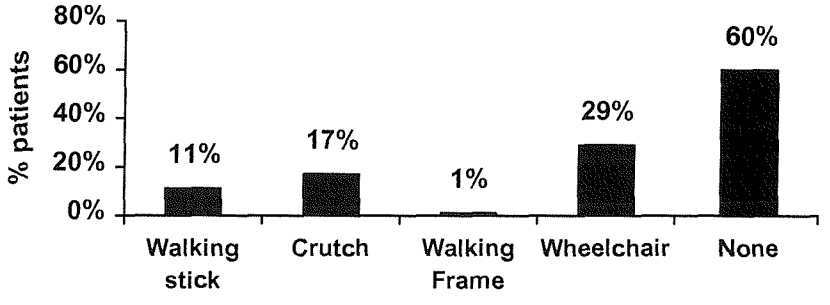
Mobility is an important factor in any patient group with a high level of disability. It has potential detrimental effects not just on travel, but also employment, social activities and economics. If mobility is compromised then in turn independence is also threatened. Patients often cope with poor mobility by adjusting their life around the problems encountered.

3.2.6 Mobility aids

Mobility aids were used by 40% (98/246) of the patient group to reduce the impact of physical impairment, with some individuals using more than one aid **Figure 3.2**

Wheelchair use was the most common aid (29% of all patients) and was found by most to be the most practical way of negotiating long distances. The wheelchair was generally used as an adjunct to walking and less than 1% (2/246) of individuals were completely wheelchair bound. The use of crutches rather than walking sticks was an indicator of poor hand function.

Figure 3.2 The use of mobility aids in patients requiring assistance



3.2.7 Accommodation

For many patients the choice of housing was influenced by their mobility. This was particularly the case when considering access to the upper storey of a house: the majority 58% (143/246) of the study group had difficulty climbing stairs; 33% (81/246) of patients had chosen single storey ground floor accommodation; 22.4% (55/246) of those with stairs required assistance in the form of stair rails or a stair lift. 21.1% (52/246) of patients had a ramp or no steps into their accommodation. 17.1% (42/246) of patients used aids within the kitchen and 37% (91/246) used aids in the bathroom.

3.2.8 Car use

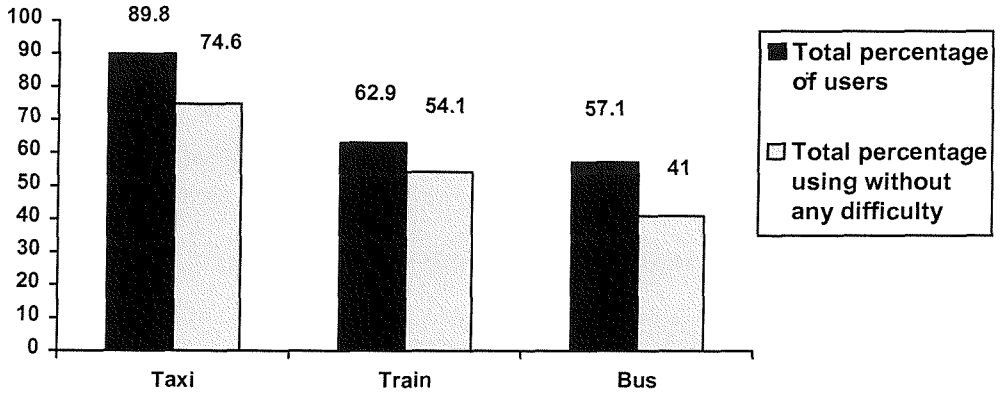
Car use is a critical aspect of independent living. 58% (143/246) of the study group received the mobility part of the disability living allowance, giving financial support to car ownership and any modifications required by disabled drivers. The vast majority of the group drove themselves; often this was despite significant physical disability as shown by their HAQ scores. 53.4% of cars driven were automatic, which required less hand dexterity and arm strength. 28.4% of cars had required between 1 and 9

adaptations, ranging from simple measures such as extra mirrors to extensive adaptations such as steering wheel, gear and brake controls.

3.2.9 Public transport

Public transport accessibility is a contentious issue amongst physically disabled pressure groups and for good reason. Access to large cities such as London, where driving and parking are troublesome, can be made almost impossible by poor disability access. However, access to large cities can be an integral part of many careers, in particular professional non-manual jobs. As shown in **Figure 3.3,** taxi services were widely used, but the use of both train and bus services to cater for the disabled population was sub-optimal. Around 60% of JIA patients had difficulty in using both trains and buses. Although not included in the study, those patients who were geographically near an underground train service almost universally found the underground hard to negotiate on their own.

Figure 3.3 Percentage of people using public transport and ease of use



3.3 Medication use

3.3.1 NSAIDs

All of the patients had required non-steroidal anti-inflammatory drugs at some stage of their illness; 72.4% (178/246) of patients still required NSAIDs while 30.1% (74/246) used simple analgesics. In total, 79.7% (196/246) of patients required some form of analgesic support.

Adverse reactions to NSAIDs necessitated their withdrawal at least once in 59% (145/246) of patients. 12.7% of all NSAIDs were discontinued because of adverse gastrointestinal side effects including: nausea, vomiting, abdominal pain, GI bleeding and iron deficiency anaemia. Gastrointestinal protection from a combination of antacids, H_2 antagonists, proton pump inhibitors, misoprostol and bismuth had been used by 53.7% (132/246) of patients. Iron supplements (other than during pregnancy) had been prescribed for iron deficiency anaemia in 53.3% (131/246) of patients, but this did not always precipitate discontinuation of the NSAID or further investigation.

3.3.2 DMARDs

74.4% (183/246) of patients had received disease modifying anti-rheumatic drugs to control their disease process. 36.3% (89/246) of patients were still taking a DMARD. There was an association between length of DMARD use and JIA subset, with enthesitis related JIA ($p < 0.005$) and oligoarticular JIA ($p < 0.001$) being prescribed DMARDs for a smaller percentage of their disease duration. Patients with systemic onset JIA ($p < 0.005$) and rheumatoid factor positive JIA ($p < 0.005$) received DMARDs for a larger proportion of their disease. The percentage of patients taking each DMARD at some time in their disease course is described in **Table 3.9.**

3.3.3 Steroids

58.9% (145/246) of patients had previously taken oral corticosteroids. 24.4% (60/246) of patients were still taking oral steroids. The average duration of steroid use was 11.6 years, but with a wide variation (range 0.2 - 46.1 years, S.D. 10.35 years). Systemic onset JIA patients took steroids for longer than other subsets (14.4 years, $p < 0.01$). The risk of corticosteroid-induced osteoporosis had been at least partially addressed by the use of anti-osteoporosis agents including bisphosphonates, calcium/vitamin D preparations and HRT, used in 25.2% (62/246) of patients.

Parenteral steroid administration was common with 83.7% (206/246) of patients receiving at least one intra-articular injection of steroid. 22.9% (56/246) had received

at least one intravenous pulse of steroid, with 6.9% (17/246) of individuals requiring more than 3 pulses.

Table 3.9 Use of DMARDs in long term JIA

DMARD	Percentage of patients previously on each drug (number of patients)	Percentage of patients presently on each drug (number of patients)
Chloroquine	33.5 (82)	0.0 (0)
Hydroxychloroquine	20.9 (51)	7.3 (18)
Sulphasalazine	30.8 (76)	10.2 (25)
Methotrexate	40.7 (100)	23.2 (57)
Penicillamine	41.8 (103)	2.8 (7)
Gold	67.6 (166)	2.0 (5)
Cyclosporin	5.5 (13)	0.4 (1)
Cyclophosphamide	0.8 (2)	0.4 (1)
Chlorambucil	8.5 (21)	1.6 (4)
Azathioprine	16.5 (41)	3.7 (9)
Dapsone	0.8 (2)	0.0 (0)

3.4 Orthopaedic intervention

The inflammation related to juvenile arthritis is sufficient to cause such severe joint damage that patients require prosthetic joint replacement, often at a young age. Prosthetic joint replacement was common in the study group, with total hip joint replacement being most frequent. 51.2% (126/246) of the patient group had at least one major prosthetic joint replacement. The frequencies of joint replacement and joint revision with JIA subset are shown in **Table 3.10.** The subgroups of systemic JIA, rheumatoid factor positive and negative polyarticular disease had the majority of orthopaedic interventions. Other joint replacements were comparatively infrequent (shoulder 4.9% (12), elbow 3.3% (8), wrist 1.6% (4) and ankle 1.6% (4)), with a negligible level of revision of these joints.

Table 3.10 Percentage of patients in each subset with prosthetic joints

Subset	Total % patients with joints replaced (number of pt)	Total % patients with hip prostheses (number of pt)	Total % patients with revision of hip prostheses (number of pt)	Total % patients with knee prostheses (number of pt)
Systemic	75.0* (39)	59.6 (31)	40.4 (21)	30.8 (16)
Oligo	13.3** (2)	13.3** (2)	13.3 (2)	6.6 (1)
Ext. oligo	38.1 (21)	32.7 (18)	9.1 (5)	23.6 (13)
RhF –ve poly	56.1 (23)	51.2 (21)	34.4 (14)	34.1 (14)
RhF +ve poly	64.9 (24)	61.3 (23)	10.8 (4)	40.5 (15)
Enthesitis	34.4** (11)	28.1 (9)	3.1 (1)	9.4 (3)
Psoriatic	15.4** (2)	15.4 (2)	0.0 (0)	7.7 (1)
All subsets	49.4 (122)	43.1 (106)	19.1 (47)	25.6 (63)

* positive correlation ($p < 0.001$)

** negative correlation ($p < 0.01$)

44.3% (47/106) of patients with total hip replacements and 7.9% (5/63) of patients with total knee replacements had undergone revision of their joint prosthesis at least once. The total number of joints replaced in individual patients was related to a number of factors. **Table 3.11.**

Table 3.11 Variables associated with prosthetic joint replacement

	Psychological variables			**Function**
	Pain	Anxiety	Depression	HAQ
p<	0.001	0.01	0.001	0.001
	Disease demography			**Inflammation**
	Disease duration	Height	Growth defects	CRP
p<	0.001	0.001	0.01	0.001

The risk of requiring a joint replacement was particularly increased in the systemic subset. Other predisposing factors were disease duration, poor function, presence of growth defects, height retardation and continuing active inflammation. Patients in the

oligoarticular, enthesitis related or psoriatic subsets required a prosthetic joint much less frequently. The strong associations with pain, depression, anxiety and poor function are likely to be secondary to the combined effects of joint surgery and severe arthritis rather than causative factors. The two patients in the persistent oligoarticular subset who required hip replacements were re-assessed to ensure that they were not misclassified and actually lay within the enthesitis related subset. Neither patient was HLA-B27 positive; one had previously had the classical occult uveitis of oligoarticular JIA and the other had a disease onset below 5 years of age. This suggests that the classification of oligoarticular JIA for these 2 patients was appropriate.

3.5 Discussion

The long-term follow-up of patients with such chronic disease highlights the impact of a chronic arthritis starting in childhood. The accurate and objective assessment of disability is an important component in measuring outcome in JIA. However, it should not be considered separately from other aspects of outcome, such as mortality, pain, economic impact and the psychosocial effects of the disease.

The majority of previous studies have not separated the disease subsets, which are known to affect prognosis and outcome. The degree of disability in our patients mirrored that found in other studies. Severe functional limitation was present in 37.1% (Steinbrocker III or IV) and 42.9% (HAQ score > 1.5) of all patients. Patients with all patterns of polyarticular disease had a higher risk of severe functional limitation that was most evident in the systemic JIA subgroup.

At the time this study was performed, 6 studies with disease duration of over 10 years had used psychological, social or functional assessment measures in addition to the crude, invalidated and physician centred Steinbrocker classification.[3]

Doherty[31] assessed 25 patients with a mean disease duration of 13 years, but only included those who were functionally independent (Steinbrocker I & II). Even in this group of patients with a good functional outcome, significant impairments were

observed in mobility, physical activity, household activity, depression, pain and health perceptions measured by the Arthritis Impact Measurement Scale (AIMS).[76]

Wirral[98] reviewed the social outcome of 61 patients with a mean disease duration of 16.8 years, by telephone interview and questionnaire. Scores for physical and social function were lower than the normal population measured by RAND 36 Item Health Survey.[99] The deficit in function was not related to disease subtype and there were normal scores for pain, emotional well-being and employment. These findings contrast to other studies and may reflect differences in study design and population.

David[34] assessed 43 patients with a mean disease duration of 19.7 years, but only included patients with polyarticular disease, thus excluding a number of subsets and skewing the patient group towards those with a poor outcome. The limited numbers of patients in each subgroup probably accounted for some unexpected findings in the study.

Ruperto 1997[15]. This was a retrospective study of 227/346 clinic attendees identified in USA and Italy. They were seen initially within 6 months of symptom onset, with a disease duration of at least 5 years. The mean disease duration was 15 years (range 5-36). The HAQ score was over 1.5 in 4% of patients and over 0.5 in 11%. Subsets at onset were pauciarticular 56%, polyarticular 24% and systemic 20%, with mean HAQ scores in the 3 groups of 0.2, 0.4, and 0.4 respectively. Quality of life scale indicated that 77% of patients were either delighted or pleased with their quality of life. Pain VAS (scale 0-3) showed a mean score of 0.5.

Peterson[18] performed the only population based long-term outcome study on 44 patients, with a mean duration of disease 24.7 years. Because it was a population-based study, a high proportion of oligoarticular arthritis (73%) was found in the study group. This makes assessing the small numbers of patients in other subgroups difficult. Even in this group of patients, where the majority had comparatively good outcome, over 35% had abnormal function.

Zak[36] reviewed a group of 65 patients with an average 26.4 years of disease. This was a thorough review of function, disease activity and symptomatic outcome, but did not include any psychological parameters. Active disease was present in 37% of patients, 11% had severe disability and 22% had undergone JIA related major surgery. The same group had also been reviewed after 10 years of disease; increased physical disability, handicap and requirement for surgery had developed in the intervening 16 years. No reduction in the proportion of patients with active arthritis was noted in the later study.

Because this study was a long-term follow up and not cohort based, the frequencies of JIA subgroups varied from those seen in the UK paediatric population (British Paediatric Rheumatology Group database).[1] Those subsets with a good outcome such as persistent oligoarticular arthritis are under represented in the study group, since many go into remission, do not require continuing hospital review or are under the care of a local adult rheumatologist. In the paediatric rheumatology population up to 50% of oligoarticular patients subsequently extend to a polyarthritis.[100] In our study population almost 80% of the oligoarticular subset had progressed to polyarticular disease, indicating the need for continuing medical review of those patients whose arthritis extends. The subsets with the worst functional prognosis (systemic and rheumatoid factor positive polyarthritis) comprised just 14% of the paediatric rheumatology population, but 36.3% of our study group.

The concept that JIA becomes less inflammatory with time and 'burns out', was not supported by the finding that around 50% of all patients continued to have detectable inflammation late in the disease course. The actual level of continuing active disease may be even higher than 50%. Deformities can worsen and synovitis may be discovered at surgery in the absence of clinically evident synovitis. The possibility of occult disease activity further increases the potential for poor outcome and the need for aggressive therapy. The systemic subset has the worst functional outcome and in the paediatric population it has the highest levels of inflammation, sufficient to cause 57% of JIA related AA amyloid.[60] In contrast, in our study, levels of clinical inflammation (TK index) were lower in systemic onset JIA than in any other subset. A reduction in the level of inflammation at long-term follow-up in systemic onset JIA has also been

described by David[34] and Svantesson[27] and suggests that the concept of arthritis 'burning out' may hold true in the systemic onset subgroup.

Mobility was commonly affected. 40% of patients used some form of mobility aid and almost 60% claimed mobility benefit. Most patients were able to get to a car unassisted and drive themselves. However, public transport posed problems with about 40% of individuals unable to use trains or buses. When travelling into large urban centres where parking and driving are troublesome, this may have a major impact on the ability of an individual to consider certain careers and to attend urban venues.

Because this was a long-term study, the DMARDs used largely reflect historical treatment regimes. More recently, there is increasing use of methotrexate[101, 102] and suphasalazine[103, 104] and a corresponding decline in the use of gold, penicillamine and chloroquine. Similarly, the patients remaining on corticosteroids are now being initiated on osteoporosis protection, when previously the osteoporotic effect of these drugs was not addressed.

The need for prosthetic joint replacements increases with severity and time. The influence of severe disease in childhood, as evidenced by the correlation between the presence of prosthetic joints with systemic onset JIA, growth defects and height retardation, highlights the importance of disease control from an early age. With the recent introduction of more effective immunosuppressive agents and earlier aggressive intervention, the proportion of these patients who go on to require surgery may well reduce in the future.

Adults with JIA have significant levels of disability, often related to severe continuing active disease over a prolonged period. There is a clear requirement for good transition from paediatric/adolescent to adult rheumatology and high quality ongoing care.

4 CHAPTER IV - Predictive Factors for Pain in JIA

4.1 Introduction

Pain is a major symptom in all chronic inflammatory arthropathies such as JIA[6] and rheumatoid arthritis. The presence of extensive active inflammatory arthritis is accompanied by increased pain and also worsening fatigue and morning stiffness. It has the potential to detrimentally affect the health status of arthritis patients. Despite increasing studies assessing pain in children with JIA and extensive literature on pain experienced in rheumatoid arthritis and osteoarthritis, pain related to JIA continuing into adulthood has been understudied.

Chronic pain is both a biological and psychological phenomenon.[105] Pain assessment methodologies tend to focus purely on one or other of these domains. For a more complete understanding of pain, methods need to be integrated together. Early studies of pain in children suggested that children with arthritis experienced less pain than their adult counterparts.[106-108] These studies are now thought to be misleading and the recent use of age appropriate measures of pain have indicated that pain related to JIA is more prevalent than previously thought.[109-112] Sherry et al[108] found that 97% of polyarticular JIA children at a routine paediatric rheumatology clinic reported some degree of pain. The levels of pain were generally mild to moderate, but there was considerable variability in pain ratings. Schanberg et al[110] found that 25% of JIA patients had pain levels in the mid to high ranges of pain measurement scales. This was despite regular attendance at a specialist centre where analgesic control might be considered to be optimal.

Most pharmacological pain treatments reduce pain by managing the underlying disease process and decreasing the symptoms of physical discomfort. However, disease severity is not the only relevant predictor of pain in children. Multiple regression models have examined multiple predictors of present pain intensity in children with JIA and results suggested that the combination of medical state and disease severity explains only a small proportion of overall pain variance. Iliowite et al[113] found that joint inflammation accounted for only 10% of the variance in pain scores. Thompson et

al[114] found that arthritis subtype and disease activity only accounted for modest amounts of variance (8% and 1% respectively) in JIA patients' reported pain.

This relatively weak relationship between disease related variables and pain variance reported by children with JIA has led to studies using multi-dimensional assessments (demographic, medical status and coping strategy variables). Schanberg et al[110] explained just over 50% of the variance in reported pain severity. Disease activity emerged as a significant predictor of pain, but coping strategies also explained a large proportion of the variance in pain. Children, like adults, who felt that their self-efficacy over pain was strong and who had little tendency to catastrophize[87] had significantly lower pain intensity scores. It appears that psychosocial variables such as coping strategies and self-efficacy are important when considering the treatment of pain in children with JIA.

Both children and adults with persistent pain develop strategies to cope with, minimize, or deal with their pain. In particular passive coping strategies and catastrophising (i.e. negative/destructive thinking) have been consistently linked to not only higher reported pain, but also altered perception of painful laboratory stimuli and poor functional outcome. Other strategies (e.g. calming self-statements, distraction, etc.) have been shown to be effective and lead to lower pain reports. Few studies however, have examined the efficacy of pain coping strategies in JIA.

Newman et al[86] classified 158 RA patients into 4 groups on the basis of their overall pattern of coping strategy, using the 'London Coping with Rheumatoid Arthritis Scale'.
Group 1 used *denial*, avoided others when in pain and looked to friends for support.
Group 2 (the largest group) did not strongly embrace or reject any of the coping strategies and are described as '*passive copers*'.
Group 3 tended to be most *open* and active in the manner in which they attempted to deal with the stresses of arthritis.
Group 4 were *dependant* upon others using friends and religion for support and also using rest, diet and distraction to cope with their arthritis.

Reports of pain and stiffness were significantly lower for group 3 '*open copers*'; similarly this group had less physical disability and higher levels of psychological well-being. This suggests that there are different groups of individuals who have differing coping strategies, and these impact on the reporting of symptoms and disability.

These studies begin to explain the variables that affect the perception of pain by children with JIA. For each patient the predictive factors influencing pain levels are likely to change as they enter adulthood. As the length of these patients' disease course increases, levels of disability and joint destruction worsen. A combination of functional limitation, reduced levels of support and increasing demands, can begin to restrict the levels of independence achieved in adolescence. As the 'learning' period of childhood and adolescence is left behind, coping skills develop and previous experiences (both good and bad) affect patients' psychosocial state. There is therefore a need for the application of multi-dimensional assessments to patients who have had JIA and continue to have symptoms into adulthood.

4.2 Methods

4.2.1 Assessment of pain

Patients rated their present levels of pain using a 100mm horizontal pain visual analogue score (VAS). The end points of the scale were 'no pain' (zero) and 'most severe pain' (100). Patients were asked to draw a line on the scale to show how much pain they had had over the past week, because of their illness. The 'Arthritis Self Efficacy Scale'[79] was also completed since this has a specific subset indicating a patient's belief that they can control their pain.

Levels of medication use, with a particular bias to non-steroidal anti-inflammatory drugs and simple analgesics were reviewed, giving an indication of the number of patients requiring continuing analgesic support. The degree of medication use was not included as a candidate predictive factor as increasing analgesic requirement is most likely to be a reaction to pain, rather than a causative factor.

4.2.2 Candidate predictive factor collection

A wide-ranging multi-dimensional assessment of the patient group was performed as described in the 'Methods' chapter. A large number of candidate predictive factors with the potential to affect pain or its' perception were reviewed as detailed below.

Patient related physical demography - gender, weight, height, physical activity, mobility and growth defects.
Patient related social demography - education, employment, marital state, offspring, discrimination encountered, housing and disability benefits.
Disease related demography - age at onset, disease duration, JIA subset, medication use, medical and surgical history including JIA associated diseases (i.e. uveitis, osteoporosis and amyloid).
Physical assessment - joint inflammation (Thompson Kirwan scale[72]), range of joint movement, modified Steinbrocker score[3, 34] and UK validated version of the 'Health Assessment Questionnaire' (HAQ).[17, 74]
Laboratory assessment for current disease activity - CRP, ESR (measured by the Westergren method), haemoglobin, white cell count, platelets and IgG.
Emotional state using the 'Hospital Anxiety and Depression Scale (HAD).[85]
Coping Strategies - using two separate scales, the 'London Coping with Rheumatoid Arthritis Scale'[86] and the catastrophising subset of the 'Coping Strategies Questionnaire'.[87]
Cognition using the 'Arthritis Self-Efficacy Scale'[79] which measured a patient's belief that they control certain symptoms or can perform certain tasks. This scale has 3 subsets assessing the areas of pain, function and 'other symptoms'.
Perceived satisfaction and level of **social support** using the Sarason 'Short Form Social Support Questionnaire'.[90]
Perceived handicap using the 'Disease Repercussion Profile'[93] - an assessment of the perceived impact of arthritis on a patient's lifestyle including physical activity, social activity, employment and finances, relationships with family, friends and partners, appearance or body image and emotional state.

4.2.3 Predictive analyses

Candidate predictive factors were initially assessed using a matrix of Spearman's correlation coefficients. Those factors with significant correlation coefficients were entered into a hierarchical multiple regression analysis, testing for variables predicting pain measured on a pain visual analogue scale.

4.3 Results

4.3.1 Disease activity and function

At the time of the study, 56% (138/246) of subjects had clinically inactive disease (Thompson Kirwan Index score 0), 25% (61/246) had moderate activity (score 1-100) and 19% (47/246) had high disease activity (score 100+). There was a significant correlation between pain measured on the pain VAS and level of clinical inflammation (Thompson Kirwan index) ($p < 0.001$ - Spearman's correlation coefficient (two tailed)).

129/239 (54%) of subjects had no evidence of activity using inflammatory markers (CRP 0-6), 88/239 (37%) had moderately raised inflammatory markers (CRP 7-50) and 21/239 (9%) had a markedly raised inflammatory response (CRP 51 or more). There was a significant correlation between the level of inflammation (CRP) and pain (pain VAS) ($p < 0.001$ - Spearman's correlation coefficient (two tailed)).

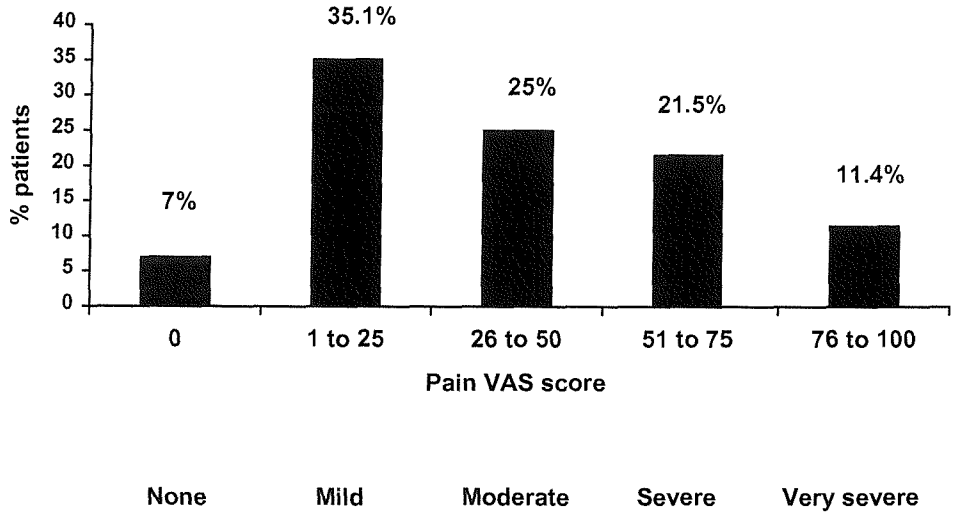
There was a high incidence of severe functional limitation within the study group, with 37.7% (93/246) of patients in Steinbrocker class III or IV. Using a more objective measure of function, the Health Assessment Questionnaire (HAQ), 39.4% (91/231) had severe functional limitation scoring 1.5 or higher.

There was a significant correlation between pain (pain VAS) and level of functional limitation (HAQ score) ($p < 0.001$ - Spearman's correlation coefficient (two tailed)). However, control over pain had no association with CRP and a weaker association with clinical inflammation ($p = 0.005$).

4.3.2 Pain

The pain VAS indicated that only 7% (7/231) of patients were pain free. 32.9% (76/231) of patients scored over 50 on the pain scale indicating severe or very severe pain. **Figure 4.1**. The mean pain score for JIA overall was 37.9. Assessing the mean pain scores for each JIA subset showed that oligoarticular patients experienced less pain (mean 20.5, $p < 0.01$) and that systemic patients experienced more pain (mean 47.9, $p < 0.05$). **Figure 4.2.** 72.4% (178/246) of patients still required NSAIDs, 30.1% (74/246) used simple analgesics and in total 79.7% (196/246) of patients required some form of analgesic support. There was a significant correlation between pain intensity and analgesic use ($p < 0.001$).

Figure 4.1 Levels of perceived pain measured by pain VAS

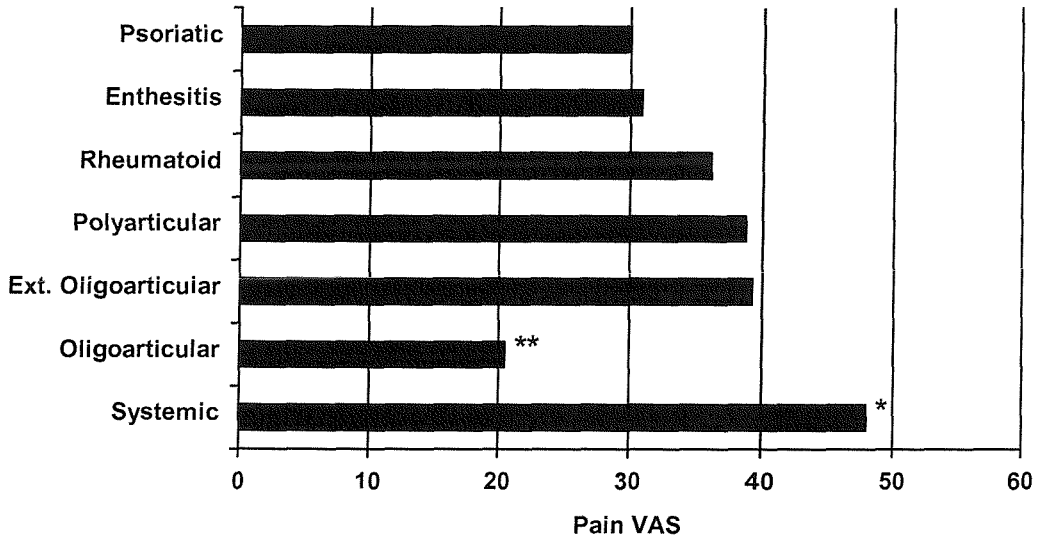


4.3.3 Pain self-efficacy

Perceived control over pain, as measured by the Arthritis Self-Efficacy Scale, was complete/good in 32% (74/231) of patients, moderate in 45.2% (104/231) and poor/very poor in 22.8% (53/231). **Figure 4.3.** The mean self-efficacy score for JIA overall was 65.0. Assessing the mean pain scores for each JIA subset showed that rheumatoid factor negative polyarticular JIA patients perceived more control over pain (mean 69.9, $p < 0.05$). There was a similar trend in oligoarticular and psoriatic JIA groups but did not reach significance due to the relatively small number of patients in

each group. Systemic patients experienced less control over pain (mean 60.4, $p < 0.05$). **Figure 4.4.** There was an inverse correlation between pain VAS and pain self-efficacy score ($p < 0.001$). Pain self-efficacy was not associated with CRP and only weakly related to clinical inflammation ($p < 0.005$).

Figure 4.2 Mean Pain VAS Related To JIA Subset



* compared to other subsets $p < 0.05$

** compared to other subsets $p < 0.01$

Figure 4.3 Level of pain self-efficacy

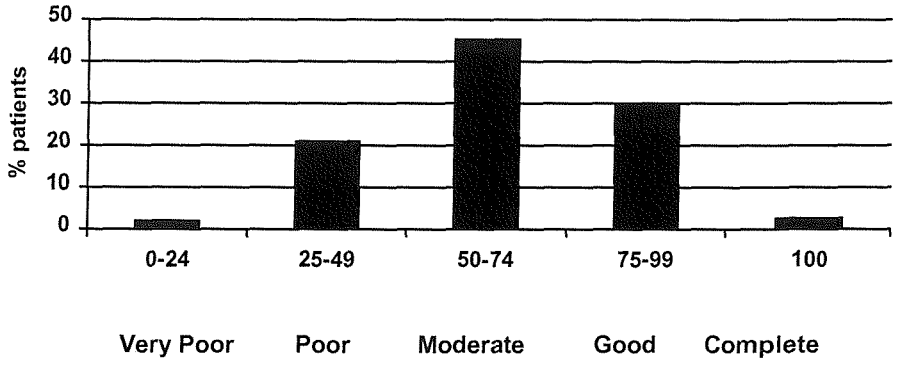
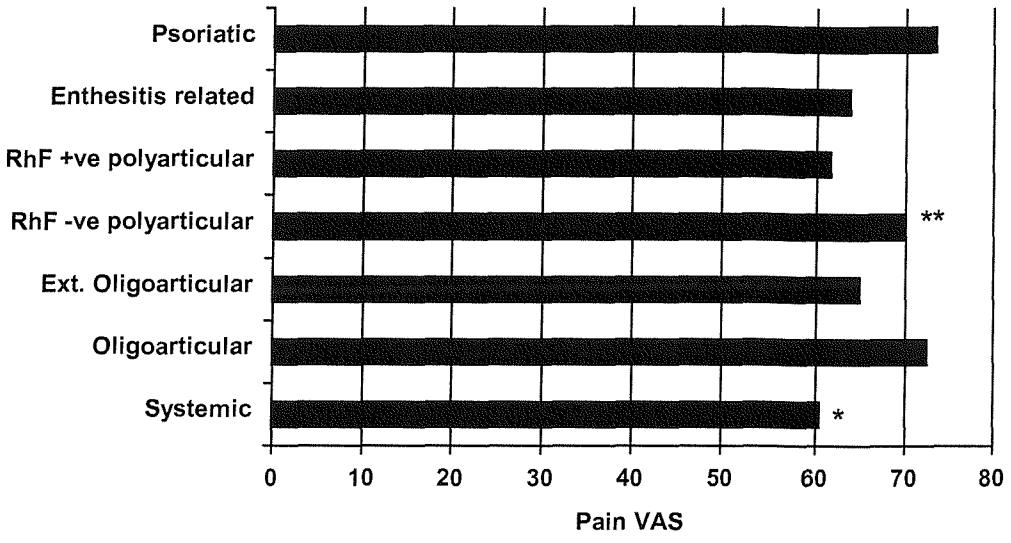


Figure 4.4 Mean Self-Efficacy For Pain VAS Related To JIA Subset



*	compared to other subsets	$p < 0.05$
**	compared to other subsets	$p < 0.05$

4.3.4 Predictive analysis

Those factors with significant correlation coefficients ($p < 0.05$) were entered into a hierarchical multiple regression analysis, testing for variables predicting pain measured on a visual analogue scale. These included: **patient demographics** (age, gender, height, education, employment and marital state), **disease demographics** (subset, age at onset, duration of disease, surgery and specific growth defects), **function** (HAQ score and Steinbrocker class), **disease activity** (Thompson-Kirwan scale, ESR and CRP) and **psychological measures** (previous depression, anxiety and depression HAD scores, London Coping with Rheumatoid Arthritis Scale, catastrophising subset, self-efficacy scales for pain and symptom control, social contact satisfaction and social contact frequency).

The best model of forward stepwise multiple regression analysis testing identified 6 variables that independently made a significant contribution to the levels of pain. This predictive analysis explained a substantial proportion (39.6%) of the total variance in pain VAS readings. **Table 4.1.** The three most important predictors of pain were physical disability as measured by HAQ, the presence of a dependant coping strategy (with patients using religion for support and distraction to cope with their arthritis) and

the degree of control patients felt they had over pain. There was only a small effect on pain by the level of current clinical disease activity and no effect from laboratory indicators of inflammation.

Table 4.1 Predictive factors for pain in adults with JIA

	% variance predicted	F	p <
Function (HAQ)	18.3	48.1	0.000
Dependant coping strategy (group 4)	10.6	32.2	0.000
Pain self-efficacy	4.9	16.3	0.000
Denial coping strategy (group 1)	2.5	9.2	0.003
Clinical inflammation (TK index)	2.2	8.3	0.005
Previous depression	1.1	4.9	0.027
Total	**39.6**		

A separate hierarchal regression analysis on the four individual coping strategies suggested that they were relatively independent of other factors. There was poor predictability varying from just 1.4% of variation for passive coping strategies to 11.3% for open coping strategies.

Hierarchal regression analysis on control of pain (self-efficacy) identified 3 categories of variables accounting for 24.3% of control. **Table 4.2.** Increasing pain levels understandably reduced the perception of pain control, whilst depression and poor coping skills also adversely affected self-efficacy.

Table 4.2 Predictive factors for self-efficacy of pain control in adults with JIA

	% variance predicted	F	p <
Depression (HAD)	14.7	37.7	0.001
Pain VAS	6.9	30.3	0.000
Catastrophising	2.7	23.8	0.005
Total	**24.3**		

4.4 Discussion

It is difficult to extrapolate the results of paediatric JIA pain studies to an adult population since changes over time are not predictable. For adults with JIA time has two conflicting effects. Firstly, patients with few problems may be lost to long-term follow-up, increasing the overall severity of the remaining non-cohort patient group. Also, increasing length of disease often leads to increasing levels of disability, which in turn can lead to lower levels of psychological well-being. Secondly, both time and transition through adolescence may lead to more effective psychological coping mechanisms. Individuals may also learn to adjust their perceptions of their role in society and become content to live within any physical constraints.

The results of this study showed that pain intensity in adults with JIA (mean score 37.9) was higher than in reports for children with JIA[110, 111, 115] (scores ranging from 16.3 to 29.7). This is likely to be related to a combination of increasing pain secondary to accumulated disease related damage over time and the severity of the group studied. However, it is also possible that adults were simply more prepared to express pain on a self-report questionnaire.

In this study, 40% of the variation of pain could be accounted for by 6 independent variables **Table 4.1**. These variables, which significantly influenced the perception of pain intensity, lay within two areas. Firstly, there was a direct physical influence on pain shown by the effects of both physical function and joint inflammation, and secondly a psychological influence on pain including self-efficacy, previous depression and coping strategies.

This contrasts to the predictive factors for pain in the paediatric JIA population. JIA most often follows a fluctuating course with periods of flare and quiescence. Periods of flare are associated with increased disease activity shown by a greater number of joints involved or a rise of inflammatory markers. Schanberg et al[110] showed that in paediatric JIA, disease activity, present in 84% of patients reviewed, predicted 28% of the variation in pain levels. In this study, however, the role of disease activity (as indicated by clinical inflammation measured on the TK index) as a predictor

for pain became less important, accounting for just 2.2% of variation in pain **Table 4.3**. This was despite a study population with long standing disease and detectable, active joint inflammation present in almost half.

Table 4.3 Predictive factors for pain (% variation) in adult and paediatric JIA

Predictors for pain in paediatric JIA (Schanberg et al)[110]		**Predictors for pain in adult JIA**	
Disease activity	28%	Function (HAQ)	18%
Control over pain	21%	Pain coping strategies	13%
Age	2%	Self-efficacy	5%
Disease duration	1%	Disease activity	2%
Pain coping strategies	1%	Previous depression	1%

In adult JIA, physical function and disability, which deteriorate with length of disease, took precedence, with the HAQ score predicting 18.3% of pain variability. Despite the high correlation of pain with emotional state, mood did not appear to have predictive value.

As a patient enters adulthood, pain coping strategies become a more important predictor of perceived pain intensity. Two subsets of coping strategy are particularly related to pain intensity. The most significant of these strategies is *dependant coping*, which utilises friends and religion for support. Individuals also rest rather than exercise and use distraction to ignore their pain. The other significant strategy is that of *denial.* This group deny the presence of their pain and avoid others when in pain. They reorganise routines around their symptoms, but also try to keep physically active. Both of these strategies tend to avoid confronting the disease and its related symptoms. In contrast, although the effect is not strong enough to be shown in the multiple regression analysis, the presence of an *open* coping strategy where disease is actively confronted, correlates well with lower levels of pain ($p < 0.005$) and disability ($p < 0.01$ - Spearman's correlation coefficient (two tailed)).

Perceived self-efficacy is a patient's belief that they can achieve a specific behaviour or control a specific symptom in the future. It is not a measure of actual accomplishment. As a psychological construct trait, it has many components, such as inherent motor or

mental skills, general sense of ability or self worth and motivation for accomplishment. It plays a role in mediating many health outcomes in arthritis. It is therefore no surprise that it mediates the degree of pain experienced by an individual. Particular learning and practising of techniques can improve an individual's self-efficacy. It has been shown that self-management courses not only improve self-efficacy but also that this improvement benefits patients' health outcomes.[79]

Surprisingly, the present emotional state of the patient did not appear to have any predictive value for pain intensity. Although there was a strong correlation between both depression ($p < 0.001$) and anxiety ($p < 0.001$) with pain intensity, this was explained by other factors in the linear regression analysis **Table 4.1.** Interestingly, it was the presence of previous depression (indicated by previous psychiatric diagnosis, previous anti-depressant use or parasuicide attempts) that predicted pain, as has been previously described in rheumatoid arthritis.[116] This is consistent with the 'scar' hypothesis[117] that suggests that proven major depression may leave a psychological scar, leaving a formerly depressed individual vulnerable to recurrent depression and to interpersonal, occupational and health deficits between depressive episodes. Similar to the other psychological predictive factors of coping strategies and perceptions of pain control, previous depression may be viewed as an indicator of how well an individual has learnt to manage their disease over time.

4.5 Summary

Chronic pain is both a biological and psychological phenomenon. 40% of the variation of pain in this study group was accounted for with 6 independent variables. These variables, which significantly influenced the perception of pain intensity, lay within two areas. There is a direct physical influence on pain shown by the effects of both physical function and joint inflammation. The psychological influences on pain include self-efficacy, previous depression and coping strategies. Despite the high correlation of pain with emotional state, mood itself did not appear to have predictive value.

There is a distinct change in the factors that influence pain, comparing JIA in childhood with adulthood. Function deteriorates with length of disease and it is this that becomes

the main determinant of pain. Pain coping strategies become more established in adulthood and if these are negative then pain perceptions may intensify. The influence of active inflammation on pain becomes less prominent with time, despite the relatively high frequency of continuing active disease in adulthood.

This study confirms the importance of addressing both physical and psychological factors when attempting to influence a patients' pain. A holistic approach is necessary, where both patients' medical and psychological needs are met. Doctors should consider multi-dimensional assessment and effective psychological strategies in coping, with the stressors of chronic arthritis being just as important as reaching for the prescription pad.

5 CHAPTER V - Education and Employment in JIA

5.1 Introduction

In the USA, only 21% of the more than 300,000 handicapped students leaving special education each year become employed. A recent Harris poll found that between 50-75% of all young adults with disabilities were jobless.[118] Of those individuals who were unemployed, 67% wanted to work.[119] The leading cause for disability in this young adult group was musculoskeletal and connective tissue disease. In the UK employers are no longer required by law to employ a certain percentage of disabled people. However, employers do have to employ on a disabled applicant's merit and make changes to the workplace as appropriate.

JIA can have a detrimental effect on both schooling and transition into employment, due to the effects of the disease during school years and also into adulthood.[18, 120] This is most likely in those patients with severe disease that remains active into adulthood. Social attitudes towards disability may be as important as disability itself. Many parents and professionals perceive school aged disabled people as 'children forever', rather than future adults and do not always consider competitive employment as a realistic goal for handicapped children. Other areas, which can cause difficulty, include: a lack of knowledge about career advice for the disabled, the practical difficulties of regularly attending work in chronic disease and poor self-advocacy skills.[121]

A successful transition from school to work is one of the most important tasks for all adolescents and young adults and is particularly difficult for adolescents with chronic illness or disability. It has been suggested that patients with chronic disease have low self-esteem, which may lead to low expectations of employment by the patients.[122] Unlike their peers, adolescents with JIA may not have worked during their summer holidays, thus missing previous work experience and an opportunity for early vocational training.

Laaksonen et al[5] followed up 544 patients for 15 years and found two thirds were in either full-time employment or education. Educational standards were higher than in the general population. Wirrell et al[98] found that in a group of 61 young adults with JIA (mean follow up 16.8 years), there were higher levels of education and the percentage of individuals employed conformed to national norms. Ansell et al[11] found that 83% of 243 patients were in education, married and running a home or were employed at 15 years follow up. Miller et al[56] followed-up 44 patients for an average of 16.1 years and showed that patients received a similar level of education to their siblings and the local population. However, patients with polyarticular onset JIA (a combination of rheumatoid factor positive and negative patients) had a significantly lower monthly salary than other subsets ($p < 0.01$). Poor physical function was more common in those adults staying in education or becoming 'homemakers', compared to those entering the workplace.

Appropriate vocational planning and support can facilitate the transition from school to work in adolescence. In the USA, White et al[123] reviewed a group of 242 patients (72% with JIA) who had been given specific prevocational assistance. They reported an employment rate of 72% and in addition 15% of patients continued to attend a university or similar establishment. The unemployment rate was just 6% while 6% were full time housewives and mothers. Less than 2% of the group with any level of educational achievement were unemployed. In the same group, 27% had completed university compared to just 7% of the control population.

There is some evidence that the longer the follow-up period, the lower the employment rate. David et al[34] studied 43 patients with a mean disease duration of 19.7 years. In this group 30% had not passed any formal examinations, 42% had obtained 'O' levels and 21% had attended university. 66% of patients were employed, but 30% were not working as a direct result of their disease. Peterson et al[18] reported in the only cohort study performed on 44 patients with an average follow up of 24.7 years, that they had similar educational achievement to a control group, but a significantly lower level of employment (70.5% vs. 87.3%, $p = 0.015$), however only 3/13 attributed their unemployment to their arthritis.

5.2 Methods

The educational achievements and employment status of 246 adult patients with JIA, was documented at interview. Data from the UK National Office for Statistics was also reviewed to determine rates of employment and education in the general population to act as a control group. Comparative data was also collected on patients' siblings, which enabled the siblings to be used as a further control group.

Educational information was gathered from both patient notes and by patient interview. This included: whether the patient went to a mainstream school, a school for the physically disabled or a combination of the two, the amount of time spent in hospital during a patient's school years, the level of national educational qualification achieved and the duration of years in full time education including university.

A full employment history from the time of entering into the workplace was taken, including the 'social class' of the employment **Table 5.1.** Reasons for a change in employment were recorded. If patients were unemployed, they were asked whether or not they attributed their unemployment to the effects of their arthritis. The incidence, nature and effects of discrimination in the workplace were also explored.

Table 5.1 Descriptions of the social class of occupation

Occupation	Social class
Professional occupations	I
Managerial and technical	II
Skilled occupations (non manual)	III
Skilled occupations (manual)	IV
Unskilled occupations	V
No occupation	VI

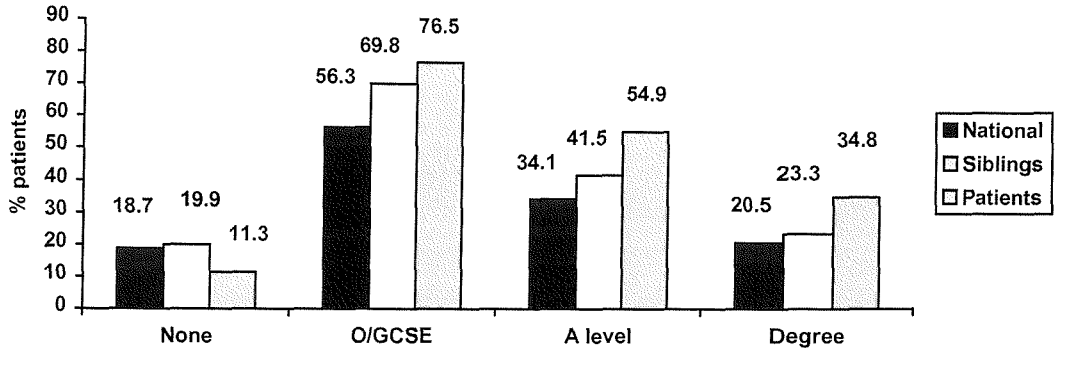
5.3 Results

5.3.1 Education

79.9% (197/246) of patients attended a mainstream school only, (mean length of stay 9.5 years, S.D. 2.9 years). 2.0% (5/246) attended a school for the physically disabled only (mean length of stay 10.5 years) and 18.1% (120/246) attended a combination of both mainstream and specialist school (mean length of stay in specialist school 4.5 years). In addition, 48.8% (120/246) of patients spent at least one month in hospital during their school years (mean 2.0 years, S.D. 1.7).

Across all levels of education from GCSEs, A levels to postgraduate degrees, the study group achieved better results when compared to both the national average and their siblings. **Figure 5.1.** The number of pupils leaving school without any formal qualification was only 11% (27/246), almost half the figure for the general population. The number attending a university or similar establishment was 1.5 times higher than their siblings and 1.7 times higher than expected from the national statistics.

Figure 5.1 Frequency of educational achievement in JIA patients, their siblings and the national population

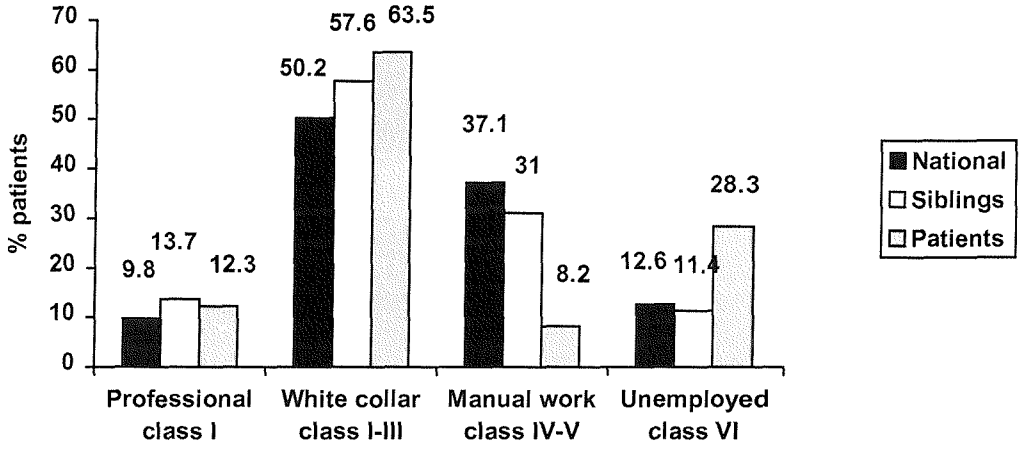


5.3.2 Employment

In contrast to the good exam results, our study group were more likely to be unemployed than the national average **Figure 5.2.** As would be expected in a physically disabled group, the incidence of manual work 8.2% (20/246) was much lower than in the control groups. Conversely, the number of patients in 'white-collar'

non-manual work was slightly higher than in both controls. The number of patients entering a profession was similar to both of the control groups. Unemployment in the patient group was 2.25 times higher than in the national population.

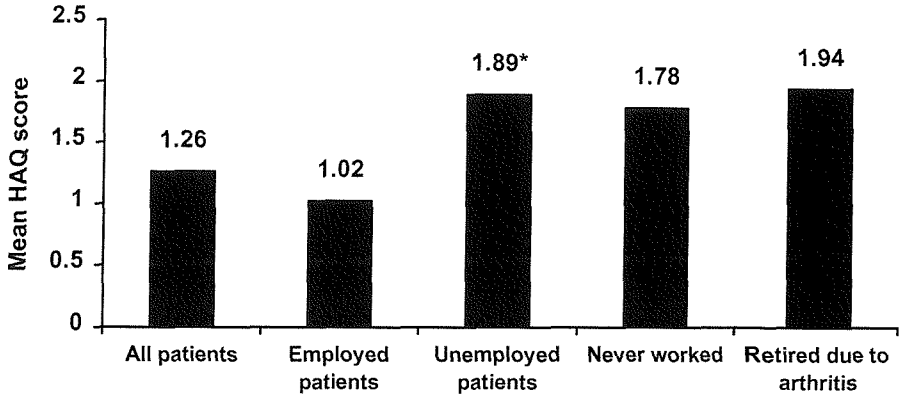
Figure 5.2 Frequency of employment status in JIA patients, their siblings and the national population



88.5% (62/70) of those patients who were not in work attributed their lack of occupation directly to disease related problems. 32% (22/70) of the unemployed had never worked. 59% (41/70) had worked for a variable period in class III white-collar jobs such as clerical workers and receptionists. The time in employment before leaving work due to disability was 10.8 years (range 1-41 years). None of the patients who had entered a professional career had subsequently become unemployed. The physical disability of these groups is shown in **Figure 5.3.**

43.8% (119/246) of all patients claimed the care component of the disability living allowance. This rose to 78.3% (55/70) in the unemployed group. In the unemployed group 43.5% (30/70) of patients claimed invalidity or incapacity benefit. Appropriately, no patients in employment claimed these benefits.

Figure 5.3 Physical disability (HAQ) related to patients work status

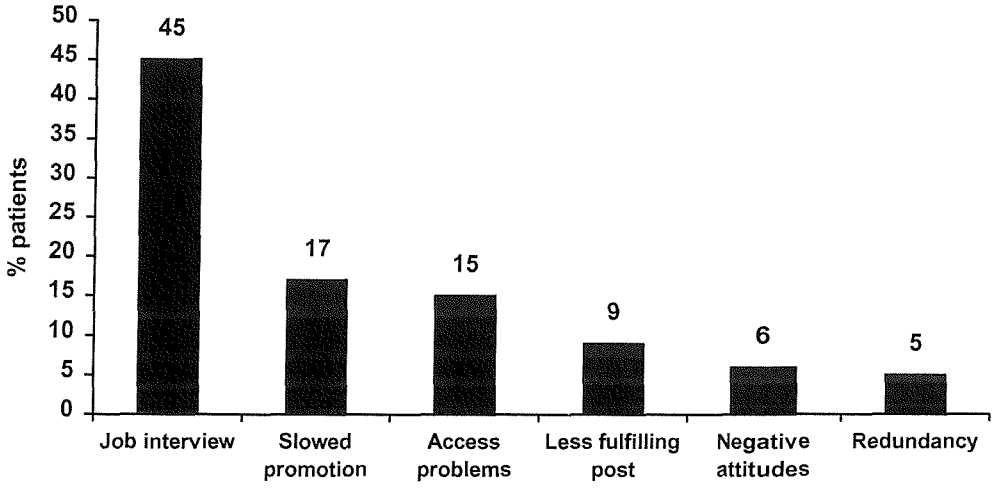


* Significantly increased physical disability in unemployed patients ($p < 0.001$) compared to 'all patients'

5.3.3 Discrimination

25.1% (62/246) of patients in the workplace and 26.5% (65/246) in a social setting had encountered discrimination **Figure 5.4**. Discrimination in the workplace was overt, with descriptions from patients such as "I was told I shouldn't work as I was taking an able-bodied persons job", but often covert with patients experiencing a general lack of support or being passed over for promotion. Issues around access to the workplace were often not addressed by employers.

Figure 5.4 Forms of workplace discrimination experienced



5.3.4 Predictive analysis

The best model of forward stepwise multiple regression analysis, identified 4 categories of variables, which independently made a significant contribution to the class of employment **Table 5.2.** and unemployment **Table 5.3.** This analysis predicted a substantial proportion (46.6%) of the total variation as to how high up the career 'ladder' a patient climbs (or falls). The degree of predictability of unemployment was lower (38.1%). The most important predictor for both occupation and unemployment was the educational level achieved by the patient. Physical disability, as measured by HAQ[17, 74] and the presence of poor coping strategies, using the 'London Coping with Rheumatoid Arthritis Scale', which separates individuals into those who cope by denial, passivity, openness and dependence,[86] had moderate effects on career (dependant coping strategy) and unemployment (denial and dependant coping strategies). Occupational class dropped as duration of disease increased, since a higher proportion of patients left the workplace later in their disease course ($p = 0.001$).

Table 5.2 Predictive factors for class of employment in adults with JIA

	% variance predicted	F	p <
Patient educational achievement	39.7	138.0	0.001
Function (HAQ)	4.6	83.1	0.001
Duration of disease	1.1	57.7	0.001
Denial coping strategy (group 1)	1.2	46.6	0.001
Total	**46.6**		

Table 5.3 Predictive factors for unemployment in adults with JIA

	% variance predicted	F	p <
Patient educational achievement	23.6	64.9	0.001
Function (HAQ)	11.8	57.2	0.001
Denial coping strategy (group 1)	1.2	40.0	0.001
Dependant coping strategy (group 4)	1.5	31.9	0.001
Total	**38.1**		

5.4 Discussion

The high level of hospital admission during school years was in part an historical effect. Patients were more likely to be admitted for prolonged periods prior to the 1985 closure of the National Centre for JIA at the Canadian Red Cross Memorial Hospital, which had an on-site hospital school. With the development of regional centres of paediatric rheumatology in the UK, prolonged admission to hospital, often distant from the parental home, has ceased. Following the Education Act of 1993, the majority of disabled children are educated in mainstream schools. The Education Act has enabled parents to become involved in obtaining the appropriate education needs for the child.[124] Both the legislative framework and professionals educating disabled children within normal schools support this change from specialised educational establishments to mainstream education. The exposure of able-bodied children to the disabled population may influence the attitude of the general population and lead to a reduction in the level of disability related discrimination.

Even before these changes began, our figures show that JIA patients had a higher level of educational achievement than average. In particular, a significantly higher proportion of patients compared to their siblings and the general population gained university degrees. Gaining employment with a disability or chronic disease is difficult. A high level of education eases the transition from education to employment. Employment is closely related to the highest education level attained ($p < 0.001$). Patients who have a degree of physical impairment may be less distracted from their studies by physical activities than their peers. If patients are educated enough to enter a profession (class I) there is little impact from their disease. No one in a professional job had had to leave work because of his or her disease.

Inclusion of the sibling group as a control initially appeared to suggest that the presence of a child in the family with JIA improved the educational achievements of the other children. It is most likely that this effect was predominantly due to patients from a better social background being able to access health care more easily. It is possible that patients (and the siblings of those patients) attending a tertiary referral centre are from more privileged backgrounds than those seen in less specialised centres. In this study,

this effect led to a significant difference between siblings and the general population. This should be considered when reviewing results from any study that is not population based, since the patients may come from a more privileged group. The sibling control group was closely matched to the patient group in terms of social background, race, education and environmental influences. However, Miller et al[14] and Ivey et al[125] suggested that when siblings have grown up in a household with a chronically disabled sibling, there may be a detrimental affect on them. In the sibling group they found poorer outcome measures than the general population, in terms of anxiety levels and health beliefs.

Poor school attendance in ill children and periods of hospitalisation or tuition at home can lead to a decline in educational progress.[126] Although home tuition is arranged for a child absent from school for prolonged periods, it is a poor substitute for classroom teaching not least because of the lack of social interaction. The effects of distance learning inevitably involve a degree of social isolation of the child from their peers and the effects continue into adult life. In this study, the number of close social contacts was significantly higher in patients with higher levels of educational achievement ($p < 0.001$) and also in patients educated solely within mainstream schools. The level of satisfaction with social support was also linked to whether individuals were mainstream educated ($p < 0.05$). However, the level of disability, as measured by the HAQ score, did not appear to adversely effect social contact satisfaction.

Despite being an extremely well educated group, unemployment was much higher in the patient group (29.9%) than in the national average (12.6%). The majority of those without work attributed their unemployment to the disabling effects of their disease. Physical disability was not as severe in employed patients compared to those without work. The 6.5% of unemployed patients who had never entered the workplace tended to be less disabled than the 21.7% of patients who could no longer work. This suggests that the factors that govern successful transition from education to employment are not solely related to physical ability. The predictive factors for unemployment were not only educational achievements and physical function but also the presence of poor coping strategies. This suggests that an individual's ability to successfully cope with their arthritis has a large impact on their success in the workplace.

Unemployment impacts in a major way upon the financial security and independence of an individual. There is also a cost implication for society, with patients who become more dependent upon the state, requiring more financial support. The majority of state support is related to the increased disability in the unemployed group, which necessitates a higher level of care and mobility support. However, a proportion of these costs would fall if patients were able to return to employment.

Depression occurred in this study in 23.3% of patients at some time and occurred most frequently in JIA patients in their late teens or early twenties. This was at the same time as they were trying to enter the workplace. There was a significant link between previous depression and unemployment ($p < 0.001$). Previous depression was particularly prevalent in those who had never worked, being present in 87.5% (14/16). Again this suggests the importance of psychological health at the transition period between school and work.

Over a quarter of patients felt they had been discriminated against at work. The majority of workplace discrimination occurred around job interviews, with problems split equally between a failure to be interviewed initially and a perception of unreasonably high levels of failure once interviewed. Once in work, discrimination was a more covert problem, with access problems and delays in promotion predominating. A number of patients reported that their posts were downgraded or they had been made redundant because of their disability. Only a small proportion (6%) had experienced overtly negative or discriminatory attitudes towards them, predominantly from direct superiors. It should be noted that the overwhelming majority of the discrimination described occurred prior to the implementation of the Disability Discrimination Act 1995.

Discrimination is by nature subjective, enmeshed irrevocably with the perceptions the patient has of the environment they live in. If an individual feels they have been discriminated against, it does not necessarily follow that the events leading to that perception were discriminatory. Conversely, the unthinking actions of others may amount to discrimination by omission.

5.5 Conclusions

Education and employment status of patients can be used as a surrogate measure for the long-term outcome of arthritis. The educational achievements and employment status of 246 adults with JIA was documented at interview. Severe disability was common with 42.9% of patients having a HAQ score of 1.5 or higher. 28.3% of patients were unemployed, the majority of these related to disability. In these patients, low levels of employment contrasted markedly with high levels of education. It is apparent that far from having a detrimental effect on the final outcome of their schooling, JIA patients have a higher level of educational achievement in all areas of education than controls, particularly with university degrees.

In the study group, employment levels were higher in well-educated patients. If patients worked in a professional career, subsequent unemployment was rare. The unsuccessful transition from education into employment was related to physical ability and education and also to coping strategies, psychological state and social attitudes.

There are a number of measures that may improve the present situation. There should be a focus on careers in adolescent rheumatology clinics, with opportunities to have contact with specialist careers advisors. Assertiveness training, interview techniques and attempts to address the psychological needs of the individual would improve their chances in the competitive job market. For adults there is a need for continuing lobbying against discrimination at work through bodies such as the Arthritis and Musculoskeletal Alliance (ARMA), Arthritis Care, the local government ombudsman and with politicians.

Additional information on this area should be forthcoming from the recently completed 'Improving the quality of life of adolescents with Juvenile Idiopathic Arthritis' ARC funded project in collaboration with British Paediatric Rheumatology Group (BPRG) now renamed British Society for Paediatric and Adolescent Rheumatology (BSPAR).

6 CHAPTER VI - Social Function, Relationships and Sexual Activity

6.1. Introduction

Adolescence is a time of change, biologically, emotionally and socially. Before reaching 'adulthood', an adolescent has to establish their identity, achieve independence from parents/carers, establish relationships outside the family and find a vocation.[123] Body image is of importance to all adolescents.[127, 128] Unfortunately, a chronic deforming disease such as JIA may be detrimental to body image. Generalised growth failure[97] and pubertal retardation[129] are seen in severe JIA and may result in patients being treated as less mature, as they appear to be younger than their actual age. Some local growth anomalies (e.g. short digit) are often hidden but may cause inappropriate concern to the patient, whilst other anomalies such as micrognathia can profoundly change facial appearance. Drug therapy in JIA may also have detrimental effects. Oral corticosteroids[130] alter the distribution of fat stores and can change skin appearance with acne and hirsuitism. Cyclosporin may also cause hirsuitism.[131] Chlorambucil frequently causes gonadal failure,[132, 133] which can have a profound effect on an individual's perceptions of their sexuality. The scars from previous orthopaedic surgery may also affect a patient's self-confidence. Peer group acceptance is difficult for adolescents, and this can only be more daunting for those with severe arthritis.

The development of social responsibilities may be impaired by an inability to perform household tasks. The avenues a young adult with arthritis has to seek independence and the consequential development of independent strategies and separation from their family can be limited by physical dependence. Limited ambulation can affect an individual's ability to participate in socializing activities.[134, 135] The consequent social isolation is not uncommon and can lead to loneliness and depression.

The establishment of relationships outside the family may be difficult for some adolescent arthritis patients, particularly if they have high levels of physical dependency and associated parental overprotection and emotional enmeshment. These problems should eventually be countered by the young person's increasing capacity for

choice and self-advocacy. Poor medication compliance is an area where patients can exercise some control of their surroundings. Discontinuing therapy has the added benefit of removing one of the differences between the patient and their peer group.

Difficulties with relationships may persist into adulthood because of delayed social maturation. If the individual is physically dependent, there will be more reliance on friends and in particular sexual partners to act as carers. This dependency may affect the way friends relate to the individual, with adult-to-adult communication more difficult to achieve. Relationships with sexual partners may take longer to establish,[136] possibly because the relationship is not just partner-to-partner but also potentially carer-to-dependant.

Sexuality includes the adoption of certain gender roles.[137] Society's definition of masculinity traditionally identifies the male as strong, practical and as the main 'bread winner' in a family. Arthritis may alter a man's capacity for displaying such 'strength'. The corresponding role for a woman traditionally identifies her as a wife, homemaker, attentive mother and, more recently, an income provider. Again, arthritis may interfere with a women's capacity to meet these demands.

An increase in the age at onset of sexual activity above that of the general population may occasionally be related to delayed puberty. However, more often delays are related to poor body image and problems with physical participation in social activities. The attitudes of society to physical deformity can also have an effect. There are also many reasons why an individual may wish to delay the timing of their first sexual encounter. The physical act of sex for an individual with mobility problems and joint pain may be daunting. Concerns about pregnancy also play a role, from physical problems of carrying a child to the teratogenic potential of some medications such as methotrexate.

Sexual activity later in a patient's disease course can be adversely affected by their arthritis. Disease related pain, the fear of pain and fatigue have the potential to quell libido, and this may cause problems in a relationship. There is a high incidence of mood disturbance (depression and anxiety) related to most forms of chronic arthritis

and this in turn can have a detrimental effect on sexuality. Surgical procedures in the immediate postoperative period may reduce sexual activity, particularly in the case of hip replacement with the associated risks of dislocating a new hip prosthesis. The reduction in pain and increased mobility in a severely affected joint that has been replaced may give considerable benefit to an individual's physical abilities including their sex life.

6.2. Methods

246 adult patients with JIA were asked about social function, relationships and sexual activity at interview. Marital status, pregnancy related problems and number of children for patients and their siblings were documented. The age of first sexual encounter, contraceptive use and sexual problems related to the patient's arthritis were discussed. If the patient had been pregnant, age at first delivery or abortion was recorded. Patient's physical and sedentary interests outside work were recorded, as a measure of social and physical function.

Physical function was measured using the UK validated version of the 'Health Assessment Questionnaire (HAQ).[17, 74] Patient's mood was assessed using the Hospital Anxiety and Depression Scale (HAD).[85] Their social support network was reviewed with the Short Form Social Support Questionnaire (SSQ6),[90] which measures the number of close supportive social contacts an individual has, and the individual's perceived satisfaction with that support. The perceived handicapping effect of a person's disease on their relationships, body image or attractiveness and social activity was measured using the Disease Repercussion Scale.[93]

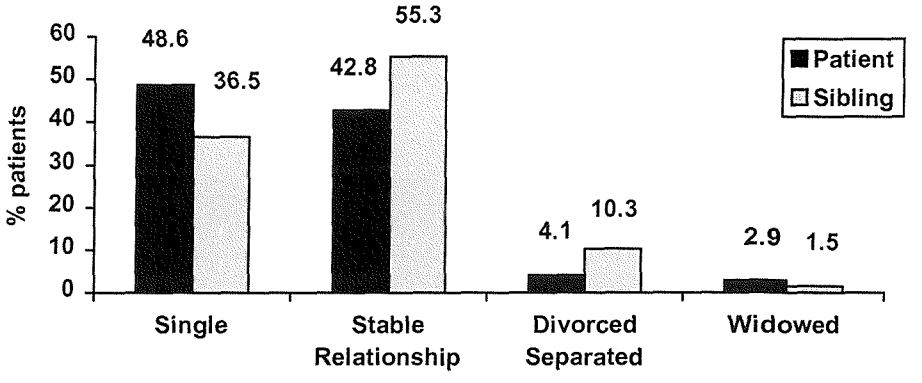
6.3 Results

6.3.1 Marital status

48.6% (120/246) of patients were single, 12.9% higher than their siblings. 42.8% (105/246) of patients were married or cohabiting, 10.7% lower than their siblings.

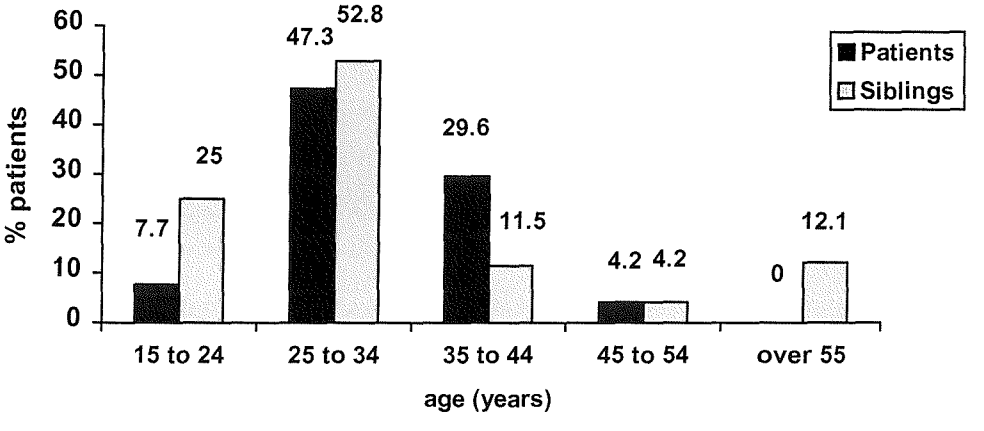
Figure 6.1.

Figure 6.1 Marital status of patients with JIA and their siblings



Compared to their siblings, patients married less frequently between the ages of 15-24 and 25-34, but married more frequently between the ages of 35-44. **Figure 6.2.** Later in life, some siblings continued to get married for the first time, but after the age of 55, none of the study group entered a stable relationship having lived alone.

Figure 6.2 Proportion of individuals marrying within each age group



6.3.2 Pregnancy, children and oral contraception

30.5% (54/176) of the females had been pregnant and the partners of 35.7% (25/70) of the males had become pregnant (32% of patients overall). The proportion of people with children was 27.5% (68/246), with an average of 1.7 children per family. 24% (36/150) of all pregnancies had resulted in an abortion; only 5.6% (2/36) of abortions were due to a termination of pregnancy. A similar proportion of men and women (11.5%) had experienced a miscarriage. There was a degree of variation in the number

of miscarriages experienced by each subset. **Table 6.1.** The average age at the end of pregnancy (abortion or delivery) was 26.8 years (range 18.3-41.5 years S.D. 4.1) and the average age at the time of delivery of a live child was 27.2 years (range 20-41.5 years S.D. 4.3). The average age at first delivery in the general UK population is 23.5 years, which is significantly lower ($p<0.02$) than the study population.

Table 6.1 Miscarriage rates related to JIA subset

Subset	Miscarriage overall % (Patient numbers)	Miscarriage in females % (Patient numbers)
Systemic	13.4 (7)	12.5 (5)
Oligoarticular	0 (0)	0 (0)
Extended oligoarticular	5.4 (3)	6.5 (2)
RhF negative polyarticular	12.8 (5)	15.1 (4)
RhF positive polyarticular	18.9 (7)	18.7 (5)
Enthesitis related	9.3 (3)	0 (0)
Psoriatic	23.1 (3)	33.3* (3)

* $p < 0.05$

Although the females with psoriatic JIA had a significantly higher incidence of miscarriage than the other groups, the numbers were small. This has not previously been reported in psoriatic arthritis,[138] although a similar miscarriage rate has been reported in psoriatic women receiving UV-A radiation (PUVA).[139] It is likely that the increased abortion rate in psoriatic arthritis is a reflection of the small numbers of miscarriages in each subset. There were comparatively few abortions within the oligoarticular, extended oligoarticular and enthesitis related subsets.

The oral contraceptive pill (OCP) had been used by 34.9% (89/176) of the women with JIA and 11.6% (20/176) continued to take the OCP. 32.4% (12/37) of women on methotrexate were taking the OCP, 10.8% (4/37) were postmenopausal and a further 13.5% (5/37) were sexually inactive. 43.2% (16/37) of patients on potentially teratogenic methotrexate were possibly at risk of becoming pregnant, either using barrier methods of contraception or no contraception.

Caesarean delivery is sometimes necessary if hip abduction is significantly limited or if there is foeto-pelvic disproportion because of a small pelvis. Of the 114 pregnancies that went to term, 26 infants (22.8%) were delivered by caesarean to 19 women. 13 (68.4%) of these women had limited hip abduction (less than 30 degrees in one or both hips) and 7 women (36.8%) were below the third centile for height.

6.3.3 Social function

The Sarason scale of social support measures two separate elements of support; the number of people giving support to the individual **Figure 6.3.** and the level of satisfaction the individual has with the level of support they are given **Figure 6.4.**

The mean number of social supports was 4.1 (S.D. 1.99). Although the number of people giving support correlated weakly ($p = 0.01$) with satisfaction, the level of satisfaction in social support was extremely high with a mean value of 5.25 (S.D. 0.85) out of a possible maximum score of 6. A patient's satisfaction with their social support was closely related to the amount their arthritis affected both body image ($p < 0.005$) and relationships ($p < 0.001$).

Figure 6.3 Social contacts

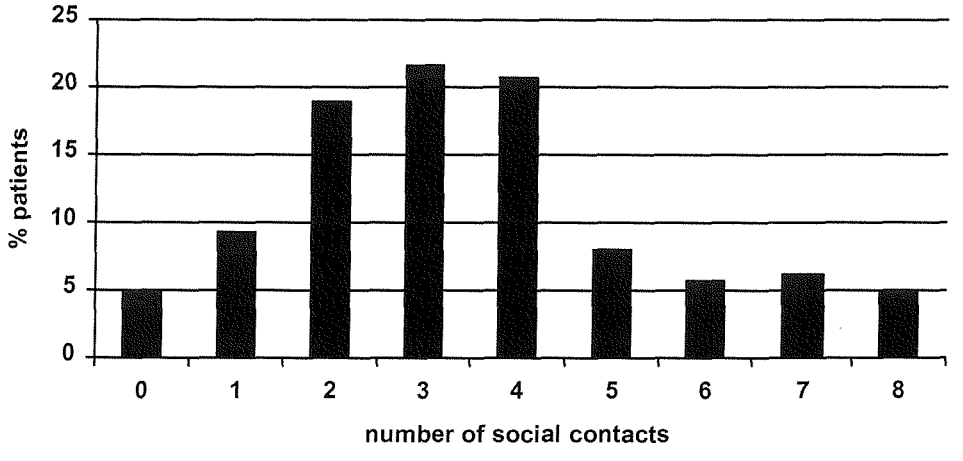
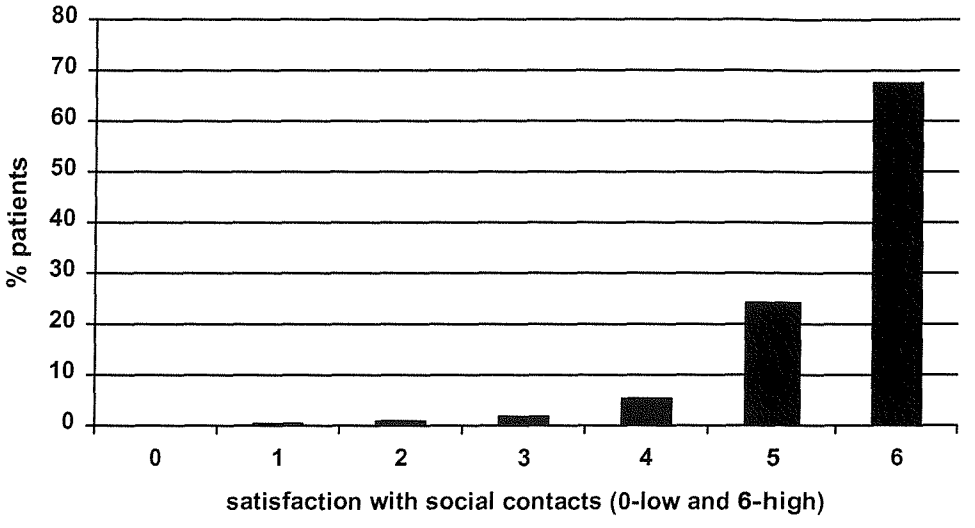
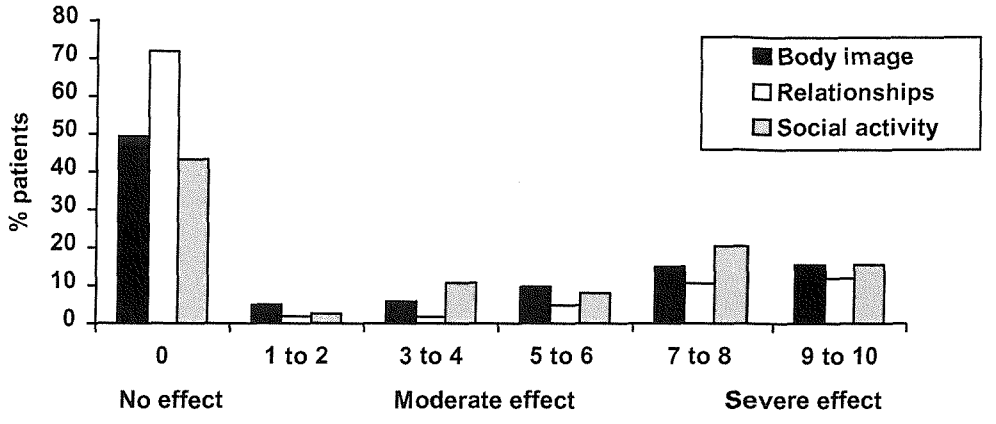


Figure 6.4 Level of satisfaction with social contacts



The disease repercussion scale is a measure of perceived handicap, assessing the effect a patient feels that their disease has had on different aspects of their life. The scoring system indicates that there is no effect with a score of '0' and a severe effect with a score of '10'. **Figure 6.5.** 50.7% (117/231) of patients felt that their body image or attractiveness had been affected by their arthritis, with a mean score of 3.4. 28.2% (65/231) of patients felt that their relationships had been negatively affected by JIA, with a mean score of 2.1. 56.8% (131/231) of patients had experienced a detrimental effect on their level of social activity, with a mean score of 3.9. In all areas, the patients who thought that there was an effect from their arthritis tended to feel that these effects were severe rather than small or moderate. Body image and social activity correlated significantly with JIA subset. Oligoarticular JIA was associated with fewer problems with attractiveness ($p < 0.05$) and social activity ($p < 0.05$) compared to other subsets. Systemic JIA was associated with patients feeling less attractive ($p < 0.05$) and having more problems with social activities ($p < 0.05$). There was also an association with height and social activity ($p < 0.005$), but no effect from micrognathia and other growth defects. Physical disability (HAQ) had an effect on body image ($p = 0.001$), social activity ($p < 0.001$) and relationships ($p < 0.01$).

Figure 6.5 Perceived effects of arthritis on relationships, social activity and body image



6.3.4 Sexual activity

80.1% (197/246) of all patients were sexually active at review. 7.1% (17/246) of patients were active before the age of 16 and 37.6% (92/246) before transfer to adult rheumatology care at the age of 18. The mean age at first sexual experience was 19.3 years (S.D. 3.9 years) with the mean age in the general population being 17.0 years. Onset of sexual activity (defined as penetrative intercourse) was similar in men and women **Table 6.2.** There were significant differences in the age of onset of activity with JIA subsets, with systemic JIA being related to a later first sexual experience and oligoarticular JIA related to an earlier first sexual encounter. There was no significant variation in the proportion of sexually active individuals within each subset. Physical disability (HAQ) correlated strongly with a delay in sexual activity ($p < 0.005$).

Table 6.2 Variation of onset and incidence of sexual activity with subset

Subset / gender	Age of first sexual experience (years)	Sexually active individuals % (number of patients)
Systemic	21.2*	78.8 (41/52)
Oligoarticular	16.4**	80 (12/15)
Extended oligoarticular	18.2	76.4 (42/55)
RhF negative polyarticular	19.6	82.9 (34/41)
RhF positive polyarticular	19.3	75.6 (28/37)
Enthesitis related	18.8	84.3 (27/32)
Psoriatic	19.6	100 (13/13)
Male	19.6	81.6 (58/70)
Female	19.1	78.6 (139/176)

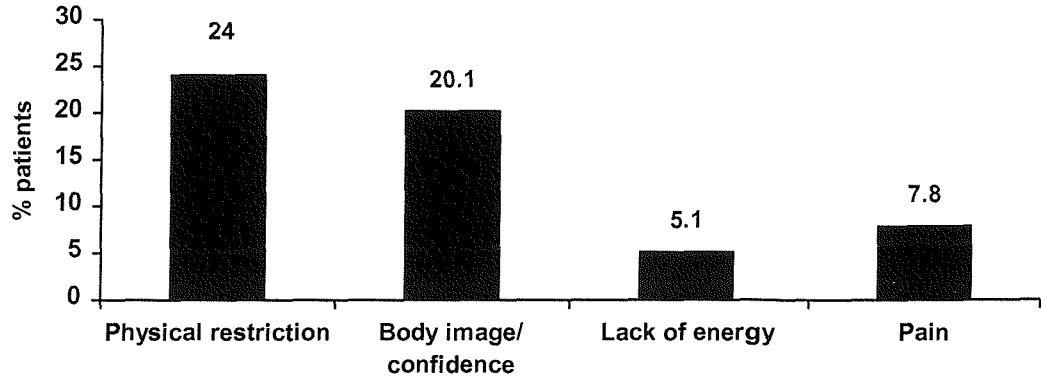
*$p = 0.001$ **$p < 0.001$

Patients who were not sexually active, also had much higher levels of physical disability (HAQ) ($p < 0.005$). Difficulty performing demanding physical activity, measured by the number of physical hobbies a patient had, was also related ($p < 0.05$). Those patients without sexual partners also had a poor body image ($p < 0.05$). There were no associations to anxiety or depression scores, gender, social contact or social satisfaction and disease subtypes.

6.3.5 Sexual problems

58.3% (115/197) of patients who were sexually active had experienced difficulties related to their disease. **Figure 6.6.** The majority of sexual problems were due to the physical effects of arthritis, pain and physical restriction together comprising 54.6% (63/115) of difficulties encountered. However, a significant minority of patients experienced body image or self-confidence problems. Less frequent problems encountered included; concerns about teratogenicity, worries about passing disease to children, hip prosthesis dislocation and azoospermia.

Figure 6.6 Percentage of sexually active individuals experiencing problems



In patients who were not sexually active, 30% (12/49) felt that this was due to their disease. Only 8.3% (1/12) of these felt that they were sexually inactive because of physical disability. 66.6% (8/12) of the problems were related to body image and self-confidence and 25% (3/12) of individuals thought that they were not perceived as sexual beings by their opposite sex peer group e.g. a male university undergraduate reported that his female friends did not regard him as a male and talked to him as if he were 'one of the girls'.

6.4 Discussion

Østensen et al[138, 140] found no differences in menarche onset in JIA adults compared to the normal population. Oral contraceptive pill (OCP) use and the age of starting the OCP matched the control group, as did age at first pregnancy. There was no evidence of fertility impairment. Sexual activity was reduced in young men with JIA and increased in females with JIA. There was a higher rate of spontaneous abortion, menstrual disturbances, pelvic inflammatory disease and ovarian pathology than in a control population. Peterson et al[18] found no difference in the proportion of JIA patients marrying or the stability of those marriages. The rates for live births (69%) and miscarriages (31%) were similar to a control group. Neither age at diagnosis of JIA, nor JIA subtype were predictors of pregnancy related outcomes. However a significant proportion (12.9%) of the female cases, compared to just 1.4% of the age-matched controls, reported being advised by their physicians against becoming pregnant.

Musiej-Nowaakowska et al[35] described good outcomes for pregnancy in the oligoarticular JIA group with pregnancy induced amelioration of disease activity, but post-partum flare of disease in 52%. Individuals in this study group were more likely than their siblings to be single and living outside a stable partnership. There are two likely causes for this finding; firstly the proportion of patients that were married to date is lower, secondly individuals with JIA may be deferring marriage for longer than their siblings to ensure that their partner is the right person to also become a potential carer. The lower divorce and separation rates suggest that deferred marriage is successful. The concept of deferred marriage is shown in **Figure 6.2** where a higher proportion of patients than their siblings enter a stable relationship between the ages of 35-44. The small numbers becoming married before the age of 25 also supports this concept. There was a slightly higher incidence of partners dying and individuals being left alone. The increased mortality in this group appears to be explained by a tendency for patients with JIA to marry other physically disabled people, who have a mortality rate higher than the general population.

The number of individuals becoming pregnant was much lower than in comparative cohort studies or the general population, suggesting that the severity of the study group's disease reduced the number of people choosing to have children. There were also a number of individuals who were infertile due to early menopause (see 8.4.4) or azoospermia, but these constituted only a small proportion of the study group and had only a minor effect on the reduced number of pregnancies. There were fewer individuals in stable relationships, which may have had an effect on the total number of offspring.

The reported miscarriage rate at 24% was higher than expected in the general population with estimates around 7-9%. [141, 142] Although miscarriage was significantly higher in patients with psoriatic arthritis than other JIA subsets, the numbers were small (3/9 patients) which may explain this unexpected association. There was a trend for patients with oligoarticular, extended oligoarticular and enthesitis related JIA to have a lower rate of miscarriage than those in other subsets.

It is concerning that over 40% (17/40) female patients on methotrexate were at risk of becoming pregnant. Although this figure is likely to be lower in reality (because it does not include forms of contraception other than the OCP), there are obvious implications on the safety of teratogenic drugs in chronic disease.

The overall caesarean rate in the study population of 37% (19/52) was higher than expected in the general population. In 2002, 22% of women delivered by caesarean.[143] The rate of caesarean section in the general population has been steadily rising over the past decade with rates of 11.3% in 1990, 15.5% in 1995 and 20.6% in 2000. As this is a retrospective study, a number of the caesarean sections in the study were carried out whilst caesarean section was carried out less frequently in the general population. Early liaison with the obstetrician is important particularly in view of the high proportion of patients who had their babies by Caesarean section delivery (78.9%) who had either poor hip abduction or short stature. These factors should be taken into consideration when counselling patients about potential problems they face during pregnancy.

In general, the level of satisfaction with an individual's perceived level of social support was extremely high. It has been shown in previous studies that it is not the actual level of support that is important, but the perceived level of support that influences an individual's ability to cope with the effects of their disability.[144] Arthritis that adversely affected patient's relationships or body image, significantly reduced satisfaction levels. The majority of patients thought that their arthritis had had a negative effect on their body image. Objective measures of physical deformity, such as growth defects and short stature, were not related to the perception of unattractiveness, which was most strongly related to poor physical function. This suggests that it is the ease with which an individual can get involved in social interaction that has most effect on their perceived attractiveness.

The majority of patients, although experiencing high levels of disability were sexually active. Despite a slightly older age at first sexual experience than the general population, a significant minority of patients became sexually active whilst still under the care of a paediatric rheumatologist. There are many reasons why an individual may wish to delay the timing of their first sexual encounter. The physical act of sex for an

individual with mobility problems and joint pain may be daunting. Concerns about pregnancy also play a role from the physical problems of carrying a child to the teratogenic potential of some medications such as methotrexate. As the frequency with which teratogenic drugs are used in the paediatric population increases, the need to address contraception in adolescent clinics becomes more essential. Sex education is frequently inadequate for young adults in the general population. Sex related issues in the context of disability and arthritis should be discussed with an open attitude and without embarrassment. Educating arthritis patients about pregnancy and delivery of a baby may relieve concerns related to a lack of knowledge. Awareness that psychological influences play a part in sexuality and sexual problems and advice about the physical aspects of lovemaking with disability should be introduced to the adolescent with JIA. It is important to stress to patients with JIA that their children have a relatively low risk of inheriting JIA.[145]

The patient group had encountered sexual problems frequently. Although the majority of these problems were related to physical disability and pain, there was a high incidence of psychological problems concerning self-confidence and perceived attractiveness. The psychological aspect of sexual health also affected those who were not sexually active. For a number of people, concerns about their attractiveness or perception by others as being non-sexual were the reasons why they were not sexually active. It should be possible to address these psychological areas of difficulty with appropriate advice, counselling, self-esteem and assertiveness training.

6.5 Conclusions

Fewer patients with JIA were in stable relationships and entry into relationships occurred later in life. A lower proportion of individuals became pregnant but levels of spontaneous abortion were similar to the general population. However, there was a significantly higher incidence of miscarriage in psoriatic JIA and a trend to more foetal loss in other polyarticular forms of JIA. Caesarean delivery was often required in patients with reduced hip abduction and short stature. A concerning number of patients on teratogenic medication were at risk of becoming pregnant.

Most patients were satisfied with the quality of social support they received. Only a quarter of patients felt that their relationships had been adversely affected by arthritis, but over half felt they were less attractive. Poor body image was particularly related to physical disability. Objective measures of physical deformity were not associated with patient's perception of the effect of their arthritis upon their attractiveness.

Most patients, despite experiencing high levels of disability were sexually active. The majority of patients had experienced a wide variety of disease related sexual problems. Many were due to physical restriction and pain but psychological problems were not uncommon. A significant proportion of individuals were sexually active before transfer to adult rheumatology services, highlighting the need to introduce sexual counselling into adolescent clinics and to develop programmes aimed at improving the self-esteem of adolescents.

7 CHAPTER VII - Predictive factors for mood

7.1. Introduction

JIA is a chronic and potentially disabling disease, impacting negatively on individuals' physical and social function. There are features of JIA that suggest that patients may have a higher risk of psychological complications such as pain, disability, chronicity, physical deformity and onset in childhood (before coping mechanisms are fully established). A number of studies have shown that psychological problems, particularly depression, are higher in people with inflammatory arthritis compared to the general population.[146-149] In these studies, the prevalence of depression in rheumatoid arthritis varied considerably between 14% and 46%.

One of the major psychological differences between any adult onset inflammatory arthritis, such as rheumatoid arthritis and the various forms of JIA, are that coping strategies are not fully developed in childhood and that adolescence with an active and chronic disease has to be negotiated. These factors may affect the long-term psychological state of the individual, and consequently their ability to cope with disability as an adult.

The long-term psychological implications of adults with JIA have not been studied in as much depth as rheumatoid arthritis.[18, 31, 34, 98, 150] David et al[34] reported clinical depression in 21% of adults with polyarticular JIA, the rate increasing with the degree of disability. Anxious preoccupation with disease also rose with worsening physical function and disease activity. The anxious and helpless forms of mental adjustment to arthritis were seen more commonly in patients whose arthritis started in adolescence. It was suggested that this was related to those individuals having less time and opportunity to adapt and develop alternative coping strategies compared to those individuals who had arthritis from early childhood. Aasland et al[150] found that 17% of adult JIA patients fulfilled the criteria for a psychiatric diagnosis, most often having an anxiety disorder; no patients met the criteria for a depressive disorder. Although 38% of these patients reported somatic symptoms, which were potentially depressive, on direct questioning these symptoms were felt to be due to their rheumatic disease. Some studies have not found an association between JIA and psychological problems.

Peterson et al[18] suggested that 'juvenile rheumatoid arthritis cases were not emotionally impaired and were able to perform social activities similar to controls'. Wirrell et al[98] found that adults with JIA scored within the normal range on the RAND 36 Item Health Survey[151] for emotional well-being, pain and energy.

Although depression plays a major role in inflammatory arthritis, it is often poorly measured. Most self-report measures of depression in the context of arthritis are biased by items that are marked positively by the patient, but represent symptoms of disease rather than mood. This problem arises because certain depressive symptoms may express themselves through somatization. Patients then experience symptoms such as fatigue, loss of appetite, difficulty in performing activities of daily living and sleep disturbance. These symptoms are common to both depression and inflammatory arthritis and this can falsely increase the levels of depression found by self-report questionnaires.

7.2. Methods

7.2.1. Assessment of mood

The Hospital Anxiety and Depression Scale[85] (HAD) (Appendix 1.11) is a specifically designed measure of emotional disturbance in patients with physical illness. Mood was measured with the HAD in 231 adults with JIA. This scale indicates both probable (score >8) and definite (score >11) anxiety and depression. It is a 14-point scale, which contains 7 questions on anxiety related symptoms and 7 depression related questions. The depression part of the scale has been constructed so that somatic items on fatigue or sleep disturbance (often caused by physical illness) are mostly excluded and anhedonia is emphasised. This reduces the risk of falsely indicating depression in patients with arthritis due to their illness, rather than mood. Previous mood imbalance was determined at interview and notes review by the presence of a psychiatric diagnosis of anxiety or depression, the prescription of antidepressant medication (at antidepressant doses) or a parasuicide attempt. The age at which any previous depressive episode occurred was also noted. The patient's perception of the negative effect of their arthritis on emotional state was measured using the Disease Repercussion

Scale.[93] Correlation between these measurements of mood and other variables was assessed using Spearman's correlation coefficient (two-tailed).

7.2.2. Candidate predictive factor collection

A wide-ranging multidimensional assessment of the patient group was performed as described in the 'Methods' chapter. A large number of candidate predictive factors with the potential to affect anxiety and depression were reviewed. Factors thought to be potential predictors for mood were assessed by forward stepwise linear multiple regression. These included gender, age at disease onset, length of disease, number of orthopaedic operations, JIA subset, height, growth defects, education, employment, previous depression, clinical joint inflammation (Thompson Kirwan Scale[72]), CRP, ESR, haemoglobin, pain (pain VAS), function (HAQ), self-efficacy (Arthritis-Self Efficacy Scale[79]), coping mechanisms (London Coping with RA Scale[86] and catastrophising[87]), perceived effect of arthritis on body image (Disease Repercussion Profile[93]) and social contact (Sarason Scale[90]).

7.3. Results

7.3.1. Present mood

At the time of the study, 31.6% (73/231) of patients had high anxiety levels (HAD score ≥8), but only 5.2% (12/231) had high levels of depression (HAD score ≥8) **Figure 7.1.** There was a significant variation in the levels of anxiety and depression found in the individual subsets of JIA. **Figure 7.2.** Patients with systemic onset JIA had significantly higher levels of anxiety ($p < 0.05$) and depression ($p < 0.05$) compared to patients within the other JIA subsets. Patients with oligoarticular JIA had lower levels of anxiety ($p < 0.05$) compared to patients within the other JIA subsets.

Figure 7.1 Proportion of adults with JIA with probable or definite mood disorder

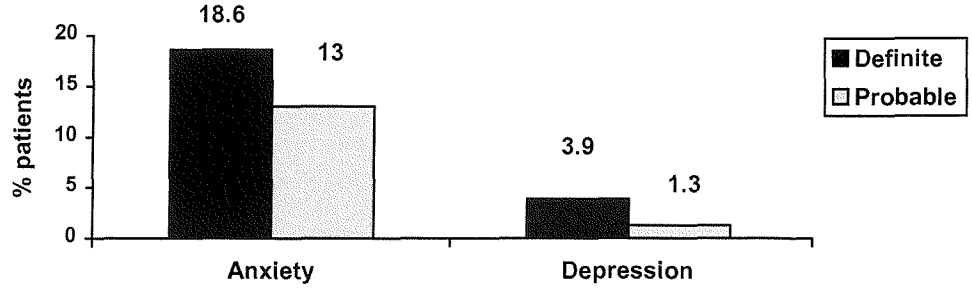
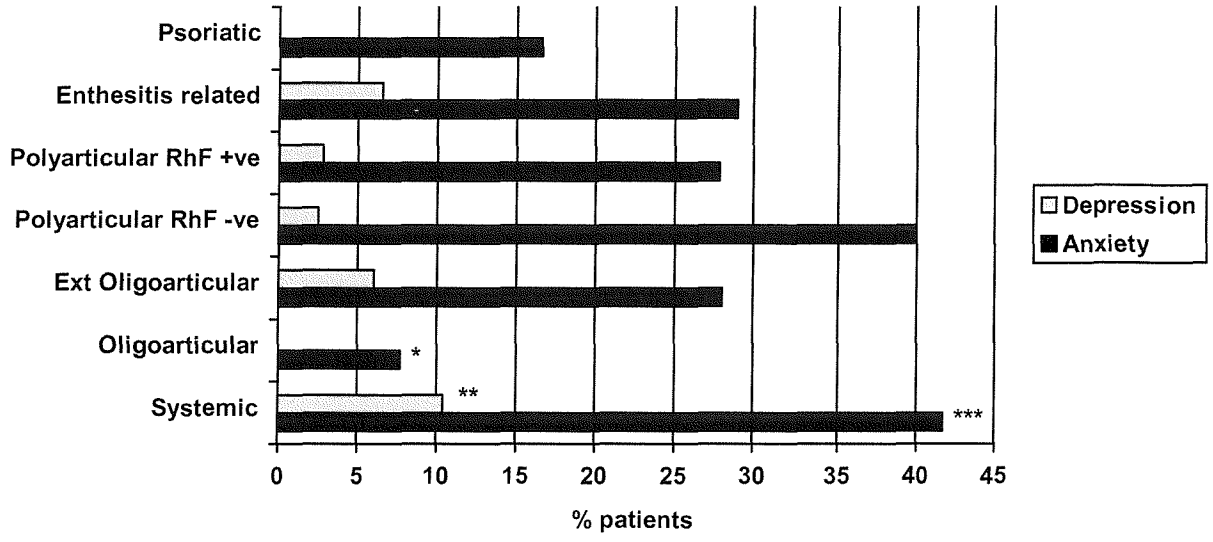


Figure 7.2 Proportion of patients with anxiety or depression in each JIA subset

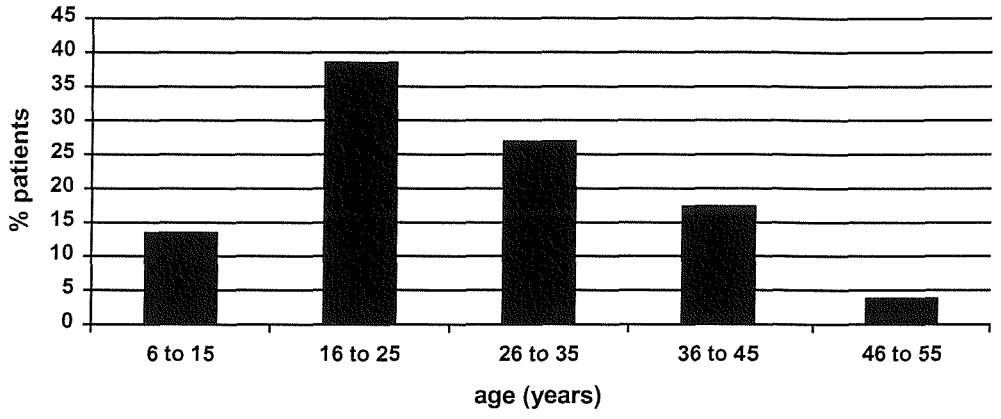


*	Oligoarticular JIA vs other subsets - less anxiety	$p < 0.05$
**	Systemic JIA vs other subsets - more anxiety	$p < 0.05$
***	Systemic JIA vs other subsets - more depression	$p < 0.05$

7.3.2. Previous mood

Despite the low level of depression in the population at review, 21.1% (52/246) of patients had experienced significant depression in the past, shown by previous use of high dose antidepressants, parasuicide or a psychiatric diagnosis of depression. The most common age at first episode of depression was between 16 and 25 years of age. **Figure 7.3.** Retrospective analysis of anxiety was felt to be inaccurate, due to underreporting and multiple use of anxiolytics.

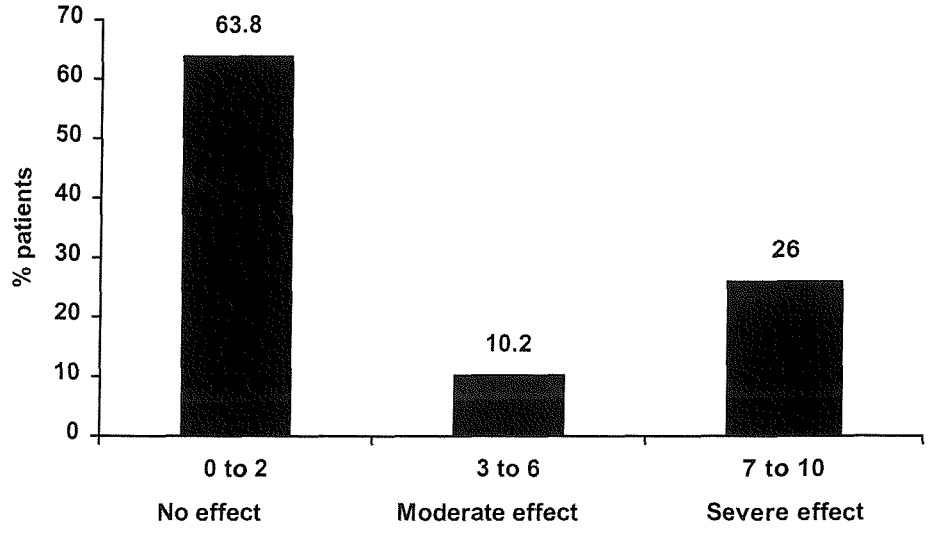
Figure 7.3 Age at first depressive episode in JIA



7.3.3. Perceived effect of arthritis on emotional state

The Disease Repercussion Scale measured perceived handicap i.e. assessed the effect a patient feels that their disease has had on different aspects of their life. 36.4% (84/231) of patients felt that their emotional state had been negatively affected by JIA, with a mean score of 2.8. **Figure 7.4.** 26% (60/231) of patients felt that their arthritis had had a severe detrimental effect (score of ≥7) on their emotional state.

Figure 7.4 Perceived effects of arthritis on mood



7.3.4. Predictive factors for mood

The best model of forward stepwise multiple regression analysis testing identified 8 variables that independently made a significant contribution (78.8%) to the variation in a patient's level of anxiety. **Table 7.1.** 4 variables accounted for 54.5% of the variation in depression levels **Table 7.2.**

Table 7.1 Predictive factors for anxiety in adults with JIA

	% variance predicted	F	p <
Self-efficacy symptoms	31.4	15.6	0.001
Social satisfaction	11.3	12.8	0.001
Perceived body image handicap	7.5	11.7	0.001
Catastrophising	8.9	12.6	0.001
Absence of 'open' coping skills	7.3	13.7	0.001
Age of onset 0-6 (protective effect)	5.4	14.6	0.001
Inflammation (TK index)	3.6	15.0	0.001
Previous depression	3.4	15.9	0.001
Total	**78.8**		

Table 7.2 Predictive factors for depression in adults with JIA

	% variance predicted	F	p <
Self-efficacy symptoms	17.8	7.9	0.01
Age of onset 7-11	13.3	8.2	0.001
Perceived body image handicap	13.8	9.7	0.001
Social contact satisfaction	9.6	10.6	0.001
Total	**54.5**		

Depression was more commonly seen when the age at onset of JIA was between 7 and 11 years, compared to early or late onset JIA. There was a non-significant trend for protection against depression in the group with onset after the age of 12. Those patients in the late onset group (over 12 years) had the highest risk of developing anxiety related problems. **Table 7.3.**

Table 7.3 Percentage adults with anxiety/depression related to age at onset of JIA

	Early onset (0-6 years)	Mid onset (7-11 years)	Late onset (12-16 years)
Anxiety	28.7%	29.6%	41.5% *
Depression	2.7%	11.1% **	0%

* Spearman $p < 0.05$ ** Spearman $p < 0.01$

7.4. Discussion

The level of current depression in this study group (5.2%) appeared to be lower than that of the general population and similar chronically disabled groups. Turner et al[152] screened 22,000 adults and identified 731 (6.7%) with physical disability sufficient to affect daily activities. Of those with physical disability, 37% and 46% scored within the range for depression and anxiety, respectively, compared to 12% and 18% of the matched comparison group. Even taking into consideration the different measures for mood used in this study, the level of depression in our study group appeared to be relatively low.

However, previous depression was relatively common. The most common time in a patient's life for a depressive episode was in their late teens or early twenties. At this age individuals tend to leave home and seek independence, consequently this is the time when coping techniques are finalised and put under most strain. Depressive episodes became less common in later life, suggesting that patients continued to learn to cope with their disease more effectively through experience. This supports the hypothesis suggested by Timko et al[153] that psychosocial adjustments continue with time as an individual adapts to their disease. Although previous depression continued to be an indicator of anxiety later in life ($p < 0.005$), it was not associated with continued depression at follow-up.

As previously reported by David[34] and Aasland[150] the levels of anxiety found in adults with JIA were well above those seen in the general population. Using a specific measure for anxiety (HAD) revealed that the incidence of anxiety in this group was even higher than previously suspected in JIA. Similar high levels of anxiety were

found in other well-controlled large studies of adults with disability related to other diseases.[152]

This study was limited by the selection of a patient group predominantly with more severe disease. It was also unfortunate that the most appropriate studies of anxiety and depression in the general population and other disabled groups used different measures of mood than the study group.

62.1% of patients did not feel that their arthritis had adversely affected their emotional state. However, 26% felt that their disease had a severe effect on mood. In the minority of patients where arthritis had an effect on emotional well-being, the influence of an individual's arthritis on mood was perceived as strong.

Patients were analysed according to their diagnostic subtypes to show specific groups at risk of poorer psychological health. Patients with oligoarticular arthritis had significantly less anxiety than other subsets, reflecting the less severe course and effects of JIA on this group. Patients with systemic onset JIA had higher scores for both anxiety and depression, which may be related in part to the high levels of physical disability and dependency seen in this subset.

Physical disease factors had little influence on the presence of a poor psychological state. All of the markers for depression had a psychological base, and clinical inflammation (Thompson Kirwan index) only accounted for 3.6% out of a total predictive total of 78.8% for anxiety. For both anxiety and depression the most important factor was the degree of influence the individual felt that they had over the symptoms caused by their arthritis (self-efficacy). This measure may indicate either a higher level of symptom unpredictability in those patients affected, or an inability to cope with a similar level of symptoms experienced by other patients. Two important shared causes of anxiety and depression were a lack of satisfaction with perceived levels of social support and poor body image. These factors were often present despite normal levels of actual social support and an attractive appearance because of a heightened perception of the effects of disease on the patient.

The age at onset of disease may have an effect later in life on the effectiveness of learned coping strategies to avoid anxiety or depression. The mid-onset (7-11 years) group had significantly higher levels of depression and the late onset (12-16 years) group had significantly higher levels of anxiety compared to those in other age groups, despite similar disease demographics between the groups. The apparent benefit to psychological health in the early onset group may be related to a lack of sufficient cognitive development[154] to comprehend the potential effects of arthritis. In the mid and late onset groups there may be a more pronounced effect of perceived loss due to JIA on the development of self-identity and self-confidence.

The importance of effective coping strategies was highlighted in this study. An open coping strategy (with patients being open and active in the manner in which they attempted to cope with their arthritis) was protective against both high levels of anxiety and catastrophising (destructive or negative thinking). Catastrophising increases the likelihood of developing an anxiety state.

7.5. Conclusions

Levels of depression in adults with JIA compared favourably to the general population. The incidence of anxiety in this group was extremely high. Depression was more common in systemic JIA and if the age at onset was between 6 and 11 years. Anxiety was less common in oligoarticular JIA and in patients whose age of onset was below 6. The most common time for patients to experience a depressive episode was between the ages of 15 to 24.

Reduced self-efficacy, poor body image and low levels of satisfaction with perceived social support mediated both depression and anxiety. Anxiety was also mediated by poor coping skills, later age at JIA onset and clinical inflammation (TK index).

The majority of mood disorders were related to imbalances within a patient's psychological state, rather than acute effects from their disease. The age at which JIA started plays an important role in the risks of depression and anxiety in later life.

Psychological variables, rather than acute effects of inflammatory disease explained the majority of variance in depression and anxiety in adults with JIA. The age at which JIA starts played an important role in the risks of depression and anxiety in later life. The effect of age at disease onset on coping strategies and their subsequent development would benefit from prospective study in children and adolescents with JIA.

8 CHAPTER VIII - Concurrent disease frequencies

8.1 Introduction

There are many extra-articular features and disease states associated with JIA. These diseases can be secondary to JIA, such as AA amyloidosis that is found in up to 7-11% of some systemic JIA populations,[25, 27, 60] and is caused by uncontrolled chronic inflammatory disease. It is likely that improved levels of inflammatory control and differences in patient referral practices are responsible for more recent reports of lower amyloidosis prevalence between 2.5%[37] and 3.3%[41]. Certain pathological states arise from the treatment of JIA, for example the high proportion of patients treated with steroids increases the risks of iatrogenic osteoporosis. There are also a group of diseases, which although not directly related to JIA, are found more commonly in association with it. These diseases include both autoimmune disorders such as hypothyroidism and genetic disorders such as Turner syndrome.[155]

Ocular involvement in JIA is a particular problem and can take many forms. An acutely painful red eye may be seen in the anterior uveitis associated with enthesitis related JIA. Sicca syndrome is known to be associated with polyarticular rheumatoid factor positive JIA, as it is in adult rheumatoid arthritis. The most common problem in the oligoarticular onset JIA subset is occult anterior uveitis, which affects around 20% of individuals. Because it is asymptomatic, it can easily be missed without appropriate screening with slit lamp examination. Untreated, it can cause blindness in up to 10% of affected patients. Topical corticosteroids and mydriatics are effective in the majority of patients, but intra-ocular injections or systemic corticosteroids are often required to prevent the formation of posterior synechiae between the lens and the iris. In severe refractory cases, immunosuppressive drugs such as methotrexate may be necessary to control the uveitis. 80-90% of patients with uveitis are positive for antinuclear factor, and girls presenting with oligoarticular disease below the age of 2 years have a 95% likelihood of developing chronic anterior uveitis. Uveitis can cause other forms of eye pathology such as glaucoma and cataracts. Iatrogenic cataract formation from long-term steroid use may also be troublesome in patients requiring oral corticosteroids for disease control.

AA amyloidosis is seen most often in systemic JIA, but has been reported in all forms of JIA. A clinical diagnosis of amyloidosis is usually suspected if a patient with active arthritis develops proteinuria, hypertension or unexplained high inflammatory markers without significant joint inflammation. The diagnosis can be made by histological examination of rectal, renal or subcutaneous fat biopsies, staining with Congo Red, which has an apple green birefringence under polarized light. The diagnosis can also be made by scintigraphy with a ^{123}I-labelled serum amyloid protein (SAP) component. Scintigraphy indicates the areas of the body significantly involved by amyloid and can also monitor response to treatment. The common sites of involvement with AA amyloid include the liver, spleen, kidneys and adrenal glands. Functional disruption occurs most commonly in the kidney and adrenals, with renal failure accounting for the majority of excess mortality. Treatment relies upon suppression of the patient's inflammatory response, and the cytotoxic drug chlorambucil has been shown to reduce mortality. Chlorambucil has a dramatic effect on the outcome of amyloidosis, reducing the mortality 15 years after the diagnosis of amyloidosis from 100% to 30%. However, chlorambucil has a significant side effect profile including an increased risk of malignancy, reversible leucopaenia or thrombocytopaenia, secondary ovarian failure and permanent azoospermia.

Osteoporosis and vertebral crush fractures are well described in JIA. Patients with JIA have a number of risk factors for osteoporosis including: steroid use, chronic inflammatory disease and immobility. The majority of investigators found diminished bone mass in patients with polyarticular and systemic JIA, particularly following treatment with oral steroids. Patients who have not received steroids still have a higher risk of reduced bone mineralization. In studies of bone metabolism in adult rheumatoid arthritis, it has been suggested that increased bone turnover is related to reduced bone mineral density. Research by Zak et al[156] suggests that this is also the case for adults with JIA. They also describe other associated risk factors in a group of 65 adults with JIA, including; continuing disease activity, physical disability, polyarticular disease, previous erosive disease and systemic steroid treatment.

Premature ovarian failure is a condition characterized by amenorrhoea, infertility, oestrogen deficiency and elevated levels of circulating gonadotrophins in women under

the age of 40 years. In the general population it affects 1% of women by the age of 40 years, and 0.1% by age 30 years.[157] Up to 32% of patients with premature ovarian failure have an associated autoimmune disorder including: rheumatoid arthritis, hypoparathyroidism, hypoadrenalism, myasthenia gravis, pernicious anaemia, diabetes mellitus and hypothyroidism, with hypothyroidism being the most common.[158] Circulating antibodies to ovarian tissue have been found in a proportion of these women, but the tests are not well-standardised, correlate poorly with ovarian histology and are highly variable.[159] There remains a lack of consensus on ovary specific antibodies as a marker for ovarian autoimmunity.[160] The gold standard for detecting immune ovarian destruction remains invasive ovarian biopsy, which shows lymphoplasma cellular infiltrate around sex steroid-producing cells.

There is no published data on whether premature ovarian failure occurs in adults with JIA. David et al[34] noted that 6/23 women with JIA treated with chlorambucil had ovarian failure. Østensen et al[138] reported that compared to healthy controls there was a significant increase in gynaecological diseases in women with JIA including: menstrual disturbance, pelvic inflammatory disease and ovarian disease.

There have been isolated reports of NSAID therapy causing female infertility.[161, 162] The likely mechanism is thought to be COX-2 inhibition causing luteinised unruptured follicle syndrome (LUF syndrome), an anovulatory condition characterised by clinical signs of ovulation in the absence of follicular rupture and ovum release. LUF syndrome does not appear to alter luteinising hormone (LH) / follicle stimulating hormone (FSH) levels, although the urinary pregnanediol:creatinine ratio is reduced post LH peak in the menstrual cycle.

8.2 Methods

8.2.1 Assessment of ocular involvement

At interview and on notes review, evidence of uveitis was sought. Medication was reviewed see if patients still required drugs to control their uveitis. Uveitis was correlated with disease subset and the presence or otherwise of anti-nuclear antibodies (ANA). The number of individuals who were registered blind in one or both eyes was

also noted. Other forms of ocular pathology were recorded, including pathology usually related to the presence of uveitis, such as glaucoma and eye surgery, and pathology unrelated to uveitis such as Sicca syndrome. Cataract formation related to both uveitis and steroid use was also recorded.

8.2.2 Assessment of amyloid

The presence of AA amyloid was recorded either by labelled SAP scan or by positive biopsy, along with use of chlorambucil and the side effects related to its administration. These specifically included the reproductive ability of men and women following chlorambucil administration. Amyloid induced chronic renal failure was noted and whether renal failure progressed to renal transplant or improved with treatment.

8.2.3 Assessment of osteoporosis

Many patients had already received a dual energy X-ray absorptiometry scan (DEXA) at the lumbar spine and femur (in those without bilateral hip prostheses) to assess for the presence of osteoporosis. In addition, patients with high risk factors such as steroid use or short stature were considered for referral for DEXA at interview. Correlative information such as length of time on steroids, daily or alternate day regimes for steroids, height, disease activity, physical function, duration of disease and JIA subset were collected. Clinical information relevant to osteoporosis such as previous low impact long bone and vertebral crush fractures were noted.

8.2.4 Assessment of premature ovarian failure

The 176 women in the study were asked whether they had a regular monthly menstrual cycles. In those patients without regular menstruation, circulating levels of gonadotrophins were measured if the presence of menopause had not previously been confirmed. The patient's age and their age at the onset of menstrual irregularity or absence were also recorded. Previous medication use and concurrent diseases including Turner's syndrome were noted.

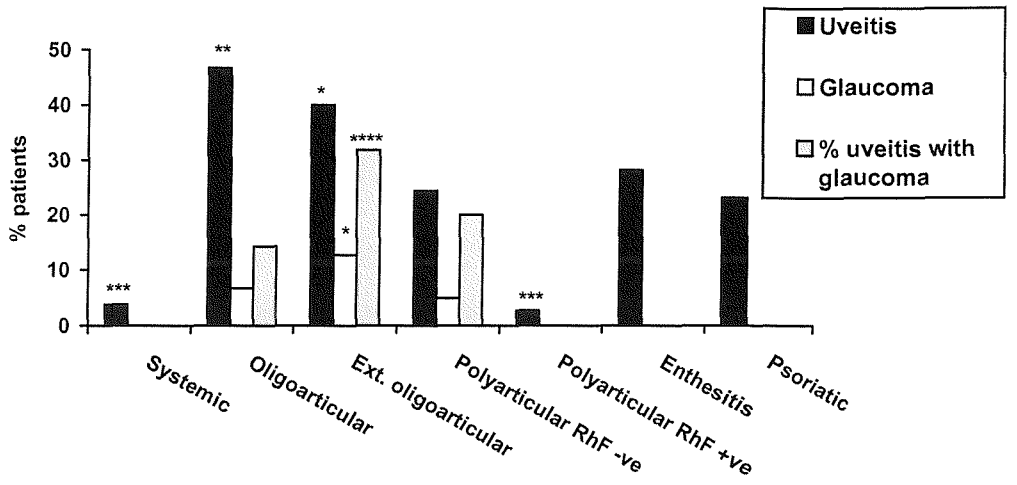
The incidence of premature ovarian failure in the study group was compared to that described by Coulam et al,[157] rather than a healthy population, because of the excessively large numbers of controls required to reliably predict such an uncommon occurrence in the general population. Non-parametric Spearman correlation was used to assess any significant differences between incidences described in the study population, compared to the expected incidences in the general population.

8.3 Results

8.3.1 Ocular involvement

Uveitis had affected 22% (54/246) of the study group at some time in their disease course. There were significantly higher levels in the oligoarticular and extended oligoarticular subsets and significantly lower levels in the systemic and rheumatoid factor positive polyarticular subsets. **Figure 8.1**

Figure 8.1 Proportion of patients with uveitis and related glaucoma in each subset



Compared to the other subsets:

* increased rate of uveitis and glaucoma in ext oligoarticular JIA $p < 0.001$

** increased rate of uveitis in oligoarticular JIA, $p < 0.05$

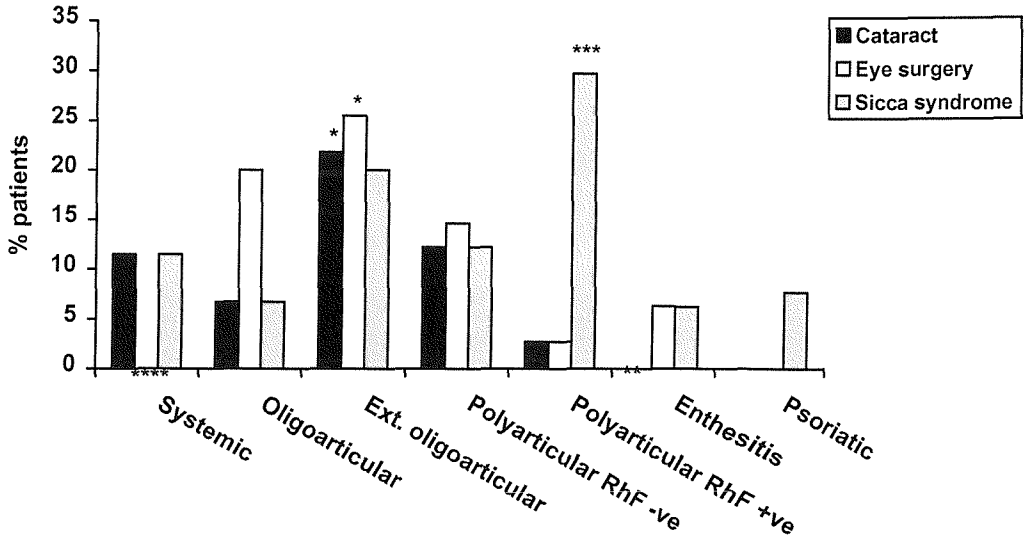
*** decreased rate of uveitis in rh. factor positive and systemic JIA $p < 0.005$

**** increased rate of glaucoma in patients with extended oligoarticular JIA and uveitis, $p < 0.05$

10.6% (26/246) of patients had required eye surgery and 10.2% (25/246) had cataracts. Both were more commonly seen in the extended oligoarticular group. There was a close relationship between eye cataracts and eye surgery, as 72.0% (18/25) of cataracts detected had already been surgically extracted. In the systemic onset JIA group, all of the cataracts were in patients with previous steroid use, but none had required surgical removal. The enthesitis related JIA group had a significantly lower incidence of cataracts than all other groups. **Figure 8.2.**

Sicca syndrome had an overall incidence of 15% (37/246) and was significantly more common in patients with rheumatoid factor positive JIA involving 29.7% (11/37).

Figure 8.2 Proportion of patients with Sicca syndrome, cataract and eye surgery in each subset



Compared to the other subsets:

* increased rate of cataract and eye surgery in patients with extended oligoarticular JIA, $p = 0.001$

** decreased rate of cataract in patients with enthesitis related JIA, $p < 0.05$

*** increased rate of Sicca syndrome in patients with rheumatoid factor positive polyarticular JIA, $p < 0.01$

**** decreased rate of eye surgery in patients with systemic JIA, $p = 0.005$

The relationship between ANA and uveitis is described in **Table 8.1.** Uveitis was significantly and directly related to ANA positivity in patients with extended oligoarticular JIA (90.5%) and rheumatoid factor negative polyarticular JIA (30%). A similar association was seen in the persistent oligoarticular group, but this did not reach statistical significance due to the small number of patients in this group. None of the patients with uveitis in the spondyloarthropathy subsets (enthesitis related and psoriatic JIA) were ANA positive and this was significant in the enthesitis related subset.

Table 8.1 Frequency of uveitis and ANA positivity related to JIA subset

	Number of patients with uveitis (%)	Number of patients ANA positive with uveitis (%)
Systemic onset JIA	2/52 (3.8)	2/2 (100)
Oligoarticular JIA	7/15 (46.7)	6/7 (85.7)
Extended Oligoarticular JIA	22/55 (40)	20/22 (90.5) $p < 0.001$
Polyarticular (RhF –ve) JIA	10/41 (24.4)	3/10 (30) $p < 0.05$
Polyarticular (RhF +ve) JIA	1/37 (2.7)	1/1 (100)
Enthesitis related JIA	9/32 (28.1)	0/9 (0) $p < 0.001$
Psoriatic JIA	3/15 (20)	0/3 (0)

8.3.2 Amyloidosis

8.9% of patients had amyloidosis, diagnosed by either rectal biopsy or serum amyloid protein (SAP) scan and presenting with either proteinuria or a CRP out of proportion to disease activity. This most commonly affected those patients with systemic JIA. **Table 8.2**. Men were affected more commonly (14.1%) than women (5.2%). A further 7 patients with amyloidosis under the care of Wexham Park Hospital (not included in the study group) had died in the preceding decade. 5 of these deaths could be directly attributed to amyloidosis and a further two were related to leukaemia occurring post chlorambucil therapy for amyloid.

Table 8.2 Frequency of amyloidosis related to JIA subset

	Number of patients with amyloid (%)
Systemic onset JIA	10/52 (19.2)
Oligoarticular JIA	0/15 (0.0)
Extended oligoarticular JIA	2/55 (3.6)
Polyarticular (RhF –ve) JIA	4/41 (9.8)
Polyarticular (RhF +ve) JIA	1/37 (2.7)
Enthesitis related JIA	1/32 (3.1)
Psoriatic JIA	1/15 (6.7)

Chlorambucil had been given to all but two individuals, who at review had well-controlled amyloidosis on methotrexate only. 15/21 remained well controlled having discontinued chlorambucil after a mean time of 4.46 years and 4/21 remained on chlorambucil for a mean time of 2.59 years. Two women treated with chlorambucil for amyloidosis had subsequently become parents. All of the men who had received chlorambucil and subsequently had sperm counts (5/9) were azoospermatic. Two of the eight women (25%) who had received chlorambucil had undergone an early menopause (before the age of 40) proven by testing follicle stimulating hormone and luteinising hormone. The mean time between starting chlorambucil and the onset of menopause was 17 years, suggesting a long-term effect from this cytotoxic agent.

8.3.3 Osteoporosis

39% of patients (95/246 comprising 79 females and 16 males) had previously had a dual energy x-ray absorptiometry (DEXA) scan. The common reasons for the scan included: steroid use, onset of menopause, low impact vertebral or long bone fracture and concurrent risk factors such as smoking and immobility. 60/95 (63.2%) of this high-risk group of patients were shown to have osteoporosis and a further 3 women in whom DEXA scans were not performed had previous low impact fractures. Lumbar spine scans had been performed in all 95 patients, but 40% of these had previously had bilateral total hip replacements thus reducing the number of patients having hip DEXA scans to 57.

Lumbar spine osteoporosis occurred in 35.6% (34/95). There was a significant association with low patient weight ($p<0.005$). Hip osteoporosis occurred in 49.1% (28/57). There were associations with low patient weight ($p<0.001$) and total steroid duration ($p<0.05$). There was an increased risk of hip osteoporosis ($p<0.05$) in enthesitis related arthritis and a reduced risk in psoriatic arthritis ($p<0.05$).

Those factors that significantly correlated with the presence of osteoporosis at any site ($p<0.05$) were entered into a hierarchical multiple linear regression analysis to assess factors for their potential for predicting osteoporosis. Potential predictive factors included height, weight, female height, rheumatoid factor positive polyarticular JIA subset, total steroid duration, average steroid dose per year of treatment and age at onset of menopause. The best model of forward stepwise multiple regression analysis identified 5 variables that independently made a significant contribution (56.0%) to the presence of osteoporosis as shown in **Table 8.3.**

Table 8.3 Predictive factors for osteoporosis in adults with JIA (ex HAQ score)

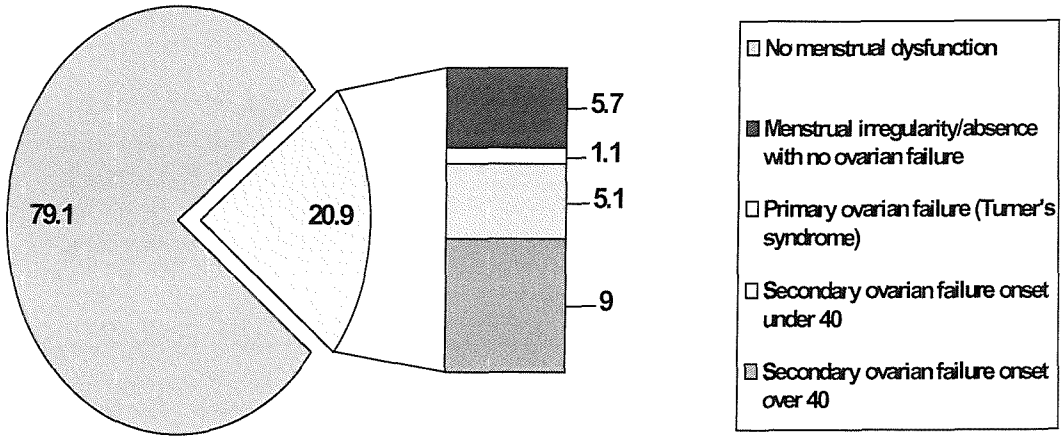
	% variance predicted	F	p <
Age at onset of menopause	39.4	9.1	0.01
Rheumatoid factor positive polyarticular JIA	7.6	5.8	0.05
Weight	7.0	4.8	0.05
Height	1.7	3.5	0.05
Total steroid duration	0.3	2.5	0.1
Total	**56.0**		

However, if functional ability measured by HAQ was included as a potential predictive factor in the regressional analysis, the best model identified just a single variable (HAQ score), which predicted 68.6% of the variance in osteoporosis ($F= 32.8$; $p<0.001$)

8.3.4 Premature ovarian failure

37/177 (20.9%) female patients were found to be either amenorrhoeic or having significant menstrual irregularity **Figure 8.3**. The gonadotrophin levels in 10 patients (5.6%) indicated that they did not have ovarian failure. 2 of the patients were known to have Turner syndrome (1.1%), which has a recognised association with JIA.[155] Of the remaining 25 patients who were menopausal, 9 (5.1%) became amenorrhoeic before the age of 40. There was no significant correlation between either amenorrhoea or premature ovarian failure and JIA subset. 3/9 of the patients with premature ovarian failure had been treated with chlorambucil (2 for JIA related amyloidosis and one for disease activity control). Chlorambucil was prescribed for a total of 9 women in the study group. In those with iatrogenic ovarian failure it had been prescribed for a period of 1.1 years from age 15, 2.7 years from age 9 and 16.1 years from age 10. The use of DMARDs in the remaining 6 patients included penicillamine, sulphasalazine, azathioprine and gold, but there was no evidence of the use of alkylating agents that could cause iatrogenic premature menopause. Two of the patients with premature ovarian failure had other autoimmune disease (hyperthyroidism and alopecia).

Figure 8.3 Percentage of women with JIA with menstrual dysfunction



The six patients with premature ovarian failure unrelated to medication use comprised 3.4% of the females in the study, compared to an expected incidence of 1%[157] in the general population ($p < 0.01$). In addition, three (1.7%) of these had onset of symptoms before age 30, compared to an expected incidence of 0.1% in the general population ($p < 0.01$).

Although there was a correlation between premature ovarian failure and the duration of NSAID treatment at review ($p<0.05$), the subgroup with premature ovarian failure were on average 6.8 years older than the rest of the study group, bringing the significance of this finding into question. Duration of NSAID treatment at review was not found to be a predictive variable in a stepwise multiple regression analysis for early menopause, with age being the only predictor of 38.9% of the variance in early menopause ($p<0.005$). This suggests that there is no real correlation between duration of NSAID treatment and premature ovarian failure.

8.4 Discussion

8.4.1 Ocular involvement

Uveitis was seen commonly, particularly in those subsets with an oligoarticular onset. Despite a relatively high frequency of uveitis in enthesitis related and psoriatic JIA, none of these patients were ANA positive and none went on to develop glaucoma, suggesting a more benign ocular disease course than the other subsets. In contrast, the oligoarticular onset groups had the highest rates for cataracts and eye surgery. 90% of the oligoarticular onset JIA patients with uveitis were ANA positive and nearly a third of these went on to develop secondary glaucoma.

The 30% incidence of Sicca syndrome in rheumatoid factor positive polyarticular JIA mirrors the incidence reported in adult onset rheumatoid arthritis.[163]

8.4.2 Amyloidosis

Amyloidosis rates match those described by other authors, with systemic onset JIA conferring the highest risk (20% in this study). The use of chlorambucil has been

shown to improve the long-term survival rates of JIA related AA amyloidosis, but also confers a high toxicity load in terms of gonadal failure and oncogenicity. There are recent reports on preserving fertility in women with SLE following treatment with chlorambucil/cyclophosphamide using concurrent gonadotrophin-releasing hormone agonist analogue (GnRH-a). This induces a temporary pre-pubertal hormonal milieu. This suggests that the ovarian toxicity of chlorambucil may be partially ameliorated.[164]

8.4.3 Osteoporosis

Although DEXA scanning was only performed on patients with high-risk characteristics, the incidence of osteoporosis in this group was remarkably high. The patients who had bilateral hip replacements correlated strongly with poor functional outcome (HAQ) ($p<0.001$) and it is probable that a high proportion of these patients would also have had osteoporosis present at the hip prior to joint replacement. Hip osteoporosis was related to classical risk factors such as low body weight and steroid use, but these factors did not appear to explain either the higher risk in the enthesitis related subset, or the lower risk in the psoriatic related subset.

The multiple regression analysis which excluded function as a predictive factor, highlighted various factors which are well recognised as having a detrimental influence on bone mass, including steroid use, low body weight, rheumatoid factor positivity and absence of female hormones. The fact that these variables disappeared from the list of predictors on adding HAQ score to the analysis shows the strong link between function and osteoporosis. It suggests that patients with significant functional disability should be considered for a DEXA scan to assess their risk of osteoporotic collapse.

8.4.4 Premature ovarian failure

As previously described a significant proportion of women with JIA have menstrual disturbances.[138] Although premature ovarian failure has been described in other autoimmune conditions such as Graves' disease,[165] insulin-dependant diabetes mellitus[166] and Addison's disease[167] it has not been previously described in JIA. Early loss of ovarian function has both significant physical sequelae (amenorrhoea, breast atrophy, mucosal dryness, fatigue and loss of libido) and psychosocial sequelae

(exclusion from 'motherhood', loss of self-esteem and poor body image). It also has major health implications, with a nearly two-fold age-specific increase in mortality rate.[168] However, premature ovarian failure should not be viewed simply as premature menopause, as half of all patients with this condition have intermittently functional ovarian follicles and a 5-10% chance for spontaneous pregnancy.[169]

Premature ovarian failure was previously considered to be irreversible and was described as premature menopause; however half of women with premature ovarian failure are now recognized to have intermittent ovarian function[170] and pregnancies do occur in premature ovarian failure.[169] Patients have a 5-10% chance of spontaneous pregnancy and pregnancies have even been reported in women with no follicles observed on ovarian biopsy. Young women with premature ovarian failure sustain sex steroid deficiency for more years than naturally menopausal women, resulting in a significantly higher risk of osteoporosis[171] and cardiovascular disease[172] with an almost two-fold increase in mortality rate.[168]

Because premature menopause occurs in 1% of the general population below 40 years and 0.1% below 30 years, the size of a control group to reliably predict the incidence of premature ovarian failure becomes prohibitively large. Published data on general population incidence was therefore used to create a theoretical control group.

At the time of this study, 1.7% (3/176) of women below 30 years of age and 3.4% (6/176) of women below 40 years of age had premature ovarian failure. However, these figures are likely to be an underestimate, as 40/176 (22.7%) patients had not reached 30, and 106/176 (60.2%) patients had not reached 40. These patients still have the potential to develop ovarian failure and subsequently increase the incidence described, in contrast to the data from the general population, which was collected in patients over 40 years of age. In contrast to other autoimmune disorders, the risk of early ovarian failure is present throughout adult life, as by definition the onset of JIA is before an individual reaches adulthood.

There are significant implications for women with JIA in terms of when they should consider starting a family, as delay may put them at risk of infertility. This is of

particular importance as the average maternal age at first delivery in the study group is 3.7 years higher than the general population (see 6.3.2.) A proportion of this increase in maternal age may be related to adults with JIA entering stable relationships (marriage or cohabitation) at an older age (see 6.3.1.).

The proportion of women 3/9 (33.3%) with premature ovarian failure related to chlorambucil therapy is comparable to other studies.[60] There is some evidence[173] that younger women are more resistant to the ovarian effects of alkylating agents than older women. In some younger patients with iatrogenic premature ovarian failure, ovarian function may return. Recent reports of the preservation of fertility in women with SLE following treatment with chlorambucil or cyclophosphamide using concurrent gonadotrophin-releasing hormone agonist analogue (GnRH-a), to induce a temporary pre-pubertal hormonal milieu, suggests that the ovarian toxicity of chlorambucil could be partially ameliorated.[164] Further study would be useful, prospectively assessing a group of individuals with JIA entering adulthood. This should include an assessment of whether ovarian auto-antibody levels predict ovarian failure and whether antibody levels change at the time of premature ovarian failure onset.

9 CHAPTER IX - Summary

This is the largest and longest follow-up study to give detailed clinical and functional information on adult patients with long-standing JIA, from all subsets of the disease. They do not represent a true cohort, but are patients who have more severe JIA, and are those most likely to be encountered in an adult rheumatologists clinical practice. Therefore the aim of this research was not to undertake cohort based epidemiological research, but to document patients' functional, psychological and social support needs, highlighting areas that commonly affect patients' function and independence. This may improve the ability of health workers to anticipate patients' requirements to keep them independent and assist a more appropriate distribution of health resources in this disabling disease.

9.1 Classification

The majority of previous studies have not separated the disease subsets, which are known to affect prognosis and outcome. This study is the first to apply the recently introduced ILAR criteria[6] rather than the EULAR criteria[8] or ARA criteria [8, 9] to patients with longstanding disease. The main differences between these classifications are an expansion in the recognised subsets as shown in **Table 1.2.**

Retrospective classification is potentially unreliable, but the documentation of clinical findings at onset of disease was felt to be sufficiently detailed to allow clear classification. The classification of patients in the study benefits from the long follow-up period, as individuals may change their classification with time after the initial diagnosis at 6 months **Table 1.3.** This is particularly true for the oligoarticular onset group who often develop disease involving 5 or more joints and enter the extended oligoarticular subset. The systemic onset subset does not change with time, as this subset is entirely dependant on the clinical features at onset rather than subsequent disease progression.

Oligoarticular onset patients without dactylitis/psoriatic nail changes, in whom a family member develops psoriasis, are at present reclassified as 'other'. This exclusion from the oligoarticular onset subsets has been identified as a difficulty in the classification[58],

and it has been suggested that 'second degree heredity for psoriasis be withdrawn as an exclusion criteria from the ILAR criteria'.[59] Family history of psoriasis was therefore not included in the classification parameters for the study. It was also felt that because of the duration of patient follow-up, any patients with initially occult psoriasis causing their arthritis would have developed skin manifestations. Subsequently, none of the patients reviewed were 'unclassified'. Unfortunately, data was not collected on family history of psoriasis, and therefore it is not possible to be exact as to the number of patients who would have become 'unclassifiable' because of their family history. Specifically, no patient with RhF positive polyarticular JIA had psoriasis and none of the enthesitis related JIA patients were ANA positive. This suggests that these subsets are well defined and the exclusion criteria are appropriate.

9.2 Demographics and physical function

Patients were referred to Wexham Park from a wide geographical area. This may have had an influence on the socio-economic mix of patients' families, with higher social class families being more likely to seek tertiary specialist care. However, it is unlikely that this effect differs significantly from any other tertiary referral centre.

Because this is a long-term follow-up study and not cohort based, the frequencies of JIA subgroups in the study group vary from those seen in a paediatric population (British Paediatric Rheumatology Group database[1]). Those subsets with a good outcome such as persistent oligoarticular arthritis are under represented in the study group, since many go into remission, do not require continuing hospital review or are under the care of a local adult rheumatologist. In the paediatric rheumatology population between 35-50% of oligoarticular patients subsequently extend to a polyarthritis.[100, 174] This suggests that compared to the 55 patients with extended oligoarthritis in this study group, there should be between 55-102 patients with persistent oligoarthritis, when the patients with oligoarthritis in the study group number just 15. There are likely to be between 40-87 individuals (between 36-79% of all oligoarticular onset patients) who no longer require ongoing rheumatology support into adulthood and are therefore not included in this study. In our study population almost

80% of the oligoarticular subset had progressed to polyarticular disease, indicating the need for continuing medical review in those patients whose arthritis extends.

The subsets with the worst prognosis as regards function (systemic and rheumatoid factor positive polyarthritis) comprise just 14% of a paediatric rheumatology population[1], but 36.3% of our study group.

The concept that JIA becomes less inflammatory with time and 'burns out', is not supported by the finding that around 50% of all patients continue to have detectable inflammation late in the disease course. The real level of continuing active disease is probably even higher than 50%, as in the absence of active synovitis on clinical examination, deformities may continue to develop and synovitis may be found at operation. The systemic subset has the worst functional outcome and in the paediatric population it has the highest levels of inflammation, sufficient to cause 57% of JIA related AA amyloid.[60] In contrast, in our study levels of clinical inflammation (TK index) are lower in systemic onset JIA than in any other subset. A reduction in the level of inflammation at long-term follow-up in systemic onset JIA has also been described by David[34] and Svantesson[27] and suggests that the concept of arthritis 'burning out' may hold true in the systemic onset subgroup.

The degree of disability in our patients mirrors that found in other studies. Severe functional limitation was present in 37.1% (Steinbrocker III or IV) and 42.9% (HAQ score > 1.5) of all patients. Patients with all patterns of polyarticular disease have a higher risk of severe functional limitation that is most evident in the systemic JIA subgroup.

The need for prosthetic joint replacements increases with severity and time. The influence of severe disease in childhood, as evidenced by the correlation between the presence of prosthetic joints with systemic onset JIA, growth defects and height retardation, highlights the importance of disease control from an early age. With the recent introduction of more effective immunosuppressive agents and earlier aggressive intervention, the proportion of these patients who go on to require surgery may well reduce in the future.

Adults with JIA often have significant levels of disability, usually related to severe continuing active disease over a prolonged period. There is a clear requirement for good transition from paediatric/adolescent to adult rheumatology and high quality ongoing care.

9.3 Education and employment

The majority of children with severe juvenile arthritis are managed within regional units and benefit from mainstream education. The attitude of the general population and the potential for discrimination may be beneficially affected by the exposure of able-bodied children to the disabled population.

JIA patients have a high level of educational achievement, with a high proportion of patients gaining university degrees. There are a number of factors that may have influenced this. Certainly, the personality and motivation of individuals who already have to cope with a chronic disabling illness during their schooling years may be affected in beneficial ways by the same need to develop coping skills and strategies. The home environment may be more conducive to academic attainment. It could be postulated that because parents have offspring who are less likely to show prowess physically, then the parents concentrate their energies and parenting skills towards enabling the child with arthritis to achieve academically. Similar effects could also have an influence in the school environment, with teachers concentrating their efforts towards the academic aspects of education for children with arthritis. This retrospective study is not designed to evaluate the factors which affect academic prowess and this would need to be addressed in a separate prospective study carried out in school aged children.

Successful education eases the transition from education to employment, which is closely related to the highest education level attained ($p < 0.001$). Patients who have a degree of physical impairment may be less distracted from their studies by physical activities than their peers. If patients are able to enter a profession (class I) there

appears to be less impact from their disease. No one in a professional career had to leave work because of his or her disease.

Poor school attendance in ill children and periods of hospitalisation or tuition at home can lead to a decline in educational progress.[126] The effects of home tuition inevitably involve a degree of social isolation of the child from their peers. In this study the number of close social contacts is significantly higher in patients with higher levels of educational achievement ($p < 0.001$) and also in patients educated solely within mainstream schools. The level of satisfaction with social support was higher when individuals were mainstream educated ($p < 0.05$). The level of disability (HAQ score) does not appear to adversely affect satisfaction with social contact.

Despite being a well-educated group, unemployment was much higher in the patient group. The majority of patients without work attribute their unemployment to the disabling effects of their disease. Physical disability is not as severe in employed patients compared to those without work. The 6.5% of unemployed patients who had never entered the workplace tended to be less disabled than the 21.7% of patients who could no longer work. This suggests that the factors that govern successful transition from education to employment are not solely related to physical ability. The predictive factors for unemployment were not only educational achievements and physical function but also the presence of poor coping strategies. This suggests that an individual's ability to successfully cope with their arthritis has a large impact on their success in the workplace.

Unemployment impacts on the financial security and independence of an individual. There is also a cost implication for society, with patients who become more dependent upon the state, requiring more financial support. The majority of state support is related to the increased disability in the unemployed group, which necessitates a higher level of care and mobility support. However, a proportion of these costs would fall if patients were able to return to employment.

The level of unemployment in the JIA group (28.3%) is similar to that found in other disease states with onset in childhood causing disability into adulthood. In cystic

fibrosis 17/49 patients (34.7%) were unemployed as a direct result of their disease.[175] In this group, disease severity was only one of many predictive factors for unemployment, these included age, single marital state, adult diagnosis of disease and female gender.

When rheumatoid arthritis employment levels are reviewed, similar levels of unemployment are described within 5 years of disease onset. Barrett et al[176] showed that rates of work disability in rheumatoid arthritis 1, 2, 5 and 10 years after symptom onset were 14%, 26%, 33% and 39% respectively. This suggests that adults with JIA are more likely to continue working long term than their rheumatoid arthritis counterparts.

Over a quarter of patients felt that they had been discriminated against at work. The majority of workplace discrimination occurred around job interviews, with problems equally split between a failure to be interviewed initially and a perception of unreasonably high levels of failure once interviewed. Once in work discrimination was a more covert problem, with access problems and delays in promotion predominating. Only a small proportion 6% had experienced overtly negative or discriminatory attitudes towards them, usually from direct superiors.

There should be a focus on careers in adolescent rheumatology clinic, with opportunities to have contact with specialist careers advisors. Assertiveness training, interview techniques and attempts to address the psychological needs of the individual would improve their chances in the competitive job market.

9.4 Mood and Pain

The incidence of depression (5.2%) in this study group is similar to that of the general population, with estimates of 6% of the population experiencing depression in any one 6 month period.[177] Depression appears to be lower than in many similar chronically disabled groups[178] **Table 9.1**

Table 9.1. Depression prevalence rates in chronic disease

Setting or disease	Depression prevalence rate %
Outpatients	2-15
Hospitalised patients	12
Cancer	18-39
Myocardial infarction	15-19
Rheumatoid arthritis	14-46
Parkinson's disease	10-37
Stroke	22-50
Diabetes	5-11

The overall prevalence of previous depression in the study group at 21.2% is higher than the general population, where epidemiological studies report a population based prevalence rate of 17%.[179]

The average age of first major depression often occurred in the late teens or early twenties. This is earlier than in the general population, where the average age of first major depression has fallen from the 45-49 in the 1960's to the 25-29 in the 1980's[180], but still remains older than the study group. It is in their late teens and early twenties that individuals tend to leave home and seek independence, consequently this is the time when coping techniques are finalised and put under the most strain.

It is at this age that patients tend to transfer care from paediatric rheumatology, under the care of a team of health professionals who may have known them for many years. They usually transfer to the care of adult rheumatologists, who may or may not have any specific interest in JIA and are unlikely to know the patient prior to transfer. This could potentially mean that depression, which occurs often in this age group, is picked up later and potentially at a more advanced stage, simply because their health care team has changed and know them less well. This highlights the need for a careful transition from paediatric to adult care, ideally with some overlap of care between paediatric and adult rheumatology teams and with a thorough transitional report. This may reduce the inherent difficulties in giving a seamless and high quality of health provision to the individual who is having their care transferred between two teams.

Depressive episodes become less common in later life, suggesting that experience enables patients to learn to cope with their disease more effectively. This supports the hypothesis suggested by Timko [153] that psychosocial adjustments continue with time as an individual adapts to their disease.[34] The levels of anxiety found in adults with JIA were well above those seen in the general population. Similar levels of anxiety are found in other well-controlled large studies of adults with disability related to other diseases.[152]

Physical disease factors had little influence on the presence of a poor psychological health. All of the indicators of depression had a psychological base, and clinical inflammation accounted for only 3.6% out of a predictive total of 78.8% for anxiety. This lack of influence from factors, which would appear to have a self-evident potential effect on mood, such as physical ability, variable degrees of disease activity and growth restriction, warrants further comment. It is likely that although the actual physical effects of JIA do have an impact upon the individual, more importantly, it is the affect that these effects have upon the psychosocial functioning of the individual that take priority. Therefore it is not the growth retardation that has the greatest impact, but the detrimental affect that this has upon body image. Similarly, physical ability impacts upon an individual's ability to socialize and those patients with variable levels of disease activity may feel less in control of their bodies (self-efficacy). Self-management courses with specific techniques being learnt and practiced not only improve self-efficacy but also benefit patients' health outcomes.[79]

There was a direct physical influence on pain from physical function and joint inflammation, and a psychological influence on pain from self-efficacy, previous depression and coping strategies. It appears that as a patient enters adulthood, pain coping strategies become a more important predictor of pain. Two coping strategies (*denial and dependence*) are detrimental to pain intensity. Both strategies avoid confronting the disease and its related symptoms.

Psychological variables, rather than acute effects of inflammatory disease, explain the majority of variance in depression and anxiety in adults with JIA, and both physical and psychological factors influence pain. A holistic approach is necessary, where both the

patients' physical and psychological needs are met. Effective psychological strategies enabling patients to cope with the stressors of chronic arthritis may be just as effective as reaching for the prescription pad.

9.5 Relationships and social function

Individuals in the study group were more likely than their siblings to be single and living outside a stable partnership. The proportion of patients married to date is lower, but individuals with JIA may be deferring marriage to ensure that their partner is the right person to also become a potential carer. However, there are likely to be negative effects from disease influencing when an individual gets married. There may be less opportunity to meet someone socially if you have physical restrictions that affect your ability to access social activities. Potential partners may discriminate against choosing individuals who have health problems, are physically restricted, or if they don't perceive their appearance as 'normal'. Once a relationship is established, partners may find it difficult to make a formal commitment. This may be either from fear of the unknown implications of JIA, or because they do not wish to become potential carers. Many individuals with disability end up married to partners with similar problems. This may be in part because they find it harder to meet or attract someone without disability. There may be more empathy and understanding between two individuals who are disabled. Often social events, which are attended by a disabled person, are also attended by other disabled people. The number of disabled people that a disabled individual comes into contact with is therefore likely to be higher than for the general population.

The level of satisfaction with an individual's social support was high. The majority of patients thought their arthritis had a negative effect on their body image. Objective measures of physical deformity, such as growth defects and short stature, were not related to the perception of unattractiveness, which was most strongly related to poor physical function. This suggests that those individuals who find physical difficulty in social interaction have the poorest perception of their own attractiveness.

The reported miscarriage rate at 24% was higher than expected, with estimates in the general population of around 7-9%. [141, 142] However, the estimates in the general population are from admission rates following miscarriage rather from directly interviewing patients. It is likely that the general population rates are an underestimate. The rates for termination of pregnancy in the UK under the 1967 Abortion act in the general population were 18% between 1994-5[141], the rates of termination of pregnancy in the study population were much lower at 5.6% of all pregnancies. This may suggest that either patients plan their families more carefully with appropriate and effective contraceptive use, or that if women become pregnant, then they are less consider termination.

The overall caesarean rate in the study population 37% (19/52) was higher than expected in general population, in 2002 22% of women delivered by caesarean[143]. The rate of caesarean section in the general population has been steadily rising over the past decade with rates of 11.3% in 1990, 15.5% in 1995 and 20.6% in 2000. As this is a retrospective study, a number of the caesarean sections in the study were carried out whilst caesarean section rate was lower than it is at present in the general population. Caesareans were more often required in patients with limited hip abduction and those below the third centile for height. These factors should be taken into consideration when counselling patients about potential problems they face during pregnancy.

The majority of patients, though experiencing high levels of disability were sexually active. Despite a slightly older age at first sexual experience, a significant minority of patients became sexually active whilst still under the care of a paediatric rheumatologist. As potentially teratogenic drugs are increasingly used in the paediatric population, the need to address contraception in adolescent clinics becomes essential. Sex education is frequently inadequate for young adults in the general population and issues around disability and arthritis should be discussed with an open attitude and without embarrassment.

Although the majority of sexual problems were related to physical disability and pain, there was a high incidence of psychological problems concerning self-confidence and

perceived attractiveness. It should be possible to address the psychological areas of difficulty with appropriate advice, counselling, self-esteem and assertiveness training.

9.6 Premature ovarian failure

As previously described a significant proportion of women with JIA had menstrual disturbances.[138] At the time of this study, 1.7% of women below 30 years of age and 3.4% of women below 40 years of age had premature ovarian failure. Although premature ovarian failure has been described in other autoimmune conditions it has not been previously described in JIA. Early loss of ovarian function has both significant physical sequelae (amenorrhoea, breast atrophy, mucosal dryness, fatigue and loss of libido) and psychosocial sequelae (exclusion from 'motherhood', loss of self-esteem and poor body image).

Young women with premature ovarian failure sustain sex steroid deficiency for more years than naturally menopausal women, resulting in a significantly higher risk for osteoporosis[171] and cardiovascular disease[172] with an almost two-fold increase in mortality rate.[168]

The proportion of women 3/9 (33.3%) with premature ovarian failure related to chlorambucil therapy is comparable to other studies.[60] There are recent reports of preserving fertility in women with SLE following treatment with chlorambucil or cyclophosphamide using concurrent gonadotrophin-releasing hormone agonist analogue (GnRH-a), which induces a temporary pre-pubertal hormonal milieu. This suggests that the ovarian toxicity of chlorambucil may be able to be partially ameliorated.[164]

There are significant implications for women with JIA in terms of when they should consider starting a family, as delay may put them at increased risk of infertility. This is of particular importance as the average maternal age at first delivery in the study group is 3.7 years higher than the general population.

9.7 Further study arising from this research

9.7.1 Changing coping strategies and other psychological parameters in adolescence

This is a retrospective study of the long-term effects of JIA. There would be obvious benefits in performing a prospective study, particularly looking at the interaction of coping strategies and psychological parameters on long-term outcome. There are no studies to date that have looked at coping strategies and how they change in chronic disease through adolescence. As coping strategies and psychological well-being have been shown to be strongly linked with long-term outcome in this study, there may be significant clinical benefit from trying to ascertain what factors during adolescence lead to a beneficial psychological profile.

The low depression rate found in the study group is in contrast to the slightly higher level of previous depression compared to the general population. This is another area where prospective study of the emotional states of JIA patients undergoing a transition through adolescence would be of interest. If the psychological parameters that assist patients in overcoming depressive tendencies could be found, then there may be the potential to influence the long-term psychological health of adults with JIA.

Another area that the study suggests would benefit from further review is the change in long-term risks for anxiety and depression from age of disease onset. A prospective trial assessing mood and attitudes to disease from disease onset may give some clues as to why patients with disease onset before age 5 appear to be relatively less affected by depression compared to patients with disease onset between 6-11 and anxiety compared to patients with disease onset over age 12.

It became evident during the course of the study that a depression scale, which is validated in patients with physical disease, would be likely to give more robust depression and anxiety data. There are a number of questions within all self-assessment depression questionnaires which a prone to over-estimate mood abnormality if used in a group of patients with physical disease. Using a question-by-question analysis, and comparing this to other disease parameter such as pain and function, those questions prone to bias from physical disease could be highlighted. These could then be removed

from the depression scale, which could then be re-validated. It is possible in this way to achieve a 'modified' depression scale for use in physical disease. It should be feasible to achieve such modification in the scales used in both adult and paediatric populations.

9.7.2 Genetic studies to date

There is the potential with the information from the study dataset to correlate the clinical findings with genetic polymorphisms. The study group have already had a general genetic screen, which was performed outside the scope of this thesis. The general genetic screen included full HLA-DR, HLA-DQA, HLA-DQB and HLA-DPB typing with a few additional polymorphisms in IL-1, IL-6, IL-10 and TNF-α. Preliminary statistical analysis of the findings on HelixTree statistical package have shown an association between HLA-DRB1*13 and uveitis. This association confirms a recent finding in an independent cohort from the British Paediatric Study Group. These two independent findings have now been amalgamated and are in the process of submission. Although these findings are outside the scope of the thesis, for interest a draft of the paper is included in Appendix 1.17. This area of subsequent research has been performed in collaboration with the ARC Epidemiology Unit, University of Manchester and includes work performed on a joint basis.

Unfortunately, related to the relatively small number of patients within each JIA subset, no other genetic polymorphisms were shown to reach significance when the dataset was run through the HelixTree statistical software package. Some of the IL-10 polymorphisms were close to reaching significance. It is hoped that some subsequent collaborative work would enable the possible IL-10 associations with clinical parameters to be confirmed.

9.7.3 Study into the genetic polymorphisms affecting methotrexate responsiveness

Subsequent areas of study include looking at the genetic influence on methotrexate responsiveness in JIA. One of the central regulatory enzymes in the folate pathway is methylenetetrahydrofolate reductase (MTHFR), which is involved in methotrexate metabolism and has had a number of polymorphisms described. It is known that expression of MTHFR is under genetic control.

Goyette et al[181] localized the gene encoding MTHFR to 1p36.3, and subsequently defined the structure of both the human and mouse MTHFR genes. The human MTHFR gene is composed of 11 exons and spans a genomic region of 20kB.[181] At least 15 polymorphisms within the gene have been described[181, 182] although functional data does not exist for all of these.

The first common polymorphism was identified by Frosst et al in 1995[183] and is C677T, which corresponds to an alanine to valine change at codon 222. This leads to the formation of a thermolabile enzyme with reduced enzymatic activity. The TT genotype (approximately 30% of the wild-type CC activity) is present in 10-16% of Caucasians. Heterozygotes (CT) have approximately 60% in vitro enzyme activity and make up approximately 40% of the Caucasian population. Thus, approximately 50% of a Caucasian population carry at least one copy of the variant allele.[184] This variant has been studied extensively in a range of diseases (reviewed by Schwahn[185] including acute leukaemia, neural tube defects, colon cancer and cardiovascular disease).

A second common polymorphism (A1298C) is a glutamic acid to alanine substitution at codon 429 and was shown by Weisberg et al[186] to lead to reduced enzyme activity. The C allele has a frequency of 32% in a Caucasian population.[184] Interestingly patients who are heterozygous for both alleles (approximately 15% of the Caucasian population) are clinically similar to individuals homozygous for the C677T polymorphism. Ulrich et al[184] hypothesised that this polymorphism may become clinically relevant under conditions of folate depletion, such as during the administration of methotrexate.

A third polymorphism has recently been identified (G1793A) which leads to the replacement of arginine by glutamine at codon 594.[187] This has an allele frequency of approximately 7%. More data is required to establish the functional role of this polymorphism.

Several studies have examined the link between polymorphisms in the MTHFR gene and outcome of treatment with methotrexate. Initial studies examined the effect of the

C677T genotype and toxicity from methotrexate in patients treated for malignancy. The first case reports by Toffoli et al[188] studied 6 breast cancer patients who developed severe toxicity with combination chemotherapy (including high dose MTX) and found that 5/6 had the 677TT genotype. A larger study by Ulrich et al[189] looked at 220 patients with chronic myeloid leukaemia undergoing bone marrow transplantation and found a higher rate of toxicity from MTX in patients with the 677TT genotype.

Two studies have examined the effect of the C677T polymorphism in RA patients on MTX. Van Ede et al[190] studied 236 RA patients on MTX. They found that 48% of patients carried at least one T allele and found that the presence of the C677CT or C677TT haplotype increased the risk of stopping MTX for adverse events (RR 2.01 95% CI 1.09-3.7), mainly due to an increased risk abnormal LFTs (RR 2.38 95% CI 1.06-5.34). No difference in MTX efficacy was seen between the groups. The predictive power of the genotype was independent of folate supplementation status.

Urano et al[191] studied the effect of both the C677T and A1298C polymorphism in a cohort of 106 Japanese RA patients. They found that MTX toxicity was more frequent in patients with C677T allele compared to those without the T allele (27% vs. 8.6% RR 1.25). No correlation was observed between this polymorphism and treatment efficacy. In 80 patients, an association was sought between the efficacy of MTX and presence of the A1298C polymorphism. Patients with the C allele required significantly lower doses of MTX than patients without the allele (RR 2.18, 95%CI 1.17-4.06, $p<0.05$). There was a trend for improved efficacy in patients with the C allele, with greater change in the ESR and CRP and greater percentage change in these variables although this was not associated with a significant change in tender and swollen joint count. However, a higher initial ESR in C/C group possibly confounded the ESR results (presentation ESR 81 compared to 56). No association was observed between A1298C polymorphism and toxicity. They concluded that the C677T polymorphism leads to increased toxicity and A1298C improved efficacy to MTX.

None of these studies have looked at the effect of the MTHFR polymorphisms in JIA. Within the dataset are clinical and laboratory measures of disease activity, numbers of patients on methotrexate and numbers failing on methotrexate, with the reason for

patients stopping the drug. As part of this study, it is envisaged that the retrospective assessment of function related to previous use of methotrexate in the context of the MTHFR polymorphisms will be evaluated. This has the potential to give a valuable insight into predicting methotrexate response and may guide any subsequent prospective studies in evaluating methotrexate response. It would also be interesting as a parallel assessment to determine whether previous methotrexate use for any period, had an independent affect upon long-term outcome

10 APPENDICES

Appendix 1.1. – Introductory letter

WRITTEN EXPLANATION FOR PATIENTS GIVING INFORMATION PARTICIPATING IN THE RESEACH STUDY

Purpose of the study

We are interested in how adults with longstanding juvenile chronic arthritis (JCA) are affected by their arthritis. This study will help us to understand better what problems your arthritis gives you and how you cope with them.
We will also be looking at how all of the patients that we see who have severe disease compare genetically to young patients with juvenile arthritis. This may allow us to give young patients with arthritis a better idea of how they might be affected in the future.

Taking part in the study

We hope to include all of the patients that are still seen by the rheumatology department who are over the age of 18 and have a diagnosis of juvenile chronic arthritis. This will be the largest and most thorough study of its type and will involve over 200 patients. Taking part in the study will involve you filling in a questionnaire at home, which should take between 1 and 2 hours. We will also see you in an out patient clinic to examine and talk to you about your JCA in some depth. This appointment will take the place of one of your normal clinic appointments.
We plan to obtain a sample of blood taken in the clinic from all patients entering the study. The blood will be tested for the activity of your arthritis, and for genetic markers of arthritis, these markers are called HLA antigens and vary in different diseases and individuals. The results of these tests will be linked with your clinical details and entered into a computerised data base to be analysed, only your hospital number will be used, your name will not appear in the data base.
All information will be treated in the strictest confidence. The only 'cost' involved will be your own time. Entering the study will have no effect on the medical care that you receive and you may withdraw from the study at any time.

If you are at all concerned about any aspect of this study Dr Packham or Dr Hall are contactable at any time via the hospital switchboard (01753-633000) or during normal working hours (01753-633165)

What to do next

We would be grateful if you would complete the attached consent form saying whether you consent to take part in this study or not. Please return the signed consent form in the pre-paid envelope enclosed.
If you enter the study, you will receive a questionnaire through the post in the near future.

Appendix 1.2. – Letter of consent

LETTER OF CONSENT

Health status of adults with chronic arthritis since childhood: a clinical, functional, psychosocial and genetic assessment

I have read the letter outlining this study and do wish to participate in it ☐

OR

I have read the letter outlining this study and do not wish to participate in it ☐

Full name: Mr A.N. Other

Signature: .....

Date: .....

Please indicate any preferred times or days for out patient attendance before the end of August 1998

Please indicate any periods of holiday or days when you would be unavailable

If you would like to participate in this study, but feel that circumstances prevent you from doing this, please comment below:

Please supply us with an up to date contact telephone number: .....

Please complete and return in the envelope provided

Thank you for your help

Appendix 1.3. – Patient review

PATIENT REVIEW

Name. D.O.B. Town at onset.

Hosp. No.

Height (cm) Weight (kg) Notes wt (kg)

Marital status

Status	Patient	Parents	Siblings			
Single						
Married/Cohabiting						
Divorced						
Separated						
Widow(er)						
Remarried						

Do you have any children? Yes ☐ No ☐
What age and sex are they? No. of pregnancies

Education

Main stream school Yes ☐ No ☐ Years
Physically handicapped school Yes ☐ No ☐ Years

'O' levels Yes ☐ No ☐ Number
'A' levels Yes ☐ No ☐ Number
Degree or equivalent Yes ☐ No ☐ Number

Employment

Student Yes ☐ No ☐
Employed Yes ☐ No ☐
Full time Yes ☐ No ☐

Job title

Siblings jobs and education

Have you had to change your job or the hours that you work because of your arthritis?

Have you encountered any discrimination related to your arthritis at work, socially or from large institutions?

Social activities

What hobbies or activities do you participate in regularly?

Do you belong to any arthritis groups?

Arthritis care	Yes ☐	No ☐
Arthritis and rheumatism council	Yes ☐	No ☐
Local patient support group	Yes ☐	No ☐
Self management programme	Yes ☐	No ☐
Other	Yes ☐	No ☐

If an adult JCA support group existed would you participate? Yes☐ No☐ Maybe☐

Are you sexually active? Yes☐ No☐ What age did you become active?
Has your arthritis affected this aspect of your life?

Have you reached the menopause? Yes☐ No☐ If 'yes' when? _____

Housing

Flat ☐ Bungalow ☐ House ☐ Other(specify)

Stairs Yes ☐ No ☐

Care assistant Yes ☐ No ☐

Do you live with anyone else?

Does your home have any special features to help you cope with your arthritis?

Do you use any special aids or appliances to help you cope with your arthritis?

Transport

Car	Yes ☐	No ☐
Automatic	Yes ☐	No ☐
Adapted	Yes ☐	No ☐
Public transport	Yes ☐	No ☐

Comments on problems with transport

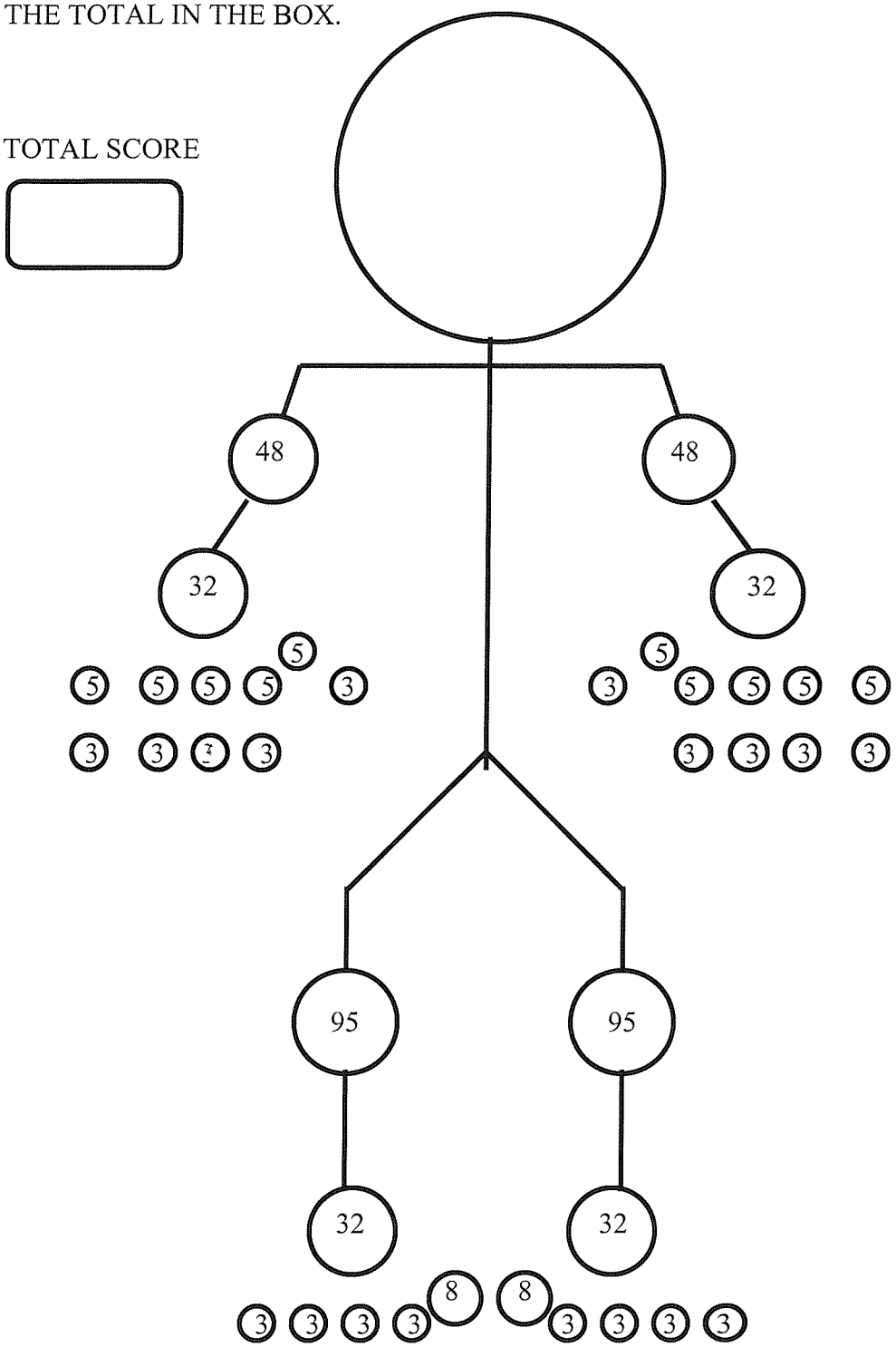
Social services/disability benefits

Registered Disabled? Yes☐ No☐

Appendix 1.4. – Thompson-Kirwan manikin

PLEASE MARK THOSE JOINTS THAT ARE TENDER TO FIRM PRESSURE AND HAVE SOFT TISSUE SWELLING OR EFFUSIONS
ADD THE RNCIRCLED NUMBERS FOR THE MARKED JOINTS AND WRITE THE TOTAL IN THE BOX.

TOTAL SCORE



Appendix 1.5. – Range of joint motion

Range of joint movement

Joint movement	Right range (degrees)		Left range (degrees)	
DIP flexion/extension				
PIP flexion/extension				
MCP flexion/extension				
Wrist flexion/extension				
Elbow flexion/extension				
Elbow supination/pronation				
Shoulder abduction				
Shoulder rotation int/ext				
Mouth opening (cm)				
Hip flexion				
Hip internal rotation				
Hip external rotation				
Hip adduction				
Hip abduction				
Knee flexion/extension				
Ankle flexion/extension				
Sub talar supination/pronation				
Mid tarsal supination/pronation				
MTP flexion/extension				
Lumbar flexion (Schoeber's)	15cm			
Lumbar lateral flexion	R		L	
Cervical flexion/extension	F		E	
Cervical rotation right/left	R		L	
Cervical lateral flexion right/left	R		L	

Right leg length (cm)
Left leg length (cm)

Specific growth defects

Appendix 1.6. – Steinbrocker functional class

Steinbrocker functional class

Class I **Complete functional capacity with ability to carry on all usual activities without handicap**

Class Iia Functional capacity adequate to conduct normal activities despite discomfort

Class IIb Functional capacity adequate to conduct normal activities despite with limited mobility or fixed flexion deformity of 1 or more joints

Class III Functional capacity adequate to perform only a little or none of the activities of usual occupation or self care procedures

Class IV Largely or wholly incapacitated with patient confined to bed or wheelchair, permitting little or no self care

Appendix 1.7. – Disease patterns, evolution and blood tests

Disease Onset Pattern

		Date of Onset	Diagnosis
Systemic	☐		
Oligoarticular	☐		
Polyarticular	☐		
JAS	☐		
Psoriatic	☐		

Evolution of Disease Pattern at 6/12

		Disease Duration
Oligoarticular	☐	
Polyarticular	☐	
JAS	☐	
Psoriatic	☐	

Blood Tests

	Positive	Negative	Not Performed
ANA			
HLA-B27			
Rheumatoid Factor			

Appendix 1.8. – Drug and surgical interventions

Current Medication

Drug	Dose/frequency	Duration

Surgical Intervention

Date	Operation

Treatment with NSAIDs

Drug	Time Period	Reason for discontinuation

Treatment with DMARDs

Drug	Time Period	Reason for discontinuation

Treatment with Steroids

Drug	Route/dose	Date/duration

Other previous medication

Drug	Dose	Date/duration

Concurrent Disease States

	Uveitis	Onset	Surgery	Sicca syndrome	Cataracts	Glaucoma
R						
L						

Amyloid	Onset/1st SAP	Creatinine clearance	24 hour protein

Osteoporosis	DEXA

Other diseases	Onset

Appendix 1.9. – Health assessment questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE

In this section 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 the 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
Dressing and grooming				
Are you able to:				
Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
Rising				
Are you able to:				
Stand up from an armless straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
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)?	☐	☐	☐	☐
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, zipper pull, long handled shoe horn, etc.)	☐
Walking frame	☐		
Crutches	☐	Built-up or special utensils	☐
Wheelchair	☐	Special or built-up chair	☐
Other (specify)			

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
Hygiene				
Are you able to:				
Wash and dry your entire body?	☐	☐	☐	☐
Take a bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
Reach				
Are you able to:				
Reach and get down a 5 lb. object (e.g. a bag of potatoes) from just above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
Grip				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open jars which have been previously opened?	☐	☐	☐	☐
Turn taps on and off?	☐	☐	☐	☐
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	☐	Jar opener (for jars previously opened)	☐
Bath seat	☐	Long handled appliances for reach	☐
Bath rail	☐		
Other (specify)			

Please tick any categories for which you usually need HELP FROM ANOTHER PERSON:

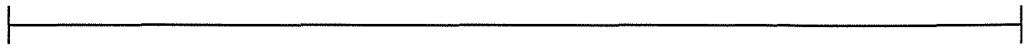
Hygiene	☐	Gripping and opening things	☐
Reach	☐	Errands and housework	☐

Appendix 1.10. – Pain VAS

How much pain have you had because of your illness IN THE PAST WEEK?

PLACE A MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

NO PAIN — MOST SEVERE PAIN



0 — 100

Appendix 1.11. – Hospital anxiety and depression scale questionnaire

This section of the questionnaire will help you let us know how you are. Read each item and underline the response that comes closest to how you have felt in the last few days.

Don't take too long over your replies. Your immediate reaction will probably be more accurate than a long thought out response.

I feel tense or 'wound up'
- Most of the time
- A lot of the time
- From time to time, occasionally
- Not at all

I feel as if I am slowed down
- Nearly all the time
- Very often
- Sometimes
- Not at all

I still enjoy things I used to enjoy
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a sort of frightened feeling like 'butterflies' in the stomach
- Not at all
- Occasionally
- Quite often
- Very often

I get a sort of frightened feeling as if something awful is about to happen
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I have lost interest in my appearance
- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

I can laugh and see the funny side of things
- As much as I always could
- Not quite so much now
- Definitely not as much now
- Not at all

I feel restless as if I have to be on the move
- Very much indeed
- Quite a lot
- Not very much
- Not at all

Worrying thoughts go through my mind

A great deal of the time
A lot of the time
From time to time but not too often
Only occasionally

I look forward with enjoyment to things

As much as I ever did
Rather less than I used to
Definitely less than I used to
Hardly at all

I feel cheerful

Not at all
Not often
Sometimes
Most of the time

I get sudden feelings of panic

Very often indeed
Quite often
Not very often
Not at all

I can sit at ease and feel relaxed

Definitely
Usually
Not often
Not at all

I can enjoy a good book or radio or TV

Often
Sometimes
Not often
Very seldom

Appendix 1.12. – London coping with rheumatoid arthritis scale questionnaire

Here are some different statements that people commonly make to describe how they personally cope with arthritis. Could you please think of the problems you may sometimes have because of your illness and say for each statement how often you adopt the particular approach to the problems?

CIRCLE the term that is nearest to the answer you would give.

1. I try to stay as active as possible

Never Almost never Sometimes Quite often Very often Always

2. I try to read articles or books about my illness

Never Almost never Sometimes Quite often Very often Always

3. I try to rest as much as possible

Never Almost never Sometimes Quite often Very often Always

4. I tell myself that the pain doesn't really hurt

Never Almost never Sometimes Quite often Very often Always

5. I find talking to friends and family about the problem of arthritis helpful

Never Almost never Sometimes Quite often Very often Always

6. I try to become involved in as many activities as possible to take my mind of the disease

Never Almost never Sometimes Quite often Very often Always

7. I keep my pain to myself, so few of my friends know that I'm in pain

Never Almost never Sometimes Quite often Very often Always

8. I try to exercise the joints as much as possible

Never Almost never Sometimes Quite often Very often Always

9. If other people are sympathetic, it helps me cope

Never Almost never Sometimes Quite often Very often Always

10. I compare myself with other people who have worse health problems

Never Almost never Sometimes Quite often Very often Always

11. Having arthritis has helped me to find new faith or some important truth about life

Never Almost never Sometimes Quite often Very often Always

12. I pray to God for relief from the arthritis

Never Almost never Sometimes Quite often Very often Always

13. My arthritis can make me self conscious, so that I avoid people

Never Almost never Sometimes Quite often Very often Always

14. I ask questions of my doctor about my illness

Never Almost never Sometimes Quite often Very often Always

15. I walk as much as I can in order to stay active

Never Almost never Sometimes Quite often Very often Always

16. I pray to God that the pain will get better some day

Never Almost never Sometimes Quite often Very often Always

17. I find it easier to cope with arthritis by expressing my feelings outwardly

Never Almost never Sometimes Quite often Very often Always

18. I tell myself that my arthritis is really not that bad

Never Almost never Sometimes Quite often Very often Always

19. I keep any worries I may have about arthritis to myself

Never Almost never Sometimes Quite often Very often Always

20. Having arthritis has made me develop into a better person

Never Almost never Sometimes Quite often Very often Always

21. When I'm in pain I prefer to be alone

Never Almost never Sometimes Quite often Very often Always

22. I try to find as much information about the problem as possible

Never Almost never Sometimes Quite often Very often Always

23. I take the view that there is very little anyone can do about the disease

Never Almost never Sometimes Quite often Very often Always

24. I find myself wishing that I never had arthritis

Never Almost never Sometimes Quite often Very often Always

25. I try to ignore the problem by looking only at the good things in my life

Never Almost never Sometimes Quite often Very often Always

26. I try to avoid situations where my arthritis would become evident

Never Almost never Sometimes Quite often Very often Always

27. When it gets bad I find myself taking it out on others around me

Never Almost never Sometimes Quite often Very often Always

28. I tell myself not to think about my arthritis

Never Almost never Sometimes Quite often Very often Always

29. Resting at times during the day helps me cope

Never Almost never Sometimes Quite often Very often Always

30. I ask other people to help with those things I can't manage because of my arthritis

Never Almost never Sometimes Quite often Very often Always

31. I find the best way to deal with morning stiffness is to push myself to get active

Never Almost never Sometimes Quite often Very often Always

32. There are some things that I avoid eating or drinking because they are not good for my arthritis

Never Almost never Sometimes Quite often Very often Always

33. There are some special things I buy to eat or drink because of my arthritis

Never Almost never Sometimes Quite often Very often Always

34. I try to keep my weight down because of my arthritis

Never Almost never Sometimes Quite often Very often Always

35. Reorganising my daily routine helps me get through the problems of arthritis

Never Almost never Sometimes Quite often Very often Always

36. One important way I cope is simply accepting the problem of my arthritis

Never Almost never Sometimes Quite often Very often Always

Appendix 1.13. – Coping strategies questionnaire

Individuals who experience pain have developed a number of ways to cope or deal with their pain. These include saying things to themselves when they experience pain, or engaging in different activities.

Below are a list of things that people have reported doing when they feel pain. For each activity, I would like you to indicate, using the scale below, how much you engage in that activity when you feel pain.

An 0 indicates that you never do that activity when you are experiencing pain, a 3 indicates you sometimes do it when you are experiencing pain, and a 6 indicates you always do it when you are experiencing pain. Remember, you can use any point along the scale.

Write the appropriate number in the box beside each question.

0	1	2	3	4	5	6
Never do			Sometimes do that			Always do that

When I feel pain …

☐ 1. It is terrible and I feel it is never going to get any better

☐ 2. It is awful and I feel that it overwhelms me

☐ 3. I feel my life isn't worth living

☐ 4. I worry all the time about whether it will end

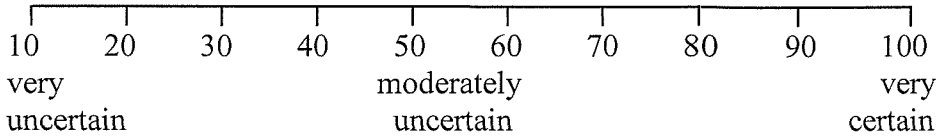
☐ 5. I feel I can't stand it any more

☐ 6. I feel like I can't go on

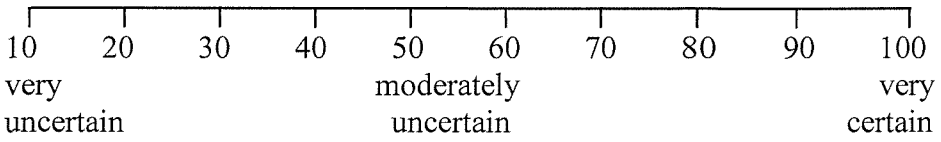
Appendix 1.14. – Arthritis self-efficacy questionnaire

In the following questions, we'd like to know how your arthritis pain affects you. For each of the following questions, please circle the number that corresponds to your certainty that you can now perform the following tasks.

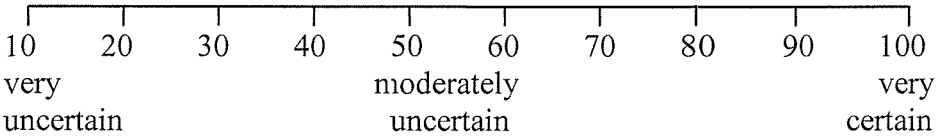
1. How certain are you that you can decrease your pain quite a bit?



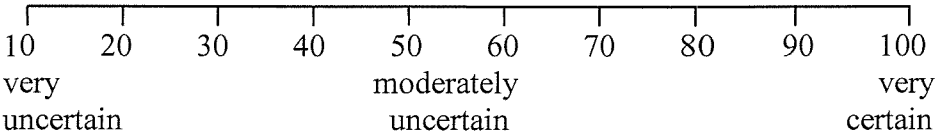
2. How certain are you that you can continue most of your daily activities?



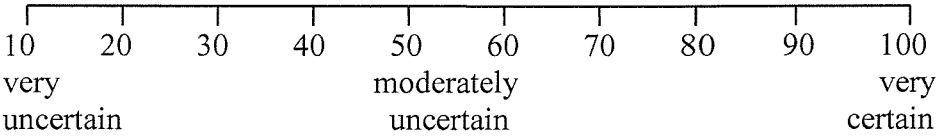
3. How certain are you that you can keep arthritis pain from interfering with your sleep?



4. How certain are you that you can make a small-to-moderate reduction in your arthritis pain by using methods other than taking extra medication?



5. How certain are you that you can make a large reduction in your arthritis pain by using methods other than taking extra medication?



---

7. Based on all the things you do to cope or deal with pain, on an average day, how much control do you feel you have over it? Please circle the appropriate number. Remember you can circle any number along the scale.

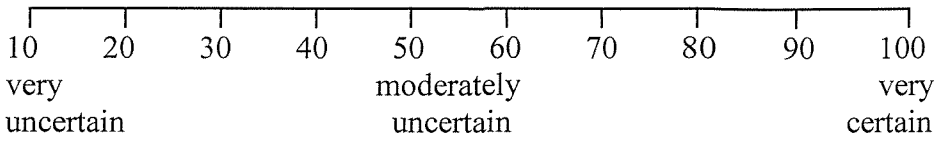
0	1	2	3	4	5	6
no control			some control		complete control	

8. Based on all the things you do to cope or deal with your pain, on an average day, how much are you able to decrease it? Please circle the appropriate number. Remember you can circle any number along the scale.

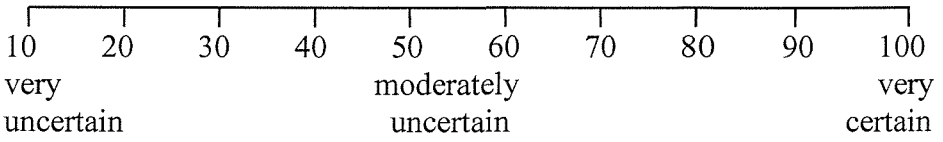
0	1	2	3	4	5	6
can't decrease at all it			can decrease it somewhat		can decrease it completely	

In the following questions, we'd like to know how you feel about your ability to control your arthritis. For each of the following questions, please circle the number that corresponds to the certainty that you can now perform the following activities or tasks.

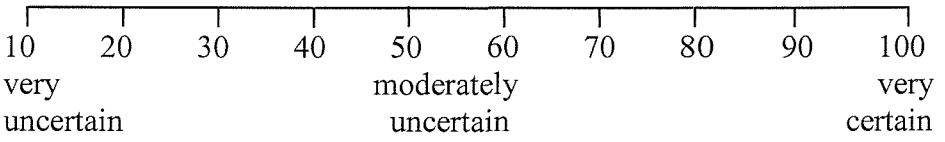
1. How certain are you that you can control your fatigue?



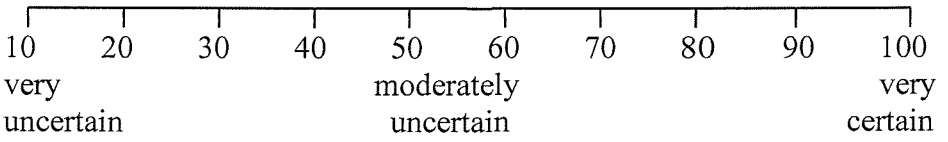
2. How certain are you that you can regulate your activity so as to be active without aggravating your arthritis?



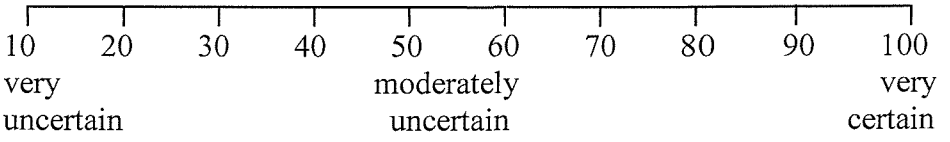
3. How certain are you that you can do something to help yourself feel better if you are feeling blue?



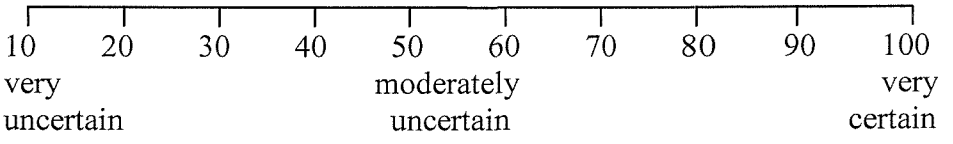
4. As compared with other people with arthritis like yours, how certain are you that you can manage arthritis pain during your daily activities?



5. How certain are you that you can manage your arthritis symptoms so that you can do the things you enjoy doing?



6. How certain are you that you can deal with the frustration of arthritis?



Appendix 1.15. – Sarason short form social support questionnaire

The following questions ask about people in your environment who provide you with help or support. Each question has two parts. For the first part, list all the people you know, excluding yourself, whom you can count on for help or support in the manner described. Give each person's initials and their relationship to you (see example). Do not list more than one person next to each of the numbers beneath each question. Do not list more than nine people per question.

For the second part, using the scale below, circle how satisfied you are with the overall support you have.

6	5	4	3	2	1
Very satisfied	*Fairly satisfied*	*A little satisfied*	*A little dissatisfied*	*Fairly dissatisfied*	*Very dissatisfied*

If you have no support for a question, tick the words 'No one', but still rate your level of satisfaction. The example below has been completed to help you. All your responses will be kept confidential.

Who do you know whom you can trust with information that could get you into trouble?

(a) No one	3)ASS (friend)	6)	9)
1)TEN (brother)	4)PEN (father)	7)	
2)LM (friend)	5)LM (employer)	8)	

(b) How satisfied? 6 5 (4) 3 2 1

(1) Whom can you really count on to distract you from your worries when you feel under stress?

(a) No one	3)	6)	9)
1)	4)	7)	
2)	5)	8)	

(b) How satisfied? 6 5 4 3 2 1

(2) Whom can you really count on to help you feel more relaxed when you are under pressure or tense?

(a) No one	3)	6)	9)
1)	4)	7)	
2)	5)	8)	

(b) How satisfied? 6 5 4 3 2 1

(3) Who accepts you totally, including both your worst and best points?

(a) No one	3)		6)		9)
1)	4)		7)		
2)	5)		8)		
(b) How satisfied?	6	5	4	3	2	1

(4) Whom can you really count on to care about you, regardless of what is happening to you?

(a) No one	3)		6)		9)
1)	4)		7)		
2)	5)		8)		
(b) How satisfied?	6	5	4	3	2	1

(5) Whom can you really count on to help you feel better when you are feeling generally down in the dumps?

(a) No one	3)		6)		9)
1)	4)		7)		
2)	5)		8)		
(b) How satisfied?	6	5	4	3	2	1

(6) Whom can you count on to console you when you are very upset?

(a) No one	3)		6)		9)
1)	4)		7)		
2)	5)		8)		
(b) How satisfied?	6	5	4	3	2	1

Appendix 1.16. – Disease repercussion scale questionnaire

Doctors are aware that arthritis can affect many different areas of people's lives, such as their living conditions and their work, as well as their joints. This questionnaire has been designed to help them to understand these different effects of arthritis so that they can help you to solve those problems which are important to you.

Please read these instructions carefully.

There are 6 questions in this questionnaire, one on each page. To answer one part of each of the questions you will need to circle the number on the 0-10 line which shows how important the effect of arthritis on your life is to you.

For example:

If your arthritis has affected how much you use public transport, how important is this to you at the moment?

(This is an example. You do not need to answer this question).

If it is not at all important, you would circle 0 on the line as shown below. If it was extremely important you would circle number 10.

Not at all Important — 0 1 2 3 4 5 6 7 8 9 10 — Extremely important

QUESTION 1

A. How does your arthritis affect your day to day activities **at the moment**?

Please tick one box.

No effect ☐

Makes activities difficult ☐

If your arthritis does not affect your day to day activities, please go to question 2.

B. If your arthritis makes your day to day activities more difficult, please list the activities which are difficult.

C. How do these difficulties affect your life?

D. How important is this effect to you **at the moment?**
Please circle a number to indicate how important this effect is to you **at the moment:**

Not at all important — 0 1 2 3 4 5 6 7 8 9 10 — Extremely important

QUESTION 2

A. How does your arthritis affect your social activities **at the moment**?

Please tick one box.

No effect ☐

Makes activities difficult ☐

If your arthritis does not affect your social activities, please go to question 3.

B. If your arthritis makes your social activities more difficult, please list those activities which are difficult

C. How do these difficulties affect your life?

D. How important is this effect to you **at the moment?**
Please circle a number to indicate how important this effect is to you **at the moment:**

Not at all important — 0 1 2 3 4 5 6 7 8 9 10 — Extremely important

QUESTION 3

A. How does your arthritis affect how much money you have or, if you are still working, how does it affect your job **at the moment**?

Please tick one box.

Situation better ☐

No effect ☐

Situation worse ☐

If your arthritis makes your situation better or does not affect your job or money, please go to question 4.

B. If your job or money situation is **worse** how does this affect your life?

C. How important is this effect to you **at the moment?**
Please circle a number to indicate how important this effect is to you at the moment:

Not at all important — 0 1 2 3 4 5 6 7 8 9 10 — Extremely important

QUESTION 4

A. How does your arthritis affect your relationships with your friends, family and partner **at the moment**?

Please tick one box.

	Better	No effect	Worse
Friends	☐	☐	☐
Family	☐	☐	☐
Partner	☐	☐	☐

If your arthritis either improves or does not affect any of your relationships, please go to question 5.

B. If any of your relationships have **worsened** how does this affect your life?

C. How important is this effect to you **at the moment?**
Please circle a number to indicate how important this effect is to you **at the moment:**

Not at all important — 0 1 2 3 4 5 6 7 8 9 10 — Extremely important

QUESTION 5

A. How does your arthritis make you feel emotionally **at the moment**?

Please tick one box.

Happy/positive ☐

No effect ☐

Unhappy/negative ☐

If your arthritis makes you feel happy/positive or has no effect on the way you feel emotionally, please go to question 6.

B. If your arthritis makes you feel unhappy or negative, how does this affect your life?

C. How important is this effect to you **at the moment?**
Please circle a number to indicate how important this effect is to you **at the moment:**

Not at all important — 0 1 2 3 4 5 6 7 8 9 10 — Extremely important

QUESTION 6

A. How does your arthritis make you feel about yourself and your appearance **at the moment**?

Please tick one box.

Feel attractive ☐

No effect ☐

Feel unattractive ☐

If your arthritis makes you feel attractive or has no effect on the way you feel about yourself and your appearance please turn over to the last page.

B. If your arthritis makes you feel unattractive in either looks or personality, how does this affect your life?

C. How important is this effect to you **at the moment?**
Please circle a number to indicate how important this effect is to you **at the moment:**

Not at all important — 0 1 2 3 4 5 6 7 8 9 10 — Extremely important

Appendix 1.17. Submitted genetics paper

Association of HLA-DRB1*13 with Susceptibility to Uveitis in Juvenile Idiopathic Arthritis in Two Independent Cohorts

Eleftheria Zeggini[1], Jonathan Packham[2], Paul Wordsworth[3], Ann Hall[3], the BPRG Study Group[4], Wendy Thomson[5]

[1]Centre for Integrated Genomic Medical Research, University of Manchester, Manchester, UK;
[2]Staffordshire Rheumatology Centre, Stoke on Trent, UK;
[3]Nuffield Orthopaedic Centre, Oxford, UK[5]arc Epidemiology Unit, University of Manchester, Manchester, UK;

[4]Contributors to the British Paediatric Rheumatology Study Group are: Dr M Abinun, Dr M Becker, Dr A Bell, Professor A Craft, Dr E Crawley, Dr J David, Dr H Foster, Dr J Gardener-Medwin, Dr J Griffin, Dr A Hall, Dr M Hall, Dr A Herrick, Dr P Hollingworth, Dr L Holt, Dr S Jones, Dr G Pountain, Dr C Ryder, Professor T Southwood, Dr I Stewart, Dr L Wedderburn, Professor P Woo, Dr S Wyatt, Dr H Venning.

Corresponding author and reprint requests to: Wendy Thomson, arc EU, Stopford Building, Oxford Road, Manchester, M13 9PT, UK. Tel.: ++44 161 275 5641; Fax: ++44 161 275 5043; Email: Wendy@fs1.ser.man.ac.uk

Short title: HLA-DRB1*13 in JIA-associated uveitis

Abstract

Objectives. Juvenile idiopathic arthritis (JIA) is the commonest rheumatic disease of childhood and, within JIA, uveitis is the commonest eye complication, potentially leading to eye surgery and / or visual loss. JIA is a complex genetic trait with well-established HLA-DRB1 associations. The aim of this study has been to investigate the involvement of HLA-DRB1 specifically in JIA-associated uveitis. **Methods**. A set of 130 UK Caucasian simplex families consisting of healthy parent(s) and child affected with juvenile oligoarthritis (of which 31 had also developed uveitis) had previously been screened for multiple markers in the major histocompatibility complex region. Associations with uveitis were investigated through haplotype pattern mining (HPM) and the extended transmission disequilibrium test (ETDT). A further set of 225 UK Caucasian patients with long-standing JIA were fully genotyped for HLA-DRB1 using PCR-SSP. Associations of HLA-DRB1 alleles in patients with uveitis (n=50) were individually examined through both the HelixTree® software package and the chi squared test. Odds ratios with 95% confidence intervals (CIs) were also calculated. **Results**. In the first cohort, HPM identified significant associations of HLA-DRB1*13 with uveitis in juvenile oligoarthritis (p=0.002). The ETDT confirmed overtransmission of this allele in the families (empirical p=0.018) In the second cohort, the significant association of uveitis with HLA-DRB1*13 was replicated (p=0.002, OR=2.91, 95% CIs: 1.46-5.79). **Conclusions**. This study has established the HLA-DRB1*13 association with uveitis in JIA. Further work is necessary in order to explore the prognostic potential of this marker.

Keywords: JIA, uveitis, HLA-DRB1, association, replication.

Introduction

Juvenile idiopathic arthritis (JIA) is the commonest chronic rheumatic disease of childhood. Complications associated with JIA can include joint deformities, growth retardation, osteopenia and uveitis. Uveitis represents the commonest form of eye involvement in juvenile idiopathic arthritis and can lead to vision impairment (Edelsten). The incidence of JIA-associated uveitis is pronounced in the oligoarthritis disease subgroups (Petty) and is additionally encountered in JIA patients with enthesitis-related and psoriatic arthritis, contributing to an overall poor long-term disease outcome (Packham). Due to the asymptomatic nature of uveitis, JIA patients in

the high-risk disease subgroups receive regular ophthalmologic examinations. The search for indicators of disease development can render valuable information with regard to possible persistence of disease activity and complications. Currently, a molecular marker (antinuclear antibody positivity) has been associated with the development of uveitis. However, the elucidation of specific genetic factors, associated with the development of JIA-associated uveitis, could serve as an invaluable tool towards predicting outcome, as well as towards designing and applying appropriate therapies.

JIA is a complex genetic disease (Glass&Giannini) with well-established associations with loci residing in the major histocompatibility complex (MHC) on chromosome 6p21.3 (Donn&Ollier; Thomson-HLA, Zeggini-TNF). The MHC region harbours multiple genes of immune relevance. The HLA-DRB1 locus has been associated with susceptibility to a wide array of complex diseases, including JIA (Thomson-HLA, Zeggini-HLA, Rubio-MS, review for RA). In addition, previous studies investigating HLA associations with uveitis have identified the involvement of the HLA-A, HLA-B and HLA-DRB1 loci (Zulian). However, as the MHC region is characterised by low recombination rates, the observed associations could be due to linkage disequilibrium with an as yet unidentified susceptibility gene. The aims of this study were to initially screen multiple markers across the MHC for associations with uveitis in juvenile oligoarthritis, the JIA subgroup with the highest incidence of eye complications, and to subsequently replicate significant findings in an independent cohort of well-characterised JIA patients.

Patients and Methods

The arthritis research campaign epidemiology unit (arc EU) holds the British Paediatric Rheumatology Group (BPRG) National JIA Repository. This is composed of a collection of samples from prevalent UK patients and available parents, as recruited through the BPRG, with the aid of 17 contributory centres. Patients have been classified according to the ILAR criteria (Petty) and clinical details of individual cases have been collected. One hundred and thirty UK Caucasian nuclear families, consisting of an offspring affected with juvenile oligoarthritis and healthy parent(s), were available for study. Of the 130 patients, 31 had developed uveitis prior to recruitment. Ethics committee approval has been obtained for the study (North-West Multi-Centre

Research Ethics Committee (MREC 99/8/84) and the University of Manchester Committee on the ethics of research on human beings). An independent cohort of 225 UK Caucasian patients with long-standing JIA was additionally available for study. These patients have also been classified according to the ILAR criteria (Petty) and their characteristics have been described elsewhere (Packham).

Twenty seven markers distributed throughout the MHC and including the HLA-A, HLA-B and HLA-DRB1 loci, as well as single nucleotide polymorphisms (SNPs) in the TNFα, HLA-E and DIF-2 genes, had previously been genotyped in the simplex families (Zeggini HLA, Zeggini TNF, Zeggini-abstract-MHC). Briefly, microsatellite markers had been typed through fluorescence-based PCR, SNPs though the SNaPshot™ primer extension method and the HLA loci through PCR-SSOP. The HLA-DRB1 locus was genotyped in the independent cohort of 225 JIA patients through PCR-SSP (details available from the authors upon request).

Genotype consistency within families was checked through the GAS software (Young). The GENEHUNTER (Kruglyak) package was used to reconstruct extended MHC inferred haplotypes occurring in the families studied. Data mining of the extracted affected haplotypes was carried out through the haplotype pattern mining (HPM) method (Toivonen). HPM screened juvenile oligoarthritis haplotypes for the presence of uveitis-associated patterns. Linkage and association for the HLA-DRB1 locus was investigated in the families with offspring affected with uveitis, using the extended transmission disequilibrium test (ETDT) (Sham). Empirical p values were obtained by running 10000 Monte Carlo simulations. The HelixTree® software package (GoldenHelix Inc, Montana, USA) was initially used to identify any HLA-DRB1 associations with uveitis in the independent cohort of 225 JIA patients. HLA-DRB1 phenotype frequencies were also compared between JIA patients with and without uveitis through the χ^2 test using the Stata v.7 package (Stata Corporation, College Station, Texas, USA). Odds ratios and 95% confidence intervals were additionally calculated.

Results

Family-based study. Screening of juvenile oligoarthritis extended MHC haplotypes for uveitis-associated patterns using HPM identified a significant association with HLA-DRB1*13 (p=0.002), while none of the other MHC loci were associated with uveitis in

juvenile oligoarthritis. The ETDT was subsequently carried out in families with offspring affected with uveitis, in order to confirm involvement of the HLA-DRB1 locus. The total number of informative transmissions was 32 and the global p value for the test was p=0.009. The empirical p value generated after running 10000 Monte Carlo simulations was p=0.018, confirming linkage and association of the locus to uveitis in juvenile oligoarthritis. HLA-DRB1*13 was transmitted from a healthy parent to an affected child 8 times and not transmitted 3, exhibiting deviation from random segregation. However, this did not reach statistical significance due to the limited sample size.

Replication study. The involvement of HLA-DRB1 in JIA-associated uveitis was examined in an independent cohort of 225 patients. Recursive partitioning of the dataset through the HelixTree® software package identified a significant association of the HLA-DRB1*13 allele with uveitis in JIA (p=0.013). No other HLA-DRB1 allele was associated with uveitis. Evidence for the involvement of HLA-DRB1*13 in susceptibility to JIA-associated uveitis was additionally obtained when comparing phenotype frequencies between JIA patients with and without uveitis through the χ^2 test (p=0.002). Carrying HLA-DRB1*13 was found to confer an approximately 3-fold greater risk of developing uveitis in patients with JIA (OR=2.91, 95% CIs: 1.46-5.79).

Discussion

Although the immunogenetic basis of JIA-associated uveitis has not been extensively investigated in previous studies, the HLA-A, HLA-B and HLA-DRB1 loci have been shown to be potentially associated with disease (Zulian). The genomic interval encompassing these loci, however, also accommodates a plethora of genes of immune relevance that could potentially be involved in pathogenic processes. This study has initially examined multiple markers across the MHC, in order to identify JIA-associated uveitis susceptibility genes. The family based study design followed for the screening process had the advantage of low false positive result generation rates and the ability to detect both linkage and association, depending on the analysis method employed. Furthermore, the use of families enabled the construction of haplotypes across the MHC region, by basing phase assignment on parental genotypic information. Haplotype pattern mining revealed an association of uveitis in juvenile oligoarthritis

with HLA-DRB1*13. None of the other loci examined were found to be associated with uveitis, including HLA-A and HLA-B, as well as SNPs in the TNFα, HLA-E and DIF-2 genes. Complementary evidence for the involvement of HLA-DRB1*13 in uveitis was additionally obtained from the extended transmission disequilibrium test. Therefore, although further effects in the region cannot be excluded, due to limited power, the involvement of HLA-DRB1*13 in juvenile oligoarthritis-associated uveitis was supported by strong evidence.

The replication of positive findings in genetic studies is important in order to instil confidence in the results generated. This study has, therefore, investigated the association of HLA-DRB1*13 in an independent cohort of patients with long-standing JIA. Confirmation of the significant association was achieved, thereby establishing the involvement of this locus in susceptibility to JIA-associated uveitis. This finding could have implications in the prognosis of the development of uveitis. However, further work is necessary in order to assess the performance and consolidate the use of HLA-DRB1*13 as a prognostic genetic marker. Prospective studies, such as the childhood arthritis prospective study (CAPS) in the UK, represent ideal settings in which to test the potential of using HLA-DRB1*13 alongside further established high risk factors, with the ultimate aim of targeting JIA patients genetically predisposed to developing eye complications for intensive screening and early treatment.

Acknowledgements

The authors are grateful to GoldenHelix Inc, Montana, USA, for making their software package HelixTree® available to us. This work was supported by the arc, UK. E.Z. is funded by the MRC, UK.

Key message: HLA-DRB1*13 is associated with uveitis in juvenile idiopathic arthritis.

References

1. Symmons D, Jones M and Osbourne J. National Diagnostic Index: Paediatric Rheumatology in the United Kingdom (1996) Data from the British Paediatric Rheumatology Group National Diagnostic Register. J Rheumatol 1996;23:1975-1980.

2. Calabro JJ, Marchesano JM and Parrino GR. Juvenile rheumatoid arthritis:long-term management and prognosis. J Musculoskeletal Med 1989;6:17-32.

3. Steinbrocker O, Traeger CH and Battman RG. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc 1949;140:659-662.

4. Scott DL, Coulton BL and Symmons DPM. Long term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-1111.

5. Laaksonen A. A prognostic study of juvenile rheumatoid arthritis: analysis of 544 cases. Acta Paediatr Scand 1966;166 ((Suppl 1):1):23-30.

6. Fink CW. A proposal for the development of classification criteria for the idiopathic arthritides of childhood. J Rheumatol 1995;22:1566-1569.

7. Wood PHN and Munthe E. Nomenclature and classification of arthritis in children. The care of rheumatic children. Basel. EULAR. 1978:47-50.

8. Brewer EJ, Bas JC and Cassidy JT. Criteria for the classification of juvenile rheumatoid arthritis. Bull Rheum Dis 1977;23:712-719.

9. Brewer ER Jr, Bass J and Baum J. Current proposed revision of JRA criteria. Arthritis Rheum 1977;20:195.

10. Jeremy R, Schaller J and Arkless R. Juvenile rheumatoid arthritis persisting into adulthood. Am J Med 1968;45:419-434.

11. Ansell BM and Wood PHN. Prognosis in juvenile chronic polyarthritis. Clin Rheum Dis 1976;2:397-412.

12. Hill RH, Herstein A and Walters K. Juvenile rheumatoid arthritis: follow-up into adulthood - medical, sexual and social status. Can Med Assoc J 1976;76:790-795.

13. Goel KM and Shanks RA. Follow up study of 100 cases of juvenile rheumatoid arthritis. Ann Rheum Dis 1974;33:25-31.

14. Miller JJ, Spitz P, Simpson U and Williams GF. The social function of young adults who had arthritis in childhood. J Pediatr 1982;100:378-382.

15. Ruperto N, Ravelli A, Levinson JE, Shear ES, Murray K, Link Yague B, et al. Longterm health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. II. Early predictors of outcome. J Rheumatol 1997;24 (5):952-8.

16. Oen KG, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Reed M, et al. Early predictors of longterm outcome in patients with juvenile rheumatoid arthrtis: subset-specific correlations. J Rheumatol 2003;30 (3):585-93.

17. Fries JF, Spitz P and Kraines RG. Measurement of patients' outcome in arthritis. Arthritis Rheum 1980;23:137-145.

18. Peterson LS, Mason T, Nelson AM, O'Fallon WM and Gabriel SE. Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis. Arthritis Rheum 1997;49 (12):2235-2240.

19. Ansell BM and Bywaters EGL. Prognosis in Still's disease. Bull Rheum Dis 1959;9:189-192.

20. Sury B. Late prognosis in juvenile rheumatoid arthritis (Still's disease). Atti del X congresso della lega internazionale contro il reumatismo, Roma 1961;2 comunicazioni:238-40.

21. Lingberg IF. Juvenile rheumatoid arthritis. A follow up of 75 cases. Arch Dis Child 1964;39:576-83.

22. Ansell BM. Serious adult disease arising in childhood. Proc Roy Soc Med 1969;62:912-3.

23. Hanson V, Kornreich H and Bernstein B. Prognosis of juvenile rheumatoid arthritis. Arthritis Rheum 1977;20:279-284.

24. Meyer O, Kahn MF, Bourgeois P, Vinceneux P and Kaplan G. Les polyarthrites juveniles revues en rhumatologie a l'age adulte. Revue du Rheumatisme 1978;45 (6):409-16.

25. Stoeber E. Prognosis in juvenile chronic arthritis: follow-up of 433 chronic rheumatic children. Eur J Pediatr 1981;135:225-228.

26. Dequecker J and Mardjuadi A. Prognostic factors in juvenile chronic arthritis. J Rheumatol 1982;9:909-915.

27. Svantesson H, Akesson A, Eberhardt K and Elborgh R. Prognosis in juvenile rheumatoid arthritis with systemic onset. A follow-up study. Scand J Rheum 1983;12:139-144.

28. Rennebohm R and Korell JK. Comprehensive management of juvenile rheumatoid arthritis. Nurs Clin North Am 1984;19:17-32.

29. Prieur AM, Bremard-Oury C and Mozziconacci P. Pronostic des formes systemiques d'arthrite chronique juvenile. Arch Fr Paediatr 1984;41:91-7.

30. Pedersen AF, Heilmann C, Friis J, Jorgensen B and Thomsen K. Juvenil reumatoid arthritis. Ugeshr Laeger 1987;149 (42):2843-5.

31. Doherty E, Rooney M, Coneroy R and Bresnithan B. Health status of functionally independent young adults with chronic arthritis since childhood. J Orthopaed Rheumatol 1988;1:51-58.

32. Levinson JE and Wallace CA. Dismantling the pyramid. J Rheumatol 1992;19 (Suppl 33):6-10.

33. Cabral DA, Oen KG and Petty RE. SEA syndrome revisited: A longterm followup of children with a syndrome of seronegative enthesopathy and arthropathy. J Rheumatol 1992;19 (8):1282-5.

34. David J, Cooper C, Hickey L, Lloyd J, Dore C, McCullough C, et al. The functional and psychological outcomes of juvenile chronic arthritis in young adulthood. Br J Rheumatol 1994;33:876-881.

35. Musiej-Nowakowska E and Ploski R. Pregnancy and early pauciarticular juvenile chronic arthritis. Ann Rheum Dis 1999;58:475-480.

36. Zak M and Pedersen FK. Juvenile chronic arthritis into adulthood: a long-term follow-up study. Rheumatology 2000;39:198-204.

37. Lomater C, Gerloni V, Gattinara M, Mazzotti J, Cimaz R and Fantini F. Systemic Onset Juvenile Idiopathic Arthritis: A Retrospective Study of 80 Consectutive Patients Followed for 10 Years. J Rheumatol 2000;27 (2):491-6.

38. Speigel LR, Schneider R and Lang BA. Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study. Arthritis Rheum 2000;43:2402-9.

39. Archenholtz B, Nodberg E and Bremell T. Lower level of education in young adults with arthritis starting in early adulthood. Scand J Rheum 2001;30:353-5.

40. Narayanan K, Rajendran CP, Porkodi R and Shanmuganandan K. A follow-up study of juvenile rheumatoid arthritis into adulthood. J Assoc Physicians India 2002;50:1039-41.

41. Minden K, Neiwerth M, Listing J, Biedermann , Bollow M, Schontube M, et al. Long-term Outcome in Patients With Juvenile Idiopathic Arthritis. Arthritis and Rheumatism 2002;46 (9):2392-2401.

42. Packham JC, Hall MA and Pimm TC. Long term follow-up of 246 adults with juvenile idiopathic arthritis: predictive factors for mood and pain. Rheumatology 2002;41:1444-1449.

43. Packham JC and Hall MA. Long term follow up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology 2002;41:1428-1435.

44. Packham JC and Hall MA. Long term follow up of 246 adults with juvenile Idiopathic arthritis: social function, relationships and sexual activity. Rheumatology 2002;41:1440-1443.

45. Packham JC and Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: education and employment. Rheumatology 2002;41:1436-1439.

46. Foster HE, Marshall N, Myers A, Dunkley P and Griffiths ID. Outcome of adults with juvenile idiopathic arthritis: a quality of life study. Arthritis Rheum 2003;48 (3):767-75.

47. Flato B, Lien G, Smerdel A, Vinje O, Dale K, Johnston V, et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. J Rheumatol 2003;30 (2):386-93.

48. Flato B, Smerdel A, Johnston V, Lien G, Dale K, Vinje O, et al. The influence of patient characteristics, disease variables, and HLA alleles on the development of radiographically evident sacroiliitis in juvenile idiopathic arthritis. Arthritis Rheum 2002;46 (4):986-94.

49. Bruinooge LN, El Moussaoui R, Taal E, Dijkmans BA and Van Soesbergen RM. Outcome in adults with juvenile idiopathic arthritis. Comparison of the DUTCH-AIMS2 between JIA and RA. Scand J Rheum 2003;32 (2):89-94.

50. Fantini F, Gerloni V, Gattinara M, Cimaz R, Arnoldi C and Lupi E. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. J Rheumatol 2003;30 (3):579-84.

51. Giannini EH, Brewer EJ and Kuzmina N. Methotrexate in resistant juvenile rheumatoid arthritis: results of the USA-USSR double blind placebo controlled trial. New Eng J Med 1992;326:1043-9.

52. Woo P, Southwood T, Prieur AM, Dove CJ, Grainger J, David J, et al. Randomised placebo-controlled, crossover trial of low dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000;43:1849-57.

53. van Rossum M, Fiselier T, Franssen MJ, Zwindermann AH, Cate R, van Suijlekom-Smit LW, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomised double-blind placebo-controlled multicentre study. Dutch Juvenile Arthritis Study Group. Arthritis Rheum 1998;41:808-16.

54. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study. New Eng J Med 2000;342:763-73.

55. Harel L, Wagner-Weiner L, Poznanski A, Spencer C, Ekwo E and Magilavy D. Effects of methotrexate on radiological progression in juvenile rheumatoid arthritis. Arthritis Rheum 1993;10:1370-74.

56. Miller JJ. Psychosocial factors related to rheumatic diseases in childhood. J Rheumatol 1993;20 (Suppl 38):1-11.

57. Still GF. On a form of chronic joint disease in children. Medical and Chirurgical Transactions 1897;80:1-13.

58. Cleary AG, Sills JA and Davidson JE. Classification of HLA-B27 positive patients according to the revised classification criteria for juvenile idiopathic arthritis. Arch Dis Child 1999;80 (Suppl 1):G158.

59. Berntson L, Fasth A, Andersson-Gare B, Herlin T, Kristinsson J, Lahdenne P, et al. The Influence of Heredity for Psoriasis on the ILAR Classification of Juvenile Idiopathic Arthritis. J Rheumatol 2002;29 (11):2454-8.

60. David J, Vouyiouka O, Ansell BM, Hall A and Woo P. Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. Clin Exp Rheumatol 1993;11:85-90.

61. Russo RAG, Katsicas MM and Zelazko M. Etanercept in systemic juvenile idiopathic arthritis. Clin Exp Rheumatol 2002;20 (5):723-6.

62. Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to onset type. Arthritis Rheum 2003;48 (4):1093-101.

63. Andersson Gare B, Fasth A, Andersson J, Berglund G, Elkstrom H, Eriksson M, et al. Incidence and prevalence of juvenile chronic arthritis: a population survey. Ann Rheum Dis 1987 Apr;46 (4):277-81.

64. Sherry DD, Mellins ED and Wedgewood RJ. Decreasing severity of chronic uveitis in children with pauciarticular arthritis. Am J Dis Child 1991 Sep;145 (9):1026-8.

65. Leak AM and Ansell BM. The relationship between ocular and articular disease activity in juvenile rheumatoid arthritis complicated by chronic anterior uveitis. Arthritis & Rheumatism 1987;30 (10):1196-7.

66. Smiley W. The eye in juvenile rheumatoid arthritis. Trans Opthal Soc UK 1974;94:817-828.

67. Evans-Jones G, FA, Jones R, et al. Ophthalmic Services for Children. London. The Royal College of Ophthalmologists and the British Paediatric Association. 1994.

68. Burgos-Vargas R, Pacheco-Tena C and Vazquez-Mellado J. Juvenile onset spondyloarthropathies. Rhem Dis Clin NA 1997;23:569-598.

69. Fuchs HA, Brooks RH, Callahan LF and Pincus T. A simplified 28-joint count quantative articular index in rheumatoid arthritis. Arthritis Rheum 1989;32:531-7.

70. Williams HJ, Ward JR and Reading JC. Low-dose d-penicillamine therapy in rheumatoid arthritis. Arthritis Rheum 1983;26:581-92.

71. Ritchie DM, Boyle JA and McInnes JM. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med 1968;37:393-406.

72. Thompson PW, Kirwan JR and Currey HLF. A comparison of the ability of 28 articular indices to detect an induced flare of joint inflammation in rheumatoid arthritis. Br J Rheumatol 1988;27:375-380.

73. Hochberg MC, Chang RW and Dwosh I. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498-502.

74. Kirwan JR and Reeback JS. Stanford Health Assessment questionnaire modified to assess disability in British patients with rheumatoid arthritis. Br J Rheumatol 1986;25:206-209.

75. Pincus T and Callahan LF. Quantitative measures to assess, monitor and predict morbidity and mortality in rheumatoid arthritis. Clin Rheum 1992;6 (161-91).

76. Meenan RF. The AIMS approach to health status measurement: conceptual background and measurement properties. J Rheumatol 1982;9:785-788.

77. Wolfe F. In: Bellamy N ed. Prognosis in the rheumatic diseases. London: Klewer Academic Publishers. 1991:37-82.

78. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277-99.

79. Lorig K, Chastain R and Ung E. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. Arthritis Rheum 1989;32:37-44.

80. Sriwatanakul K, Kelvie W and Lasagna L. The quantification of pain: an analysis of words used to describe pain and analgesia in clinical trials. Clin Pharmacol Ther 1882;32:143-148.

81. Beck AT, Ward CH, Mendelson M, Mock J and Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatr 1961;4:561-571.

82. Weissman M M, Sholomskas D, Pottenger M, Prusoff BA and Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiology 1977;106 (3):203-14.

83. Husaini BA, Neff JA and Stone RH. Psychiatric impairment in rural communities. J Community Psychology 1979;7 (2):137-46.

84. Callahan LF, Kaplan MR and Pincus T. The Beck Depression Inventory, Center for Epidemiology Studies Depression Scale (CES-D), and General Well-Being Schedule depression subscale in rheumatoid arthritis. Criterion contamination of responses. Arthrit Care Res 1991;4 (1):3-11.

85. Zigmund AS and Snaith RP. The hospital depression and anxiety scale. Acta Psychiatrica Scand 1983;67:361-370.

86. Newman S and Revenson TA. Coping with rheumatoid arthritis: psychological aspects of rheumatic disease. Ballieres Clin Rheumatol 1993;7 (2):259-280.

87. Keefe FJ and Brown GK. Coping with rheumatoid arthritis pain: catastrophising as a maladaptive strategy. Pain 1989;37:51-56.

88. O'Reilly P. Methodological issues in social support and social network research. Social science and medicine 1988;26:863-73.

89. Power MJ, Champion LA and Aris SJ. The development of a measure of social support: the Significant Others Scale (SOS). Br J Clin Psychol 1988;27:349-58.

90. Sarason I, Levine HM and Basham RB. Assessing social support: the social support questionnaire. J Pers Soc Psychol 1983;44:127-139.

91. World Health Organisation. Classification of impairments, disabilities and handicaps. Geneva: WHO 1980.

92. Carr AJ and Thompson PW. Towards a measure of patient-perceived handicap in rheumatoid arthritis. Br J Rheumatol 1994;33:378-382.

93. Carr AJ. A patient-centred approach to evaluation and treatment in rheumatoid arthritis: the development of a clinical tool to measure patient-perceived handicap. Br J Rheumatol 1996;35:921-932.

94. Thompson PW, Silman AJ, Kirwan JR and Currey HLF. Articular indices of joint inflammation in rheumatoid arthritis: correlation with the acute phase response. Arthritis Rheum 1987;30:618-623.

95. Ansell BM. Heberden Oration, 1977. Chronic arthritis in childhood. Ann Rheum Dis 1978;37:107-120.

96. Ansell BM and Bywaters EG. Growth in Still's disease. Ann Rheum Dis 1956;15:295.

97. Stoeber E. Corticosteroid treatment of juvenile chronic polyarthritis over 22 years. Eur J Pediatr 1976;121:141-147.

98. Wirrell E, Lang B and Canfield C. Social outcomes in young adults with juvenile arthritis: implications for the development of transition clinics. Arthritis Rheum 1995;38:S184.

99. Hays RD, Sherbourne CD and Mazel RM. The RAND 36-Item Health Survey 1.0. [see comments]. Health Economics. 2(3):217-27, 1993 Oct. Health Economics 1993;2 (3):217-27.

100. Guillaume S, Prieur AM, Coste J and Job-Deslandre C. Long-term outcome and prognosis in oligoarticular-onset juvenile idiopathic arthritis. Arthritis & Rheumatism 2000;43 (8):1858-1865.

101. Giannini EH, Brewer EJ and Kuzmina N. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the USA-USSR double blind, placebo controlled trial. The Pediatric Rheumatology Collaborative Study Group and the Cooperative Children's Study Group. New Eng J Med 1992;326:1043-1049.

102. Woo P, Wilkes H and Southwood T. Low dose methotrexate is effective in extended oligoarticular arthritis but not in systemic arthritis of children. Arthritis Rheum 1997;40:S47.

103. Van Rossum M, Fiselier T and Frannsen M. Sulfasalazine in the treatment of juvenile chronic arthritis. Rev Rheum (Engl Edn) 1997;64:S247.

104. Dougados M, Van der Linden S and Leirisalo-Repo M. Sulfasalazine in the treatment of spondyloarthropathy: a randomized, double blind, placebo controlled study. Arthritis Rheum 1995;38:618-627.

105. Rapoff MA and Lindsey CB. The pain puzzle: A visual and conceptual metaphor for understanding and treating pain in pediatric rheumatic disease. J Rheumatol 2000;27 (Suppl 58):29-33.

106. Laaksonen A and Laine V. A comparative study of joint pain in adult and juvenile rheumatoid arthritis. Ann Rheum Dis 1961;20:386-387.

107. Scott PJ, Ansell BM and Huskisson EC. Measurement of pain in juvenile chronic polyarthritis. Ann Rheum Dis 1977;36:186-187.

108. Sherry DD, Bohnsack J, Salmonson K, Wallace CA and Mellins E. Painless juvenile rheumatoid arthritis. J Pediatr Psychol 1990;12:241-255.

109. Benestad B, Vinge O and Veierod MB. Quantative and qualative assessments of pain in children with juvenile chronic arthritis based on the Norwegian version of the Pediatric Pain Questionnaire. Scand J Rheum 1996;25:293-299.

110. Schanberg LE, Lefebvre JC, Keefe FJ, Kredich DW and Gil KM. Pain coping and the pain experience in children with juvenile chronic arthritis. Pain 1997;73:181-189.

111. Varni JW, Thompson KL and Hanson V. The Varni/Thompson Pediatric Pain Questionnaire. I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis. Pain 1987;28:27-38.

112. Abu-Saad HH and Uiterwijk M. Pain in children with juvenile rheumatoid arthritis: a descriptive study. Pediatr Res 1995;38:194-198.

113. Ilowite NT, Walco GA and Pochaczevsky R. Assessment of pain in patients with juvenile rheumatoid arthritis: Relation between pain intensity and degree of joint inflammation. Ann Rheum Dis 1992;51:343-346.

114. Thompson KL, Varni JW and Hanson V. Comprehensive assessment of pain in juvenile rheumatoid arthritis: An empirical model. J Pediatr Psychol 1987;12:241-255.

115. Gragg RA, Rapoff MA, Danovsky MB, Lindsley CB, Varni JW, Waldron SA, et al. Assessing chronic musculoskeletal pain associated with rheumatic disease: further validation of the Pediatric Pain Questionnaire. J Pediatr Psychol 1996;21:237-250.

116. Fifield J, Tennen H, Reisine S and McQuillan J. Depression and the long-term risk of pain, fatigue, and disability in patients with rheumatoid arthritis. Arthritis Rheum 1998;41 (10):1851-7.

117. Lewinsohn PM, Hoberman HM and Rosenbaum M. Probability of relapse after an episode of depression. J Abnorm Psychol 1989;97:251-64.

118. *1995 Louis Harris and Associates Poll.* 1995, National Organization on Disability: Washington.

119. *NOD/Harris Survey of People with Disabilities Study, No 942003.* 1998, Louis Harris Association: Washington.

120. Martin K and Woo P. Outcome in juvenile chronic arthritis. Rev Rheum (Engl Edn) 1997;10:S242.

121. White PH. Future expectations: Adolescents with rheumatic diseases and their transition into adulthood. Br J Rheumatol 1996;35:1-5.

122. White PH, Gussak DG, Fisher B and Hixson D. Career maturity in adolescents with chronic illnesses and disabilities. J Adolescent Health Care 1990;11:S777.

123. White PH and Shear ES. Transition/job readiness for adolescents with juvenile arthritis and other chronic illness. J Rheumatol 1992;19 (Suppl 33):23-27.

124. Hanna D. Education and schooling. Children at school can have their 'special needs' assessed to ensure they get the care they require. *Children have arthritis too (CHAT).* Arthritis Care 1997:23-25.

125. Ivey J, Brewer EJ and Giannini EH. Psychosocial functioning in children with juvenile rheumatoid arthritis (JRA). Arthritis Rheum 1981;24:S100.

126. Strurge C, Garralda ME and Biossin M. School attendance and juvenile chronic arthritis. Br J Rheumatol 1997;36 (11):1218-1223.

127. Strax TE. Psychosocial issues faced by adolescents and young adults with disabilities. Pediatr Ann 1991;20:501-506.

128. Selekman J and McIlvain-Simpson G. Sex and sexuality for the adolescent with a chronic condition. Pediatr Nursing 1991;17:535-538.

129. Fraser P, Hoch S and Erlandson D. The timing of menarche in juvenile rheumatoid arthritis. J Adolescent Health Care 1988;9:483-487.

130. Nelson JL, Koepsell TD, Dugowson CE, Voight LF, Daling JR and Hansen JA. Fecundity before disease onset in women with rheumatoid arthritis. Arthritis 1993;36:7-14.

131. Lutz G. Effects of cyclosporin A on hair. Skin Pharmacology 1994;7 (1-2):101-4.

132. Shalet S and Howell S. Female infertility disorders: Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin North Am 1998;27:927-943.

133. Richter P, Calamera JC, Morgrsfeld MC, Kierszenbaum AL, Lavieri JC and Mancini RE. Effect of chlorambucil on spermatogenesis in the human with malignant lymphoma. Cancer 1970;25:1026-30.

134. Barlow JH, Shaw KL and Harrison K. Psychosocial impact of juvenile chronic arthritis. Br J Rheumatol 1997;36 (suppl 1):139.

135. Wilkinson VA. Juvenile chronic arthritis in adolescence: facing the reality. International Rehabilitation Medicine 1981;3 (1):11-17.

136. Hamilton A. Sexual problems in arthritis and allied conditions. Int Rehab Med 1980;3:38-42.

137. Majerovitz SD and Revenson TA. Sexuality and rheumatoid disease: the significance of gender. Arthrit Care Res 1994;7:29-34.

138. Østensen M and Almberg K. Sex, reproduction and gynaecological disease in young adults with a history of juvenile chronic arthritis (JCA). Ann Rheum Dis 1999 (XIV EULAR Congress, 6-11 June):Abstract 1449.

139. Stern RS and Lange R. Outcomes of pregnancies among women and partners of men with a history of exposure to methoxsalen photochemotherapy (PUVA) for the treatment of psoriasis. Arch Dermatol 1995;127 (3):347-50.

140. Østensen M. Pregnancy in patients with a history of juvenile rheumatoid arthritis. Arthritis Rheum 1991;34:881-887.

141. Office of National Statistics UK. Estimated number of pregnancies in England and Wales 1976-1993 and UK 1991-1996. 1998.

142. Gindler J, Li Z, Zhang J, Correa A and Sux X. Folic acid supplements during pregnancy and risk of miscarriage. Lancet 2001;358:769-800.

143. Office of National Statistics UK. Caesarean deliveries in NHS hospitals. Social Trends 34. 2003.

144. Cohen S. Psychosocial models of the role of social support in the etiology of physical disease. Health Psychol 1988;7 (3):269-297.

145. Glass DN and Giannini EH. Juvenile Rheumatoid Arthritis as a Complex Genetic Trait. Arthritis and Rheumatism 1999;42 (11):2261-8.

146. Creed F. Psychological disorders in rheumatoid arthritis: a growing consensus? Ann Rheum Dis 1990;49:808-812.

147. Baum J. A review of the psychological aspects of rheumatic diseases. Semin Arthritis Rheum 1982;11:352-361.

148. Bishop D, Green A, Cantor S and Torresin W. Depression, anxiety and rheumatoid arthritis activity. Clin Exp Rheumatol 1987;5:147-150.

149. Frank FG, Beck NC and Parker JC. Depression in rheumatoid arthritis. J Rheumatol 1988;15:920-925.

150. Aasland A, Flato B and Vondivik LH. Psychosocial outcome in juvenile chronic arthritis: a nine year follow-up. Clin Exp Rheumatol 1997;15:561-568.

151. Hays RD, Sherbourne CD and Mazel RM. The RAND 36-Item Health Survey 1.0. Health Economics 1993;2 (3):217-27.

152. Turner RJ and Mclean PD. Physical disability and psychological distress. Rehabilitation Psychology 1989;34:225-242.

153. Timko C, Stovel KW, Moos Rh and Miller JJ. Adaptation to juvenile rheumatic disease: A controlled evaluation of functional disability with a one-year follow-up. Health Psychol 1992;11:91-100.

154. Brainerd CJ. Piaget's Theory of Intelligence. New Jersey: Prentice Hall, Inc 1978.

155. Zulian F, Schumacher HR, Calore A, Goldsmith DP and Athreya BH. Juvenile arthritis in Turner's syndrome: a multicenter study. Clin Exp Rheumatol 1998;16 (4):489-94.

156. Zak M, Hassager C, Lovell DJ, Nielsen S, Henderson CJ and Pedersen FK. Assessment of bone mineral density in adults with a history of juvenile chronic arthritis. Arthritis Rheum 1999;42 (4):790-798.

157. Coulam CB, Adamson SC and Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol 1986;67:604-606.

158. Kim TJ, Anasti JN and Flack MR. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol 1997;89:777-779.

159. Yan G, Schoenfeld D, Penney C, Hurxthal K, Taylor AE and Faustman D. Identification of premature ovarian failure patients with underlying autoimmunity. J Womens Health Gend Based Medicine 2000;9 (3):275-287.

160. Luborsky J. Ovarian autoimmune disease and ovarian autoantibodies. J Womens Health Gend Based Medicine 2002;11 (7):585-599.

161. Mendonça LLF, Khamashta MA, Nelson-Piercy C, Hunt BJ and Hughes GRV. Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility. Rheumatology 2000;39 (8):880-882.

162. Smith G, Roberts R, Hall C and Nuki G. Reversible ovulatory failure associated with the development of luteinized unruptured follicles in women with inflammatory arthritis taking non-steroidal anti-inflammatory drugs. Br J Rheumatol 1996;35 (5):458-462.

163. Matsuo T, Kono R, Matsuo N, Ezawa K, Natsumeda M, Soda K, et al. Incidence of ocular complications in rheumatoid arthritis and the relation of keratoconjunctivitis sicca with its systemic activity. Scand J Rheum 1997;26 (2):113-6.

164. Blumenfeld Z, Shapiro D, Shteinberg M, Avivi I and Nahir M. Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated by chemotherapy. Lupus 2000;9 (6):401-5.

165. Jackson RA, Haynes BF and Burch WM. Ia and T cells in new onset Graves' disease. J Clin Endocrinol Metab 1984;59:187-90.

166. Jackson RA, Morris MA and Haynes BF. Increased circulating Ia antigen bearing T cells in type I diabetes mellitus. New Eng J Med 1982;306:785-788.

167. Rabinowe SL, Jackson RA and Dluhy RG. Ia and T lymphocytes in recently diagnosed Addison's disease. Am J Med 1984;77:597-601.

168. Snowdon DA, Kane RL and Beeson WL. Is early natural menopause a biologic marker of health and aging? Am J Public Health 1989;79:709-714.

169. Kreiner D, Droesch K and Navot D. Spontaneous and pharmacologically induced remissions in patients with premature ovarian failure. Obstet Gynecol 1988;73:926-928.

170. Nelson LN, Anasti JN and Kimzey LM. Development of luteinized graafian follicles in patients with karyotypically normal spontaneous premature ovarian failure. J Clin Endocrinol Metab 1994;79:1470-1475.

171. Ohta H, Sugimoto I and Masuda A. Decreased bone mineral density associated with early menopause progresses for at least ten years: Cross sectional comparisons between early and normal menopausal women. Bone 1996;18:227-231.

172. Van der Schouw YT, Van der Graff Y and Steyerberg EW. Age at menopause as a risk for cardiovascular mortality. Lancet 1996;347:714-718.

173. Koyama H, Wada T and Nishizawa Y. Cyclophosphamide-induced ovarian failure and its therapeutic significance in patients with breast cancer. Cancer 1977;39:1403-1409.

174. Fink CW. The clinical features, course, prognosis and treatment of juvenile arthritis. Recenti Progressi in Medicina 1991;82 (10):554-560.

175. Gillen M, Lallas D, Brown C, Yelin E and Blanc P. Work disability in adults with cystic fibrosis. Am J Respir Crit Care Med 1995;152 (1):153-6.

176. Barrett EM, Scott DG, Wiles NJ and Symmons D. The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. Rheumatology 2000;39 (12):1403-9.

177. Holden C. Depression Research Advances: Treatment Lags. Science 1986;233:723-6.

178. Rodin G and Voshart K. Depression in the medically ill: an overview. Am J Psych 1986;143 (6):696-705.

179. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshelman S, et al. Lifetime and 12 month prevalence of DSMIIIR psychiatric disorders in the United States. Arch Gen Psychiatr 1994;51:8-19.

180. Weissman M M and the Cross national Collaborative group. The changing rate of major depression: Cross national comparisons. J Am Med Assoc 1992;268 (21):3098-3105.

181. Goyette P, Pai A, Milos R, Frosst P, Tran P, Chen Z, et al. Gene structure of human and mouse methylenetetrahydrofolate reductase (MTHFR). Mammalian Genome 1999;9 (8):652-6.

182. Rozen R. Molecular genetics of methylenetetrahydrofolate reductase deficiency. J Inherited Metabolic Disease 1996;19 (5):589-94.

183. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nature Genetics 1995;10 (1):111-3.

184. Ulrich CM, Robien K and Sparks R. Pharmocogenetics and folate metabolism - a promising direction. Pharmacogenetics 2002;3 (3):299-313.

185. Schwahn B and Rozen R. Polymorphisms in the methylenetetrahydrofolate reductase gene: clinical consequences. Am J Pharmocogenetics 2001;1 (3):189-201.

186. Weisberg I, Tran P, Christensen B, Sibani S and Rozen R. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Molecular Genetics and Metabolism 1999;64 (3):169-72.

187. Rady PL, Szucs S, Grady J, Hudnall SD, Kellner LH, Nitowsky H, et al. Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) in ethic populations in Texas: a report of a novel MTHFR polymorphic site G1793A. Am J Med Genetics 2002;107 (2):162-8.

188. Toffoli G, Veronesi A, Boiocchi M and Crivellari D. MTHFR gene polymorphism and severe toxicity during adjuvant treatment of early breast cancer with cyclophosphamide, methotrexate and fluorouracil (CMF). Ann Oncology 2000;11 (3):373-4.

189. Ulrich CM, Yasui Y, Storb R, Schubert MM, Wagner JL, Bigler J, et al. Pharmogenetics of methotrexate: toxicity among marrow transplantation patients varies with the methylenetetrahydrofolate reductase C677T polymorphism. Blood 2001;98 (1):231-4.

190. van Ede AE, Laan RF, Blom HJ, Huizinga TW, Haagsma CJ, Giesendorf BA, et al. The C677T mutation in the methylenetetrahydrofolate reductase gene: a genetic risk factor for methotrexate-related elevation of liver enzymes in rheumatoid arthritis. Arthritis Rheum 2001;44 (11):2525-30.

191. Urano W, Taniguchi A, Yamanaka H, Tanaka E, Nakajima H, Matsuda Y, et al. Polymorphisms in the methylenetetrahydrofolate reductase gene were associated with both the efficacy and the toxicity of methotrexate used for the treatment of rheumatoid arthritis, as evidenced by single gene locus and haplotype analysis. Pharmacogenetics 2002;12 (3):181-2.