Unravelling the biological, environmental, physical and psychosocial factors impinging on outcomes in early rheumatoid arthritis

Predictors of disease activity and disability and the relationship between the two

Sarah Twigg

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The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

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YEAR Management Team: Paul Emery, Philip Conaghan, Ann Morgan, Anne-Maree Keenan and Elizabeth Hensor.

YEAR Medical Staff: Mark Quinn, Andrew Gough, Michael Green, Richard Reece, Lesley Hordon, Philip Helliwell, Richard Melsom, Sheelagh Doherty, Ade Adebajo, Andrew Harvey, Steve Jarrett, Gareth Huston, Amanda Isdale, Mike Martin, Zunaid Karim, Dennis McGonagle, Colin Pease, Sally Cox, Dr Victoria Bejarano, Jackie Nam, Edith Villeneuve.

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Abstract

Objective

The aim was to study the course of disease activity and disability in early rheumatoid arthritis (RA) and the relationship between the two over 24 months. Baseline predictors of adverse outcome were sought as potential tools for targeting future therapy in RA.

Methods

Yorkshire Early Arthritis Register (YEAR) recruited patients with a clinician-made diagnosis of RA and symptoms of ≤24 months. Change in disease activity, measured using disease activity score from counts of 28 joints (DAS28) and disability, measured using the disability index component of the health assessment questionnaire (HAQ-DI), after 6 and 12 months, were outcomes in linear regression models. In order to take advantage of the longitudinal data and examine change in DAS28 and HAQ-DI over time, latent growth curves were applied to the data. Latent class growth analyses (LCGA) identified trajectories of change in DAS28 and HAQ-DI over 2 years. Multinomial logistic regression identified predictors of trajectory group membership. Finally, a dual trajectory analysis explored the relationship between DAS28 and HAQ-DI trajectories. Missing data were handled using multiple imputation and maximum likelihood estimation.

Results

Data from 1416 YEAR cases were included. Baseline fatigue visual analogue score (VAS) consistently predicted worse outcome including lesser change in DAS28 and HAQ-DI after 6 and 12 months and adverse DAS28 and HAQ-DI trajectories. There were 2 DAS28 and 2 HAQ-DI trajectories and 4 dual trajectory groups: half of patients followed the most favourable, low DAS28/low HAQ-DI, trajectory and only 1% followed a high DAS28/low HAQ-DI trajectory. High DAS28/high HAQ-DI and low DAS28/high HAQ-DI trajectories were more likely for females, cases from more deprived socio-economic areas, and those reporting greater fatigue at baseline. The high DAS28/high HAQ-DI trajectory was more likely in cases with higher baseline DAS28, but baseline DAS28 did not predict low

DAS28/high HAQ-DI trajectory group membership. Membership of the low DAS28/high HAQ-DI group was more likely in cases with greater contribution of subjective components to baseline DAS28 .

Conclusion

Baseline fatigue consistently predicted adverse DAS28 and HAQ-DI over 2 years. In some cases, there was persistent disability and disease activity, whilst another group had greater disability despite less disease activity. Compared to those with low disease activity and disability, membership of these 2 groups was more likely with greater baseline fatigue. Further research into the drivers of fatigue in RA may help target therapies and limit disability in RA.

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Abbreviations

ACPA	Anti citrullinated peptide antibodies
ACR	American College of Rheumatology
AIC	Akaike information criteria
AP	Attributable portion
ARA	American Rheumatism Association
BARFOT	Better Anti-Rheumatic FarmacOtherapy
BIC	Bayesian information criteria
BLRT	Bootstrap likelihood ratio test
BRASS	Brigham and women's hospital Rheumatoid Arthritis Sequential Study
BROSG	British rheumatoid outcome study group
BSRBR	British Society for Rheumatology Biologics Register
CCP	Cyclic citrullinated peptide
CDAI	Clinical disease activity index
CFA	Confirmatory factor analysis
CFI	Comparative fit index
CI	Confidence interval
cm	Centimetres
CRP	C-reactive protein
CT	Computed tomography
DAS	Disease activity score
DAS28	Disease activity score based upon counts of 28 joints
DAS28-P (CRP)	Pain index component of the disease activity score based upon counts of 28 joints and CRP.
df	Degrees of freedom
dl	Decilitre
DMARD	Disease modifying anti-rheumatic drug
GDP	Gross domestic product
EMS	Early morning stiffness
ERAN	Early Rheumatoid Arthritis Network
ERAS	Early Rheumatoid Arthritis Study
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism

FLS	Fibroblast like synoviocytes
GMM	Growth mixture modelling
HAQ	Health assessment questionnaire
HAQ-DI	Disability index component of the health assessment questionnaire
HCQ	Hydroxychloroquine
HLA	Human leucocyte antigen
HR	Hazard ratio
Kg/m^2	Kilograms per metre squared
Ig	Immunoglobulin
IHD	Ischaemic heart disease
IL	Interleukin
ILD	Interstitial lung disease
IMD	Index of multiple deprivation
KCS	Kerato-conjunctivitis sicca
LCGA	Latent class growth analysis
LMR-LRT	Lo, Mendell and Rubin likelihood ratio test
LSOA	Lower layer super output area
MAR	Missing at random
MCAR	Missing completely at random
MCP	Metacarpophalangeal joint
m-DAS28	Modified disease activity score based upon counts of 28 joints
mg	Milligrams
mg/dL	Milligrams per decilitre
mg/L	Milligrams per litre
MI	Multiple imputation
MLM	Multilevel modelling
MLS	Macrophage like synoviocytes
mm	Millimetres
MMP	Matrix metalloproteases
MNAR	Missing not at Random
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MNAR	Missing not at random

MTP	Metatarsophalangeal joint
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOAR	NOrfolk Arthritis Register
NSAID	Non steroidal anti- inflammatory drug
NSIP	Non specific interstitial pneumonia
OMERACT	Outcome Measures for Rheumatology Clinical Trials
OR	Odds ratio
PIP	Proximal inter-phalangeal joint
Pmm	Predictive mean matching
PTPN22	*Protein tyrosine phosphatase receptor type 2*
PUK	Peripheral ulcerative keratitis
RA	Rheumatoid arthritis
RAI	Ritchie articular index
RANKL	Receptor activator of nuclear factor κβ ligand
RF	Rheumatoid factor
RMSEA	Root mean square error of approximation
RR	Relative risk
SDAI	Simplified disease activity index
SE	Socioeconomic status
SJC	Swollen joint count
SPA	Spondyloarthropathy
SSA	Sulphasalazine
TJC	Tender joint count
TNF	Tumour necrosis factor
UIP	Usual interstitial pneumonia
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
USS	Ultrasound scanning
VAS	Visual analogue scale
χ^2	Chi Square
XR	X-ray
YEAR	Yorkshire Early Arthritis Register

Chapter 1 Introduction

Rheumatoid arthritis (RA) is a chronic, debilitating multi-system disease characterised by symmetrical inflammation of synovial joints. For the sufferer, it represents a potential cause of pain and disability for which disease modifying medication is necessary to optimise long term outcomes. For decades, rheumatologists have faced the challenge of reducing joint inflammation and pain and assisting patients to manage the resulting impairment of daily function. Owing to research into the optimal management of RA and advances in its pharmacotherapy (which are discussed in Section 1.6), control of inflammation in RA has vastly improved over recent years. However, despite these advances, RA is not 'cured' and continues to challenge patients and rheumatologists, in terms of suppression of inflammation and prevention or management of disability. There has been much research into factors predicting adverse outcomes in RA (discussed in Sections 1.8.2 and 1.8.4), but relatively little into how disease activity influences disability (Section 1.8.5). This relationship warrants investigation, as current therapies mainly target inflammation. Therefore, if disability ensues despite the suppression of synovial inflammation, alternative approaches may be indicated. Furthermore, owing to the heterogeneous nature of RA, outcomes are likely to vary between individuals. Identification of predictors of a given outcome would be a useful step towards personalised medicine in RA. The present Chapter introduces the history, epidemiology, pathogenesis and clinical features of RA before discussing methods previously described in the study of this chronic illness. Literature reviews of methods used to measure RA outcomes, as well as predictors of disease activity and disability are then presented, before the hypothesis central to this Thesis is outlined.

1.1 Rheumatoid arthritis: an ancient or modern disease?

There has been some debate as to whether RA is an ancient disease or one that has emerged more recently. Images of people with joint deformities that are alike those seen due to RA have been depicted by artists in work produced as early as 1441(Yeap, 2009). However, it cannot be assumed that these images represented the true physical form and furthermore, the physical characteristics of RA can be similar to those of other diseases. On the other hand, the appearance of joint swelling and deformity characteristic of RA, produced by an artist whose other works do not capture this same appearance of the joints (and is therefore less likely to be due to artistic interpretation), may be more compelling evidence (Yeap, 2009, Entezami *et al.*, 2011). The first description of RA in the medical literature has been attributed to Augustin Jacob Landré-Beauvais in Paris in 1800 (Landre-Beauvais, 2001). In his doctoral dissertation, Landré-Beauvais described a form of arthritis in 9 patients which he observed was different to 'ordinary gout', because it tended to affect females from poor backgrounds, was associated with general poor health, and had a chronic course. He named this disease 'asthenic gout'. The name 'rheumatoid arthritis' was applied 90 years later by Archibald Garrod, who believed RA was not a modern disease and that archaeological evidence had confirmed that the disease had afflicted ancient populations (Garrod, 1890). However, archaeological findings can be affected by the preservation of samples and Garrod's theory and the reliability of evidence gathered from skeletal remains have since been disputed. In the post-mortem state, damage to the skeleton can lead to difficulties in differentiating RA from other inflammatory arthritidies and furthermore, bones of the hands and wrists, which are typically involved in RA, may be difficult to find in ancient skeletons (reviewed by Entezami *et al.*, 2011). An alternative theory, proposed following evidence obtained from skeletons in North America, is that the disease originated in the 'new world' and was then transferred to the 'old world' following the pursuits of Christopher Columbus in 1492 (Rothschild *et al.*, 1992). Some researchers have suggested that the introduction of tobacco in Europe could have been key to the emergence of RA in the old world (Appelboom and Soyfoo, 2010).

Although compelling archaeological evidence (discussed in the following paragraph) suggests that RA was prevalent in Europe prior to the introduction of tobacco to the old world, this theory was popular because tobacco consumption is currently the strongest environmental risk factor for the development of RA (discussed further in Section 1.2).

More recent evidence that RA is an ancient disease arose from the examination of a mummy exhumed from an Italian church (Ciranni *et al.*, 2002). The so called 'Braids Lady' (named after her hair, which was found in long braids upon her chest) was believed to have died between 1550 and 1650. Not only were there macroscopic skeletal deformities consistent with RA (discussed in Section 1.5.1.1), such as subluxation and reduction in joint space of the metacarpophalangeal (MCP) and proximal inter-phalangeal (PIP) joints, ulnar deviation at the MCPs and 'Z' deformity of the thumb, X-ray examination of the mummified left hand (the right was skeletonised) confirmed erosions of the MCP joints, which are susceptible to erosions in RA. The authors concluded that this evidence of incident RA in Italy prior to the movement of goods such as tobacco from America to Europe contradicted theories that RA was either introduced to Europe through pathogens transported with these goods, or due to the introduction of tobacco. Despite the findings presented by Ciranni, which in a live patient would be highly suggestive of RA, Rothschild (2002) argued that an alternative diagnosis could be spondyloarthropathy (SPA) with involvement of the small joints. He suggested that the finding of bony fusion between wrist bones was a finding consistent with SPA, referencing his earlier work, which indicated that joint fusion in RA was a modern phenomenon resulting from treatment with corticosteroids. However, confirmation that the Braids lady carried an allele of the Human Leucocyte Antigen DRB1 (*HLA-DRB1)* gene known to be associated with RA (*0101*) and absence of the *HLA-B27* allele, which is strongly associated with SPA, provided further support that she did indeed have RA (Fontecchio *et al.*, 2012).

1.2 Epidemiology of rheumatoid arthritis

There have been significant developments in the field of RA epidemiology over the last 60 years. In the 1950s and 1960s, although the aetiology of RA was generally accepted as multi-factorial, there was some debate regarding the importance of genetics. For example, Sidney Cobb advocated that genetic factors were likely to be of less importance in the development of RA than "*faulty immune mechanisms plus infection and/or joint injury, and a personality plus a social environment that lead to low self-esteem and resentment."* (Cobb, 1965). Cobb claimed that although evidence from family studies suggested a genetic predisposition to RA, such findings could be explained by selection bias, publication bias and shared environments amongst families. However, the notion of RA as a hereditary disease remained popular, and even at this early stage, consideration was given to a separate aetiology of RA in which rheumatoid factor (RF) antibodies were observed: so called 'seropositive' RA (Lawrence, 1970). In 1976, Stastny first suggested that certain HLA genes, which encode major histocompatibility complex (MHC) class II molecules found on the surface of white blood cells, were associated with susceptibility to RA (Stastny, 1976). This is now recognised as the most significant genetic association of RA, representing about 30% of the genetic risk for RA (reviewed by Raychaudhuri, 2010). Later, Gregerson proposed the currently accepted 'shared epitope' hypothesis, which is discussed in further detail in Section 1.4.1. Throughout the years, environmental risk factors for RA have remained under scrutiny, and although several different agents have been suggested as possible triggers of immunological modification and autoimmunity in RA, tobacco smoking is the most widely reported environmental association. The association was first observed by Vessey and colleagues, who noted a greater prevalence of RA amongst smokers in their cohort of female patients enrolled into a study aimed at examining the relationship between oral contraceptive use and arthritis (Vessey *et al.*, 1987). The discovery of these genetic and environmental associations of RA, which are further discussed in Section 1.4.2, has had a significant impact upon the understanding of RA epidemiology.

The prevalence of RA varies geographically, from 0.2% to 0.3% in China and Japan, to 5.3% and 6.8% in Native American Pima and Chippewa Indians, respectively (reviewed by Silman and Pearson, 2002). Such geographical variation could be due to underlying genetic or environmental factors that predispose certain populations to RA, and studies of the prevalence of RA in migrant populations may be key to understanding this effect. In one study, which evaluated the prevalence of RA in a Pakistani population living in the United Kingdom (UK), individuals from 749 households in Luton, south east and east London, UK were interviewed. One criterion for inclusion was that the senior member of the household had been a UK resident for at least 10 years. The results were compared to those of a similar survey conducted in 1215 households in Pakistan (Hameed and Gibson, 1997). The researchers uncovered 6 cases of known RA from the 2056 people surveyed in the UK (2 of the 6 were born in the UK) and 6 out of 4232 individuals in Pakistan. Although this study did not prove a significantly lower prevalence of RA in Pakistani immigrants living in the UK compared to the native UK population (the estimated standardised morbidity ratio, SMR was 0.62; 95%CI 0.12 to 1.12), it did find a higher prevalence of RA amongst Pakistani immigrants living in the UK compared to the native Pakistani population surveyed (estimated SMR was 2.1; 95% confidence interval, CI, 1.1 to 3.1), suggesting a role for environmental influences on the risk for RA. It appears that there have not been any attempts to replicate the work carried out by Hameed and Gibson, but the use of modern medical databases by UK primary care practitioners may facilitate a less labour intensive method for repeating part of this study that could also encompass a wider geographical area.

The nature of RA as a chronic disease with variable severity and a tendency to flare means that prevalence has limited value for investigations of RA aetiology. Although estimates of prevalence, which examine a cross section of a population at a given time point, can be useful when assessing the burden of disease in a population, there is a risk of excluding cases in clinical remission at the time of the study, or that more severe cases are omitted due to premature death. A more useful measure, when considering

the aetiology of RA, is the incidence rate, which may provide some insight into how genetic and environmental elements interplay to make certain populations susceptible to RA. The only prospective study of RA incidence in the UK was published two decades ago and came from the Norfolk Arthritis Register (NOAR) (Symmons *et al.*, 1994). This study recruited patients presenting to their primary care physician with 4 or more weeks history of swelling in 2 or more joints, with onset of symptoms during 1990. The annual incidence of RA, whose diagnosis was based upon the 1987 American College of Rheumatology (ACR, formerly American Rheumatism Association) criteria proposed by Arnett and colleagues (1988) and described in Section 1.3, was 14 per 100,000 men and 36 per 100,000 women. Incidence increased with age for men, but for women, it rose until reaching a plateau at 45 years and then declined so that the incidence in elderly women was significantly less than in elderly men. Following the joint publication of new classification criteria for RA by the ACR and European League Against Rheumatism (EULAR) in 2010 (described in Section 1.3) the new criteria were retrospectively applied to the same population. At induction to the study, more patients met the 2010 criteria for RA; however, when the criteria were applied over 5 years of follow up, similar numbers of cases were classified as RA by both systems (Humphreys *et al.*, 2013a). There have been relatively few studies exploring the trends in incidence rate of RA, which are difficult to carry out as they require prolonged periods of follow up of a large population and consistent methods of case identification. Doran and colleagues studied the incidence of RA in Minnesota in the United States of America (USA), over a 40 year period (Doran *et al.*, 2002). They used medical records to identify cases of RA meeting the 1987 ACR criteria between 1955 and 1995 and reported a cyclical pattern of RA incidence, with a significant overall reduction in incidence of RA in both women and men. The authors also considered a “birth cohort” effect on the incidence of RA and found that participants of the study who were born during earlier time periods were more likely to have been diagnosed with RA than participants who were born later, but had reached a similar age. Such an effect could be explained by changing exposures to environmental

agents, or perhaps an infectious agent. Later, an extension to this study was conducted to examine the incidence of RA between 1997 and 2005, and a rise in incidence amongst women was uncovered (Myasoedova *et al.*, 2010). The authors commented that this trend may reflect the rates of smoking amongst women from the population under study, which was declining at a rate less marked than for men.

These estimates of incidence of RA in Minnesota are probably under-representative of the true value, as they were based upon the older 1987 ACR classification criteria for the diagnosis of RA, which were based upon a study of patients with longstanding RA. Therefore, early RA cases from Minnesota could have been missed. The discovery of anti-citrullinated peptide antibodies (ACPA) (Schellekens *et al.*, 1998), which are now commonly measured using the anti-cyclic citrullinated peptide (anti-CCP) antibody assay, (Schellekens *et al.*, 2000) was a significant advance in RA diagnosis that facilitated the introduction of new criteria. These highly specific antibodies (95% specificity reported in a meta-analysis by Nishimura *et al.* (2007) can be present in the blood up to 9 years prior to the development of clinical features of RA, (Rantapaa-Dahlqvist *et al.*, 2003) and have been very useful in the diagnosis of early RA. Clinically, the ability to diagnose RA at its early stages is beneficial, as there is consistent evidence that the initiation of early and aggressive therapy is associated with improved long term outcomes (Knevel *et al.*, 2010). In order to investigate the impact of treatment in patients with early RA within clinical trials, an updated classification system was required (Aletaha *et al.*, 2010).

1.3 Classification criteria for rheumatoid arthritis

The 1987 ACR criteria (Arnett *et al.*, 1988), which were derived in order to distinguish RA from other types of inflammatory arthritis, were based upon studies of patients with established disease and included features associated with long term RA, such as radiographic erosions. To define RA, 4 of the 7 following features must be satisfied:

- Morning stiffness of the joints lasting at least one hour

- Arthritis of at least 3 joint areas simultaneously with soft tissue swelling observed by a physician. Valid joint areas include MCPs, PIPs, wrists, elbows, knees and metatarsophalangeal joints (MTP)
- Arthritis of the hand joints with swelling of the MCPs, PIPs and wrists
- Symmetrical arthritis of the joint areas listed in point 2
- Rheumatoid nodules noted by a physician
- Serum rheumatoid factor positivity
- Typical radiographic changes observed on posteroanterior radiographs of the hand and wrist, which could include erosions or periarticular osteopenia.

The 2010 ACR/ EULAR classification criteria were designed so that they could be applied in early RA and are displayed in Table 1-1. In order to classify RA, subjects must obtain a score of 6 or more, from a possible 10. The criteria may be applied to patients with evidence of soft tissue swelling of least one joint, in whom an alternative diagnosis does not offer a more suitable explanation of the symptoms. For cases of RA presenting at a later stage, RA is also defined if there is radiographic evidence of "erosions typical of RA", together with a typical clinical history for RA (Aletaha *et al.*, 2010). At assessment, joints are considered involved if they are swollen or tender, or if there is evidence of inflammation confirmed by ultrasound examination. Furthermore, the criteria distinguish between large and small joint involvement, where large joints are the shoulders, hips, elbows, knees and ankles and small joints are the MCPs, PIPs, MTPs, (2^{nd} to 5^{th}), wrists and the interphalangeal joints of the thumbs. Further distinction is made between 'low' and 'high' titres for RF and ACPA. Here, a negative result is one below the upper limit of normal (ULN) for the specific laboratory assay; low titre is above the ULN, but less than 3 times the ULN and a high titre is one that is greater than 3 times the ULN. The duration of symptoms refers to the length of time that the involved joints (identified by the physician assessment) had been symptomatic for, according to the patient.

Table 1-1 The American College of Rheumatology / European League Against Rheumatism 2010 criteria for the classification of rheumatoid arthritis (adapted from Aletaha *et al.*, 2010)

Joint Involvement	**Score**
1 Large	0
2-10 Large	1
1-3 small	2
4-10 small	3
>10 joints (including at least one small joint)	5
Serology	**Score**
Negative RF and negative ACPA	0
Low –positive RF or low-positive ACPA	2
High positive RF or high positive ACPA	3
Acute phase reactants	**Score**
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	**Score**
<6 weeks	0
≥6 weeks	1

ACPA, anti citrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

1.4 Pathogenesis of rheumatoid arthritis

RA causes pain, swelling and stiffness of synovial joints. Figure 1-1 is an illustration of a synovial joint which shows articular cartilage lining the bony interface and synovial membrane forming the remainder of the joint lining. Also called the synovium, this usually hypocellular membrane consists of 2 layers: the superficial intimal layer which produces synovial fluid to cushion

the space between articular surfaces and the deeper, sublining layer. The intimal layer is only 2 or 3 cells deep and consists of 2 cell types: fibroblast-like synoviocytes (FLS) and macrophage –like synoviocytes (MLS) (Bartok and Firestein, 2010). Bursae, found between bones and tendons or muscles, consist of synovial fluid encapsulated by connective tissue and synovial membrane which absorbs impact as the joint moves (Kapit W, 1993). Ligaments stabilise the joint.

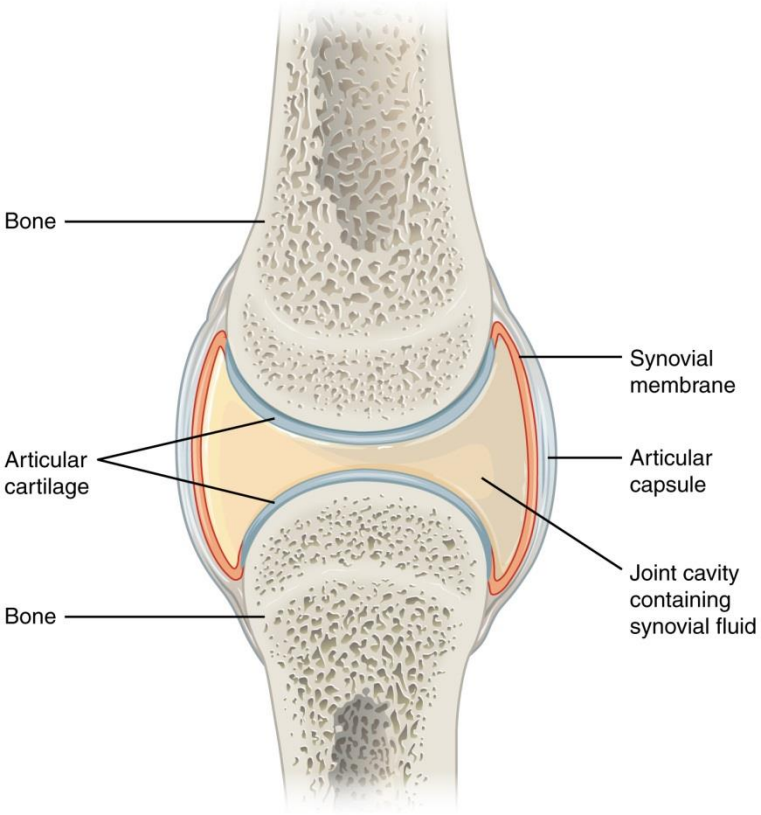

Figure 1-1 Diagram of a synovial joint
Reproduced with kind permission from OpenStax College. Synovial Joints, OpenStax-CNX Web site. http://cnx.org/contents/6c5b58ca-6c6d-4ab3-8b41-60c8733a3144@4. Jun 28, 2013.

1.4.1 Genetic influences on rheumatoid arthritis susceptibility

A genetic component to the pathology of RA is evident from family studies, with twin studies showing higher concordance between monozygotic than dizygotic pairs (Aho *et al.*, 1986, Lawrence, 1970, Bellamy *et al.*, 1992, Silman *et al.*, 1993). By far the most significant genetic influence on susceptibility to RA is the *HLA-DRB1* shared epitope, which is estimated to explain approximately 30-50% of this risk (reviewed by Bax *et al.*, 2011).

Alleles of *HLA-DR* genes that are associated with RA encode a common peptide sequence within the third hypervariable region of the MHC class II molecule at positions 70 to 74. The location of the amino acid sequences encoded by shared epitope alleles (including *HLA DR *0101, *0102, *0401, *0404, *0405, *1010*) is within the antigen binding grove, which could explain the pathogenic role of this association: that is, the shape of the antigen binding site, determined by the amino acid sequence, permits presentation of certain antigens to T-cells, resulting in downstream immune activation (Gregersen *et al.*, 1987).

In addition to the shared epitope, other genes reported to be associated with RA are usually involved with immune response; however, only protein tyrosine phosphatase receptor type 2 (*PTPN22)* reached genome-wide significance levels in the initial genome-wide association study (Consortium, 2007), although the list continues to grow (Eyre *et al.*, 2012). *PTPN22* encodes lymphoid protein tyrosine phosphatase which has a role in signalling between B and T lymphocytes and is implicated in the susceptibility to other autoimmune diseases in addition to RA, although the exact mechanisms for this are not fully understood. A recent meta-analysis found that a single nucleotide polymorphism of this gene (C1858T) associated with autoimmune diseases such as RA and type 1 diabetes had a far weaker association with autoimmune diseases that involve the skin (such as systemic sclerosis), gastrointestinal tract (inflammatory bowel disease) and diseases involving sites, such as the central nervous system, that are considered 'immune privileged': that is, sites which are regarded as less susceptible to the actions of immune cells (Zheng *et al.*, 2012). The authors postulated that this variation in *PTPN22* influences susceptibility to autoimmune diseases that arise due to changes in immune cells, but not those that arise due to changes in target organs and tissues.

1.4.2 Environmental influences on rheumatoid arthritis susceptibility

Whilst genetic susceptibility to RA is likely due to variations in immune mechanisms such as antigen presentation (as in the shared epitope) and T-cell signalling pathways (as in variations of *PTPN22*), environmental

influences may contribute to the development of autoimmunity in RA by modifying the epitopes which are recognised by immune cells. Smoking is the strongest environmental factor associated with RA (as noted in Section 1.2) and is implicated in the post-translational modification of proteins, citrullination, whereby an arginine residue of a peptide is converted to citrulline (reviewed by Klareskog *et al.*, 2007). By this mechanism, smoking has been linked to the formation of ACPA. Citrullinated proteins have been identified in fluid from bronchiolar lavage of smokers and have also been observed in synovial fluid in greater quantities than in serum of patients with RA, suggesting they may also arise within the joints themselves (reviewed by Cooles and Isaacs, 2011). A possible mechanism of RA pathogenesis in susceptible individuals is the formation of ACPA as a result of a gene-environment interaction between *HLA-DRB1* shared epitope alleles and tobacco smoke (Klareskog *et al.*, 2006). Klareskog and colleagues reported a modest increase in incidence of RA amongst smokers with no copies of the *HLA-DRB1* shared epitope with a relative risk (RR) of 1.5, with 95% CI 0.8–2.6, which increased for smokers with one copy of the *HLA-DRB1* shared epitope: RR of 6.5; 95% CI 3.8–11.4, and was significantly more for smokers with two copies of the *HLA-DRB1* shared epitope: RR of 21.0; 95% CI 11.0–40.2. Evidence of a biological interaction was quantified by the calculated attributable portion (AP) of risk of developing RA that was due to the interaction of the effects of *HLA-DRB1* shared epitope and smoking and was greater than the sum of the risks conferred by these variables independently. The AP is represented by a value between 0 and 1 and in this analysis was equal to 0.4 (95% CI 0.2, 0.7) in smokers with one copy of the *HLA-DRB1* shared epitope and 0.7 (95% CI 0.5, 0.9) in smokers with two copies of the *HLA-DRB1* shared epitope.

Recent evidence points towards periodontal disease as a potential trigger for RA. Although both conditions share common predisposing factors, such as smoking, which could explain why they often occur together, there is evidence of increased risk of RA in patients with periodontal disease that persists after age, race and smoking are controlled for (de Pablo *et al.*, 2008). A micro-organism associated with periodontal disease called

Porphyromonas gingivalis produces its own form of the enzyme necessary for citrullination, peptidyl arginine deiminase, which has been shown to trigger citrullination of human peptides fibrinogen and α-enolase. Infection with *P. gingivalis* has been proposed as causative in the development of autoimmunity and subsequent RA (reviewed by Lundberg *et al.*, 2010).

1.4.3 Inflammation in rheumatoid arthritis

Both adaptive and innate immune mechanisms are involved in synovial inflammation in RA. However, although the associations between RA and *HLA-DRB1* shared epitope alleles, which are likely to directly affect antigen presentation, and the formation of ACPA in RA (Sections 1.4.1 and 1.4.2) are well recognised, their role in the pathogenesis of RA is not fully understood. In early synovitis, new blood vessels are formed within the synovium in response to local hypoxia and the induction of angiogenic mediators, such as vascular endothelial growth factor (Szekanecz *et al.*, 2010). This neovascularisation provides nutritional and oxidative support for the proliferating tissue whilst vascular endothelial cells produce cytokines and can present antigens (Colville-Nash and Scott, 1992). T-lymphocytes are abundant in the synovium and are mainly helper T-cells (Th1 and Th17) with relatively few regulatory T-cells, so that the T-cell population is of a pro-inflammatory preponderance (McInnes and Schett, 2011). Cytokines such as tumour necrosis factor (TNF) and interleukin (IL) 17 are produced by Th17 lymphocytes and can activate chondrocytes and fibroblasts. B lymphocytes are of interest in RA, owing to the association with antibodies, however, their role in pathogenesis is likely to extend beyond formation of antibodies. Rituximab, a monoclonal antibody that depletes B cells through binding to CD20 (discussed in Section 1.6), is a useful treatment for RA, but administration of this drug results in inconsistent alterations in antibody levels and does not target the antibody producing plasma cells. Thus, there is likely to be an alternative role of CD20 positive B cells, such as antigen presentation or cytokine production which is supressed by rituximab and leads to clinical improvement in RA (McInnes and Schett, 2011).

Inflammation through the innate immune system is mediated by the action of cells such as macrophages and neutrophils. Macrophages located within

the synovium are likely to play a key role in inflammation through production of cytokines and chemokines. A correlation between their presence in the synovial biopsies and RA disease activity has been reported (Tak *et al.*, 1997), and furthermore, a reduction in their number has been demonstrated with effective treatment for RA (Haringman *et al.*, 2005). Neutrophils are found within the synovial fluid and under inflammatory conditions release proteases and reactive oxygen species that can cause localised tissue damage. Furthermore, usual mechanisms of neutrophil apoptosis are altered in RA so that their lifespan is prolonged and they may also adopt other roles, such as antigen presentation, under these conditions (Cascao *et al.*, 2010).

1.4.4 Synovial and cartilage responses to inflammation

In RA there is expansion of synovial tissue to form 'pannus' at the interface of bone and cartilage, which contains macrophages, osteoclasts and FLS, and is instrumental for the invasion of cartilage and destruction of bone (Walsh and Gravallese, 2010, Bartok and Firestein, 2010). FLS are responsible for direct invasion into cartilage, as demonstrated by Geiler and colleagues (1994), who implanted synovial tissue from RA patients into mice, together with normal human cartilage. FLS also produce inflammatory mediators, pro-angiogenic factors and matrix metalloproteases (MMPs) (Mor *et al.*, 2005). Excess production of MMPs leads to biomechanical dysfunction through collagen disruption.

1.4.5 Bony erosions in rheumatoid arthritis

Characteristic bony erosions, first described in 1878 by Austrian pathologist and bacteriologist Anton Weichselbaum, are now considered pathognomonic of RA (reviewed by Schett *et al.*, 2005). They are of importance as a sign of bony destruction due to RA and are associated with poor functional outcome (reviewed in section 1.8.4). Therefore, the prevention or retardation of the erosive process is a therapeutic goal in the management of RA.

Osteoclasts, derived from the monocyte cell lineage, are the only cell-type capable of bone resorption. Their precursors are found within pannus and differentiation into mature osteoclasts occurs once intracellular signalling

mechanisms are triggered by activation of receptor activator of nuclear factor κβ (RANK) through binding with its ligand (RANKL) (reviewed by Schett *et al.*, 2005). RANKL, expressed by T lymphocytes and FLS, is up-regulated by cytokines that are abundant in the rheumatoid synovium, including IL-1, IL-6, IL-17 and TNF. The formation of erosions in RA can be slowed by inhibition of TNF, IL-6 and RANKL; however, inhibition of RANKL does not reduce synovitis (reviewed by McInnes and Schett, 2011).

1.4.5.1 Detecting erosions in rheumatoid arthritis

Although the traditional method of detecting erosive damage is using radiographs, modern imaging techniques, such as magnetic resonance imaging (MRI) and ultrasound scanning (USS), offer more sensitive methods of examining structural changes within bone and also have the advantage of providing views of the surrounding soft tissues and synovium (reviewed by Conaghan *et al.*, 1999). Bone marrow oedema, also called osteitis, is a term used to describe MRI findings consistent with increased water content of the bone marrow, which usually has a high fat content. It has been described in the joints of patients with RA, occurring more often in joints affected by synovitis (McGonagle *et al.*, 1999). Further evidence from MRI studies indicate that bony erosion occurs in conjunction with, and at a rate proportional to, the degree of synovitis within in a joint (Conaghan *et al.*, 2003). The presence of bone marrow oedema at baseline assessment has been associated with subsequent radiographic erosions in 84 patients with RA (Haavardsholm *et al.*, 2008). Furthermore, from the same group of patients, time-integrated bone marrow oedema was also associated with risk of radiographic erosions, indicating a cumulative effect of inflammation and lending support to the body of evidence that erosive damage in RA occurs due to persistent inflammation (Boyesen *et al.*, 2011).

Histological examination of samples obtained from patients undergoing joint replacement showed that the apparent ‘oedema’ of the bone marrow in patients with advanced RA was consistent with histological evidence of inflammatory cell infiltration (Jimenez-Boj *et al.*, 2007). Furthermore, erosions identified by MRI in these patients corresponded to inflammatory infiltration of peripheral bone marrow, together with a breach of integrity of

the adjacent cortical bone. This histological examination of the bone marrow in RA was the first report of inflammation occurring at a site other than the synovium, which is an important step in the understanding of RA pathogenesis.

Progression of erosive change is slowed by disease modifying anti-rheumatic drugs (DMARDs) (Boers *et al.*, 2001) and studies utilising MRI have suggested that erosions even may be reversed by TNF inhibitors when used in combination with methotrexate (MTX) (For example, Ostergaard *et al.*, 2011, Quinn *et al.*, 2005).

1.5 Clinical features of rheumatoid arthritis

1.5.1 Musculoskeletal features

1.5.1.1 Articular disease

RA is a multisystem disease characterised by pain, stiffness and swelling of the joints in a symmetrical distribution, typically affecting the small joints of the hands and wrists. Stiffness of the joints is commonly maximal on waking and during the early morning, and is typically prolonged (lasting more than one hour). This feature can be significantly debilitating and have a significant impact upon daily function (da Silva *et al.*, 2011). If untreated, the synovial inflammation associated with RA can result in structural damage of joints and deformity. Typical deformities associated with chronic RA include ulnar deviation and subluxation of the MCP joints and 'swan neck' deformities of the fingers, in which there is fixed flexion of the distal interphalangeal joint with hyperextension of the PIP joint. In the early stages of disease, the pain and stiffness associated with joint inflammation results in impairment of function, whereas in the later stages of chronic RA, disability is correlated with structural damage and joint deformity (Reviewed by Smolen and Aletaha, 2004).

1.5.1.2 Tendon disease

Tenosynovitis of the hand and wrist is common in RA and may manifest as pain and tenderness with associated swelling overlying the affected area. There may be triggering of a finger or neurological compression (for

example, carpal tunnel syndrome) and if it remains untreated, tenosynovitis can result in tendon rupture and loss of function. Similarly, tenosynovitis is a common cause of foot pain for patients with RA and can be a contributing factor towards foot deformity (Coakley *et al.*, 1994).

1.5.1.3 Bursitis

This is common in RA and can be a cause of significant pain and loss of function. Subacromial bursitis presents with pain and restricted shoulder movement, whilst soft tissue swelling overlying the elbow joint may be due to olecranon bursitis. Tenderness overlying the greater trochanter of the femur, causing discomfort when lying on one side, is a feature of trochanteric bursitis. Iliopsoas bursitis has been reported, which may have varying presentations including hip pain, (Toohey *et al.*, 1990) femoral nerve palsy, (Letourneau *et al.*, 1991) and lower limb oedema (Pellman *et al.*, 1986, Rodriguez-Gomez *et al.*, 2004)

1.5.2 Involvement of other organ systems

1.5.2.1 Skin

The most common skin manifestation of RA is rheumatoid nodulosis. Nodules mainly occur on extensor surfaces subject to pressure, such as the skin overlying the elbow, and are often painless, representing little more than a nuisance. However they can be painful, or cause neurological compression, for which surgical intervention may be indicated. Rheumatoid nodules are more common in patients with RF antibodies and have been associated with the occurrence of other extra-articular manifestations (reviewed by Sayah and English, 2005).

Ulceration of the skin in a patient with RA may be due to comorbidities, such as diabetes mellitus, venous insufficiency or arterial disease, but may also be due to rheumatoid-related vasculitis. There is evidence that the aetiology of skin ulceration in RA is multifactorial. In one study, 11 of 20 RA patients with skin ulceration had histological evidence of vasculitis, and of these, 5 had evidence of venous insufficiency, 2 had evidence of arterial insufficiency or diabetes and 3 had mixed arterial / venous disease (Oien *et al.*, 2001). Pyoderma gangrenosum is another cause of cause of skin ulceration in RA.

Typically, lesions occur as rapidly progressive and painful areas of ulceration with a violaceous border. There are no characteristic histopathologic findings, so diagnosis is based upon clinical features and biopsy consistent with sterile neutrophilic infiltration, together with exclusion of other possible causes, which could be venous, arterial, vasculitic, or infectious (reviewed by Schadt, 2012).

1.5.2.2 Lungs

Pulmonary involvement is relatively common in RA (reviewed by Lake and Proudman, 2014) and has been demonstrated as a strong predictor of mortality in a cohort of cases with RA (Young and Koduri, 2007). It may manifest in several ways. Interstitial lung disease (ILD) is a term that can be applied to a range of disorders, classified according to radiological and histological description, of which usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP) are the most common. Although NSIP is more frequently seen with other connective tissue diseases, UIP predominates in RA-associated ILD and carries a poorer prognosis (reviewed by Massey *et al.*, 2012). In one series of 81 autopsy cases with longstanding RA, ILD was discovered in 35% of specimens (Suzuki *et al.*, 1994). Patients most at risk are those with more severe RA and a history of smoking tobacco. Radiological evidence of ILD may be present in asymptomatic individuals and has been described in patients with recent onset RA (Gabbay *et al.*, 1997).

Rheumatoid nodules may be present in the lung parenchyma as well as the skin. They are usually asymptomatic, but can sometimes rupture, resulting in pneumothorax or bronchopleural fistula. Caplan's syndrome is a condition originally described in coal miners with RA, in which there are multiple peripheral pulmonary nodules. The syndrome may follow exposure to inorganic dusts such as silica, asbestos and coal dust, and may be accompanied by pneumoconiosis (reviewed by Schreiber *et al.*, 2010).

The pleura may also be involved in RA and although patients may complain of symptoms due to pleuritis, pleural thickening is often asymptomatic. Pleural effusions are frequently unilateral and can be recurrent.

Pseudochylothorax (a milky pleural effusion with high cholesterol content) is a recognised, but rare association of RA.

1.5.2.3 Cardiovascular system

Premature death in patients with RA is often due to ischaemic heart disease (IHD). There are many potential factors that may contribute towards the increased incidence of IHD in RA, such as treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, hypertension (Panoulas *et al.*, 2008), dyslipidaemia (van Halm *et al.*, 2007) and the metabolic syndrome (da Cunha *et al.*, 2012). Although shared risk factors for RA and IHD, such as smoking, may partially explain the association of these two conditions, persistent inflammation in RA is thought to accelerate the development of coronary artery disease. Levels of inflammatory markers have been associated with cardiovascular events in RA; however, the exact mechanisms linking inflammation and accelerated atherosclerosis are incompletely understood (reviewed by Kerola *et al.*, 2012).

There is evidence that coronary micro-vascular dysfunction, which has been shown to precede the onset of atherosclerotic cardiovascular disease, is present in asymptomatic patients with RA. For example, coronary flow reserve (a ratio of maximal coronary blood flow to diastolic coronary blood flow where values ≥2 are considered normal) measured by transthoracic Doppler echocardiography was lower in 22 RA patients compared to 52 healthy controls (2.36 compared to 2.71, p=0.002) (Ciftci *et al.*, 2008). In this study, the group of RA patients were similar to the control group in terms of proportion of males and means of age, body mass index (BMI), blood pressure, and blood lipids, homocysteine and insulin levels and all participants were non smokers at the time of the study (defined as current non-smoking); however, numbers of patients with a previous history of smoking were not mentioned in the paper. Further work has shown that asymptomatic patients with RA and carotid plaques identified on ultrasound were more likely than control subjects with similar traditional cardiovascular risk factors to have coronary arterial disease identified on dopamine stress echocardiography in small study involving 18 patients with RA (Toutouzas *et al.*, 2013). Of the 8 RA patients who then had coronary angiography,

significant obstructive lesions that explained the ischaemic findings were identified in only 2 cases, compared to 8 of 11 control subjects. The authors of this hypothesis- generating study proposed that in patients with RA, coronary ischaemia may be due to causes other than obstructive coronary vessel disease. Although these studies are small, the evidence presented here suggests that further investigations into coronary microvascular changes in RA are warranted in order to further investigate the aetiology of cardiovascular disease in RA.

1.5.2.4 Neurological

Commonly observed neurological associations of RA result from neurological compression due to synovial inflammation. Carpal tunnel syndrome, due to compression of the median nerve at the wrist, and ulnar nerve entrapment at the elbow are two common examples. A well recognised complication of RA is atlanto-axial subluxation, which occurs due to rheumatoid involvement of the joint between the first 2 cervical vertebrae and the surrounding structures leading to instability and subsequent neurological impingement (Robinson, 1966). There may also be compression of the vertebral artery, leading to symptoms that include vertigo, confusion and syncope (Jones and Kaufmann, 1976). Mononeuritis multiplex describes sensory and motor impairment of one or more peripheral nerves resulting from vasculitis of the vasa nervorum. Its onset is often rapid, affecting one distal nerve initially, but further neuropathy may develop if treatment is delayed or unsuccessful. Central nervous system vasculitis has been described in RA, but is uncommon (Gobernado *et al.*, 1984).

1.5.2.5 Ocular

Rheumatoid disease may be associated with eye conditions, causing redness, pain, impaired vision and sometimes blindness. One of the more common ocular manifestations of RA is dryness of the eyes, or kerato-conjunctivitis sicca (KCS), which occurs due to impaired lacrimal gland function in secondary Sjogren's syndrome. Occasionally occurring in conjunction with KCS, peripheral ulcerative keratitis (PUK) is an ocular manifestation of rheumatoid vasculitis that requires prompt immune-suppressive treatment in order to prevent visual loss (Squirrell *et al.*, 1999).

In PUK, there is vasculitis affecting the peripheral cornea (the avascular centre of this structure is unaffected) manifesting as inflammation of the episclera, conjunctiva and sclera, which can lead to perforation of the cornea (corneal melt) (reviewed by Messmer and Foster, 1999). Due to its association with systemic vasculitis, PUK is linked to high mortality and emphasis has been placed upon prompt and aggressive treatment for patients with this condition (Foster *et al.*, 1984).

A painful red eye in a patient with RA may be due to inflammation of the sclera (scleritis) or episclera (episcleritis). Episcleritis is uncomfortable, but usually self limiting with no long-term sequelae. Conversely, scleritis can be associated with significant morbidity. Different types of scleritis have been described, including diffuse anterior, nodular anterior, necrotising anterior and posterior (which can also be further categorised into nodular, diffuse and necrotising). Of these, the diffuse anterior type is most common and usually responds well to treatment, but can cause visual loss. Posterior types are associated with significant risk of visual impairment and require prompt treatment (McCluskey *et al.*, 1999). Necrotising anterior scleritis can be further categorised into two types, the “inflammatory” variant presents with severe pain that improves with treatment, whereas the rarer variant, scleromalacia perforans, is usually painless. Scleromalacia perforans may present as an area of blue discolouration where underlying choroid becomes visible through thinned sclera and perforation has been reported in some cases (Stone and Dana).

1.5.2.6 Systemic features

Systemic symptoms may include fatigue, weight loss and episodes of sweating and there may also be an associated normocytic, normochromic anaemia of chronic disease. Fatigue in RA is recognised as a common and intrusive symptom, the cause of which is likely to be multifactorial (Repping-Wuts *et al.*, 2009). In recognition of the impact of fatigue on wellbeing in RA, it has become a focus of research activity and was identified as an important outcome for measurement in RA studies by an Outcome MEasures in Rheumatology Clinical Trials (OMERACT) consensus group (Kirwan *et al.*, 2007).

In a conceptual model of fatigue in RA described by Hewlett and colleagues (2011), biological factors related to RA (such as those due to drug side effects, pain, disturbed sleep, anaemia of chronic disease, and alteration in cortisol response of the hypothalamic-pituitary-adrenal axis) were considered as contributing to fatigue, alongside cognitive and behavioural factors including anxiety and depression, as well as personal factors such as work, caring responsibilities and level of social support. In the proposed model, it was suggested that factors contributing to the development of fatigue may impact upon one another (for example, pain may adversely effect sleep, and vice versa) and furthermore, fatigue itself may perpetuate possible triggers of fatigue, such as depression and poor sleep. The contributions of RA disease activity, sleep disturbance and mood disturbance to RA fatigue were tested in a structural equation model that included data from 106 patients (Nicassio *et al.*, 2012). This model explained 62% of variance in fatigue and demonstrated that increased RA disease activity was associated with mood disturbance, which in turn influenced sleep quality, which was associated with fatigue. There were also direct effects of disease activity and mood on fatigue.

The term ‘rheumatoid cachexia’ is used to describe the loss of muscle mass with stable or increased fat mass that is attributable to the inflammatory state and protein catabolism associated with RA. It has been associated with increased morbidity and mortality and although it is proposed to affect up to two thirds of patients with RA (Rall and Roubenoff, 2004), several methods of assessing nutritional status in patients with RA have been described (Summers *et al.*, 2008) and at present there are no definitive criteria for the diagnosis of rheumatoid cachexia, so its prevalence is difficult to quantify. Criteria for the diagnosis of cachexia have been published (Evans *et al.*, 2008). However, in one recent study of 103 patients with RA in which the median disease duration was 8 years and mean disease activity score, based upon assessment of 28 joints (DAS28) was 3.32, only one patient met the criteria for cachexia and one met the criteria for ‘pre-cachexia’ (van Bokhorst-de van der Schueren *et al.*, 2012). Other patients in the cohort exhibited observations associated with cachexia such as reduced fat free

muscle index, increased fat mass index and reduced grip strength, so the authors concluded that the new criteria for cachexia did not perform well for patients with RA. However, these measures of nutritional status have yet to be validated in the RA population and therefore further research is required.

1.6 Treatment of rheumatoid arthritis

There has been enormous progress in the pharmacological management of RA over the last 60-70 years, beginning with the use of synthetically produced corticosteroids in 1948 (reviewed by Weiss, 1989). Although steroid therapy produces rapid and dramatic improvement in synovitis and can also retard erosive damage in RA (Kirwan, 1995, van Everdingen *et al.*, 2002, Bakker *et al.*, 2012), long term use is associated with considerable side effects (reviewed by Weiss, 1989). Current EULAR guidelines recommend the concomitant use of low dose corticosteroid and DMARD in early RA (Gaujoux-Viala *et al.*, 2014).

"DMARD" was a term initially applied to drugs used for the treatment of RA that reduce levels of acute phase reactants such as erythrocyte sedimentation rate (ESR), but has since been applied to drugs that limit the progression of RA and in particular, radiographic erosion (Goldbach-Mansky and Lipsky, 2003). In the late 1980's and early 1990's, treatment of RA usually followed a 'step-up' approach, where DMARDs such as gold, D-penicillamine, hydroxychloroquine (HCQ), azathioprine, cyclosporine, MTX and sulphasalazine (SSA) were used as second line agents once conservative measures such as the use of physiotherapy, NSAID and aspirin had failed to provide symptomatic benefit (Ward, 1988, Furst, 1990). Evidence published in the new millennium lead to a 'paradigm shift' in treatment strategies for RA, as it was demonstrated that early and aggressive treatment with DMARDs was superior to the traditional approach, with less radiographic progression amongst patients treated more aggressively, compared to traditional methods (Lard *et al.*, 2001, Nell *et al.*, 2004). The term 'window of opportunity' is often used to describe the period in early RA during which aggressive DMARD therapy is essential to reduce risk of joint damage; usually between 3 and 24 months of symptom onset

(reviewed by Smolen and Aletaha, 2015). Today, a 'treat to target' approach is employed, whereby therapy is initiated as early as possible and adjusted with the aim of achieving remission (which is defined as absence of symptoms or signs of RA) (Smolen *et al.*, 2010)

SSA is cleaved into 5-aminosalicyclic acid and sulphapyridine in the colon, and both of these constituents, together with SSA itself, may modify disease activity in RA via several mechanisms. This drug exerts weak anti-inflammatory properties via inhibition of cyclo-oxygenase and also inhibits the release of pro-inflammatory mediators such as IL-1, IL-6 and TNF (reviewed by Smedegard and Bjork, 1995). Evidence from long term studies of patients with RA have shown that MTX, and to some extent SSA, can retard the formation of erosions when used in early disease (reviewed by Pincus *et al.*, 2002). MTX is currently the first line treatment of choice for RA in the UK (according to treatment guidelines summarised in Figure 1-2). It has various actions that may account for its disease modifying properties such as reducing cell proliferation, promoting T-cell apoptosis and increasing adenosine production, which is an anti-inflammatory substance (Wessels *et al.*, 2008).

The paradigm shift in treatment strategies for RA was accompanied by the evolution and application of 'biologic agents' etanercept and infliximab, which antagonise the effects of TNF. Etanercept is a fusion protein consisting of the Fc portion of human immunoglobulin G1 and two molecules of the soluble TNF receptor, which binds to TNF in the circulation and prevents interaction with cell surface TNF receptors (Breedveld, 1998). Infliximab is a human / mouse chimeric monoclonal antibody that binds both soluble and membrane bound forms of TNF (Elliott *et al.*, 1994). Several additional TNF inhibitors have since been developed and applied to clinical practice, including adalimumab (Lorenz, 2002), golimumab (Zhou *et al.*, 2007) and certolizumab (Choy *et al.*, 2002). Other cytokines have also been the targets of drug therapies for RA including interleukin 1 (IL-1) (anakinra, (Arend, 1993)) and IL-6 (tocilizumab, (Ding and Jones, 2003). Co-stimulation of T-cells is inhibited by abatacept (Harper *et al.*, 1991), which binds to CD80 and CD86 on the surface of T cells. Rituximab (Anderson *et*

al., 1997) reduces circulating B cells through binding to CD20. The application of biological therapies over recent decades has significantly improved disease control and long term outcomes for patients with RA. However, these drugs are costly and, due to their immune suppressive mode of action, are associated with significant risk of infection. At present, their use in the UK is monitored and restricted to patients with 'severe' RA. Figure 1-2 summarises current National Institute for Health and Care Excellence (NICE) guidelines on the use of biological therapies for UK patients with RA. These guidelines exclude anakinra which is not recommended by NICE for treatment of RA.

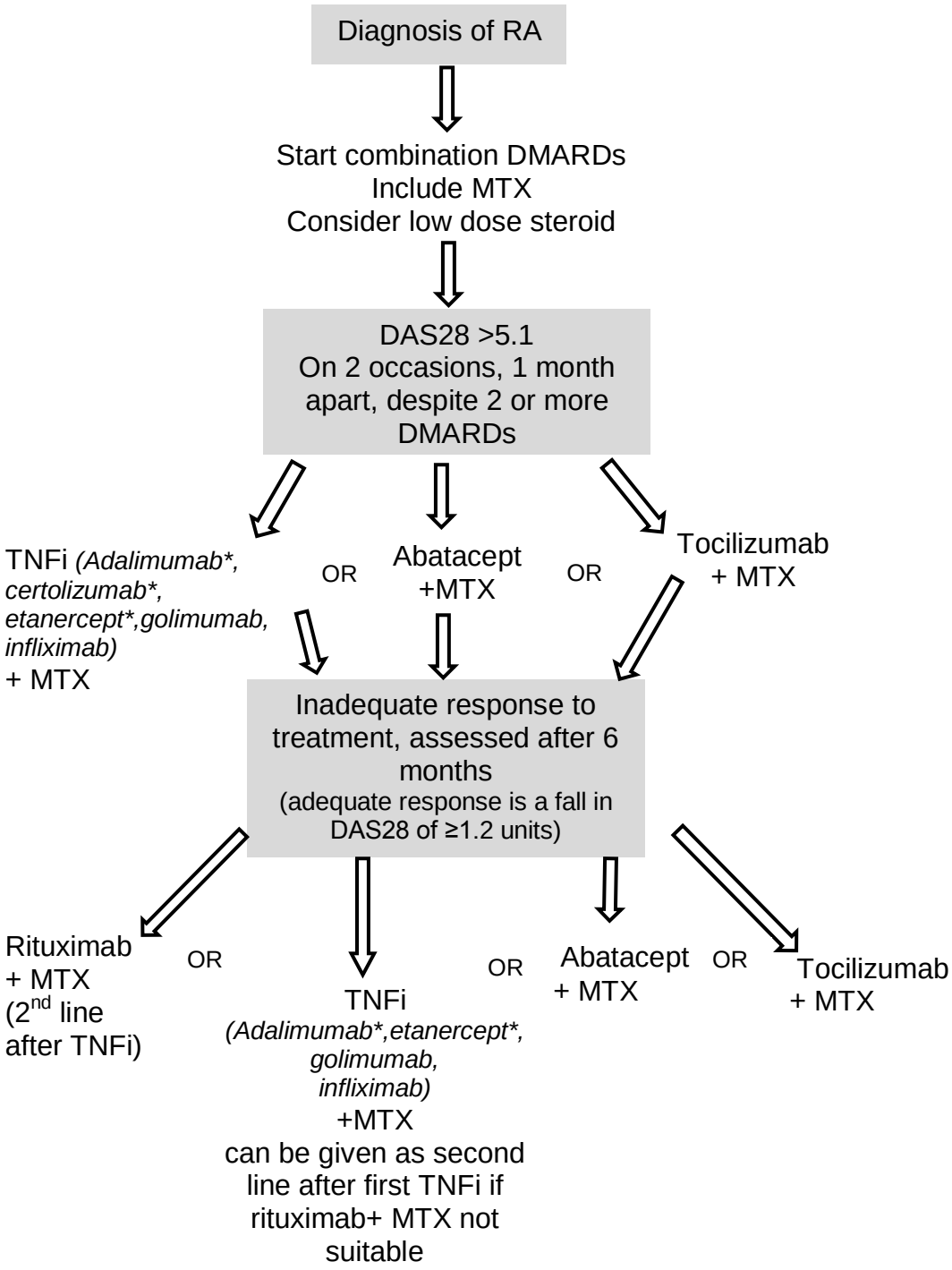

Figure 1-2 National Institute of Health and Care Excellence on the use of biological treatments in rheumatoid arthritis

*Adalimumab, certolizumab and etanercept may be used as monotherapy in patients unable to take MTX.

DAS28, disease activity score based upon counts of 28 swollen and tender joints; DMARDs, disease modifying anti rheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor. (Adapted from technology appraisals: National Institute for Health and Care Excellence, 2009, 2010, 2012, 2013, 2007, and 2011)

1.7 Epidemiological methods in rheumatoid arthritis research

1.7.1 Disease registers and inception cohorts

Inflammatory arthritis disease registers have provided invaluable information about the treatment and outcomes in RA that would not have been possible to obtain from randomised controlled trials alone. For some registries, established to investigate the disease course of RA, meeting classification criteria is a pre-requisite for subject inclusion, whilst other cohorts have broader inclusion principles and include all cases with inflammatory arthritis suspicious of RA so that questions such as the incidence of RA and prognostic markers for the development of RA in such patients can be addressed. Examples of the latter include NOAR from the UK and the French study ESPOIR (Etude et Suivi des Ployarthrites Indefférénciées Récentes) (Table 1-2). Inception cohorts are designed to capture patient data from the very early stages of disease and follow their progress through medical care that reflects routine clinical practice. In some cases, the capture of long term data for such patients has spanned many years. These registers have allowed researchers to address questions such as the incidence of RA, how the disease course changes over time and what factors contribute to mortality. Table 1-2 summarises UK RA disease registers and inception cohorts, together with worldwide registries mentioned elsewhere in this Thesis. Baseline values for mean age, gender and RF are given, but as most cohorts are ongoing and the data are continuously updated, these values are approximate. Furthermore, researchers have often published work using data from a subset of the whole cohort and therefore the values in Table 1-2 reflect the most recent or most complete published data. Cohorts such as NOAR and the Canadian early arthritis cohort, CATCH, have fewer cases who are RF positive at baseline, which is probably because these cohorts have captured inflammatory polyarthritis that is not always RA. The reason for the low numbers of RF positivity in the older Middlesex cohort is not clear, but may be due to different laboratory techniques for measuring RF. The mean baseline age of the cohorts is quite consistent, at 51-58 years, although the Brigham and women's hospital

rheumatoid arthritis sequential study (BRASS) included all prevalent cases of RA and therefore the age at inclusion was not the age of disease onset. Furthermore, there were more women in the BRASS study, which was possibly because the hospital at which it was based was formed by the merger of 3 hospitals, including one women's hospital, in 1980; however, the authors did not comment on the relatively high proportion of females in their sample.

Table 1-2 Rheumatoid arthritis disease registers and inception cohorts

Name of cohort (references)	Year of initiation	Number of cases (N) and entry criteria	Centres (location)	% Female	Mean age at presentation	% RF positive baseline	Notes
UK Registers							
Bath (Jacoby *et al.*, 1973)	1957	100 Seen within 1 year of onset of RA Fulfilling ARA criteria for RA (1958)	Single (Bath, UK)	64	51	76 (within 12 months)	
Middlesex (Corbett *et al.*, 1993)	1966	102 Disease duration < 1 year	Single (Middlesex, UK)	57	51	41	Patients recruited 1966 -1971 Followe until 1984
ERAS and ERAN (Young *et al.*, 2000, Young *et al.*, 2011)	1986 (ERAN from 2002)	2866 (up to 2009) Diagnosis of RA made by rheumatologist Disease duration < 2 years DMARD naïve	9 (ERAN) 30 (ERAS) (both UK)	66	55	70	
NOAR (Symmons and Silman, 2003, Humphreys *et al.*, 2014)	1990	2519 Age >16 years 2 or more swollen joints lasting 4 or more weeks Onset since 1.1.1989 Presenting to primary or secondary care	Multiple: recruited from primary care in Norwich (UK)	65	55	55 (of those meeting 2010 EULAR/ACR criteria for RA)	1419 cases fulfilled the 2010 EULAR/ ACR criteria for RA baseline.

+

Table 1-2 continued

Name of cohort (references)	Year of initiation	Cases (N) Entry criteria	Centres (location)	% Female	Mean age at presentation	% RF positive baseline	Notes
Worldwide registers							
Leiden EAC (van Aken *et al.*, 2003, van Nies *et al.*, 2010)	1993	2079 (in 2008) Recent onset arthritis (<2 years)	Single (The Netherlands)	69	57	58	
CATCH (Arnold *et al.*, 2014)	2007	1821 Age >16 6 weeks to 12 months persistent synovitis, plus one or more of: RF, ACPA, EMS ≥45 minutes, response to NSAIDs, painful MTP squeeze.	17 (Canada)	73	53	44	1152 cases fulfilled the 2010 EULAR/ ACR criteria for RA baseline.
BARFOT (Forslind *et al.*, 2007, Andersson *et al.*, 2013)	1992	2800 >18 years old Early RA meeting 1987 ACR criteria Disease duration ≤ 2 years	6 (Sweden)	64	58	60	
BRASS (Lu *et al.*, 2014)	2003	1100 All cases with RA attending the Brigham and women's arthritis centre.	Single (USA)	81-85	54-61	73	Mean disease duration 15 years

ACPA, anti citrullinated peptide antigen; ACR, American College of Rheumatology; ARA, American rheumatism association; BARFOT, Better Anti-Rheumatic FarmacOTherpay; BRASS, Brigham and women's hospital Rheumatoid Arthritis Sequential Study; DMARD, disease modifying anti rheumatic drug; EMS, early morning stiffness; ERAN, Early RA Network; ERAS, Early RA Study; ESPOIR, Etude et Suivi des POlyarthrites Indefférénciées Récentes; EULAR/ACR, EUropean League Against Rheumatism / American College of Rheumatology; MTP, metatarsophalangeal; NOAR, NOrfolk Arthritis Register; NSAID, non steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RF, rheumatoid factor; UK, United Kingdom; USA, United States of America.

1.7.2 Statistical methods in rheumatoid arthritis epidemiology

1.7.2.1 Cross sectional and longitudinal analysis

A cross-sectional analysis uses absolute change between two time points as an outcome variable. It is limited because variation in the outcome between the two time points is unaccounted for and important changes can be overlooked. Examples of cross sectional analyses applied to RA include linear regression analyses where the outcome variable is a change in DAS28 or HAQ between two time points, such as the linear regression analyses described in this Thesis. Longitudinal analysis is of particular importance to RA research, as activity of this disease is known to wax and wane: sometimes a 'flare' of arthritis can occur without an obvious precipitating cause, or it can be in response to intercurrent illness; for example, a viral infection. Similarly, treatment with corticosteroids and DMARDs are expected to reduce disease activity. A longitudinal analysis can capture these fluctuations, which are ignored in a cross-sectional analysis.

1.7.2.2 The problem of missing data in cohort studies

Missing data is a common problem encountered in analysis of longitudinal data (Haukoos and Newgard, 2007). A common approach to analysis of data with missing values is complete case analysis, whereby cases with missing data are simply excluded. However, this method has several drawbacks: the number of incomplete (and therefore excluded) cases increases with the number of covariates analysed and results in loss of statistical power. Furthermore, if the cases with complete data are not a true representation of the whole sample, there is greater probability of obtaining biased results (Mackinnon, 2010, Janssen *et al.*, 2010, Olsen *et al.*, 2012). Other approaches to managing missing data include the missing indicator method (in which a dummy variable indicating missingness of a given covariate is included in the analysis) and imputation techniques such as using the mean value of a variable wherever it is missing, or the last observation carried forward method (reviewed by Horton and Kleinman, 2007). These older approaches to handling missing data are often still used in contemporary studies, but results can be biased (Knol *et al.*, 2010).

Modern techniques including multiple imputation (MI) and maximum likelihood estimation perform better (van der Heijden *et al.*, 2006, Greenland and Finkle, 1995). For these approaches to be suitable certain assumptions must be met and the first of these is that the data are missing at random (MAR). Three mechanisms, or causes, of missing data have been described (reviewed by Graham, 2009). The first of the three mechanisms is the least common and is called missing completely at random (MCAR). It occurs, for example, when a single specimen is lost on the way to the laboratory. The fact that this piece of data is missing, together with its value (had it been possible to record), is unrelated to the values of the other observed variables. If analysis of the complete cases (CC) was undertaken, the results would not be biased, but power may be diminished. The second pattern of missing data is called missing not at random (MNAR) and is problematic. This occurs when missingness of a value is directly related to its value: for example, if people with higher salaries are less likely to answer a survey question asking about income than other respondents. The third mechanism of missing data is MAR, which occurs when the fact that a piece of data is missing, or its value, is related to observed variables. For example, missing blood test results could be described as MAR if these data were more likely to be missing in patients with higher levels of anxiety recorded as part of the study. This is considered the most common type of missing data and both MI and maximum likelihood estimation are used under the assumption that data is MAR.

It is not possible to test whether data is MNAR, although sensitivity analyses have been described by Carpenter *et al.* (2007), which are post-hoc tests to determine how the results of a study would have differed had the MAR assumption not been met. Although MI applications are now incorporated into many commonly used statistical packages, sensitivity analysis to check the validity of the MAR assumption is a complex procedure that is infrequently reported from studies where this method of missing data management has been applied. However, as the application of MI continues to grow, we may anticipate the emergence of sensitivity analysis within statistical packages.

The overall pattern of missing data determines which type of imputation is suitable and is either monotone or non-monotone. A monotone missing data pattern requires a simpler imputation method, but is uncommon. It can occur due to participants dropping out of a study. When the pattern of missing data is monotone, the missingness of variable, V_n, predicts that all subsequent variables (V_{n+1}, $V_{n+2,}$ etc.) will be missing and similarly, if V_n is non-missing, all preceding values (V_{n-1}, V_{n-2} etc.) will also be non-missing. Missing data patterns are illustrated in Figure 1- 3 and methods for managing missing data are further described in Section 2.5.5.

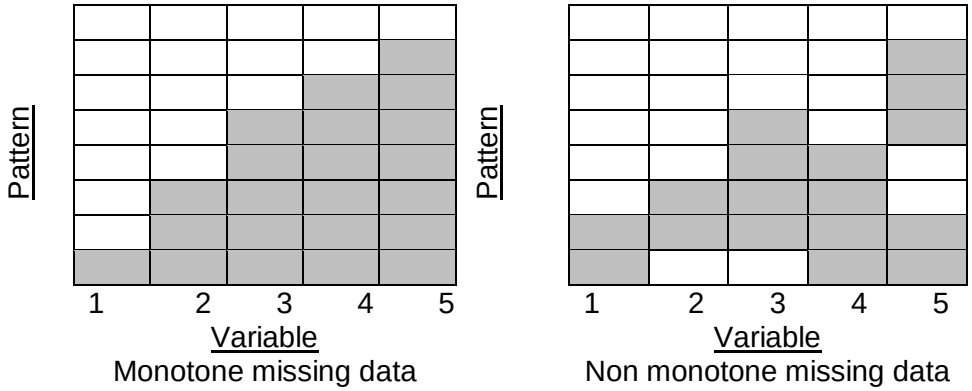

Figure 1-3 Illustrative example of monotone and non monotone missing data patterns.
Grey bars indicate values missing from the dataset, whilst white bars indicate observed values. Columns represent variables and are ordered such that the frequency of missingness increases from left to right (variable 1 is the least frequently missing and variable 5 is the most frequently missing.) Rows represent patterns of missing data within the dataset and are arranged from top to bottom, starting with groups of cases with least missing data for the far right variable, and then the next most frequently missing variable, and then the next and so on.

1.8 Outcomes in rheumatoid arthritis

There are several measures by which outcome in RA may be quantified, with different outcome measures suiting different research purposes. For example, when assessing the efficacy of a DMARD or biologic drug, a composite measure of RA disease activity is useful. For researchers investigating the economic burden of disease relating to RA, a work productivity or instability scale may be required, and for investigating the impact of RA on general wellbeing, a quality of life questionnaire may be

useful. In 1992, the first OMERACT conference was held, with the aims of reviewing the use of outcome measures in RA and agreeing which should be recommended for use in RA research. This was so that results from different studies could be compared and meta-analyses conducted. It culminated in the publication of a 'core set' of International League Against Rheumatism and World Health Organisation recommended outcome measures for RA studies (Boers *et al.*, 1994). As scales for measuring outcome in RA are so numerous, the present Section will focus on the two outcomes that are the focus of this Thesis: disease activity and disability.

1.8.1 Measures of disease activity in rheumatoid arthritis

Disease activity in RA may be measured by a multitude of parameters, for example, numbers of swollen and tender joints, duration of early morning stiffness (EMS), pain, and functional impairment. Whilst all of these indicators may inform clinical decision making, the perceived importance of different indicators of disease activity varies between physicians (Kirwan *et al.*, 1983a, Kirwan *et al.*, 1983b). Monitoring of disease activity has been standardised through the development and application of composite indices and furthermore, comparison of results from clinical trial results has been simplified by application of measures such as the disease activity score (DAS) (van der Heijde *et al.*, 1990).

The DAS and its abbreviated form, the DAS28 (Prevoo *et al.*, 1995) are measures of RA disease activity that encompass the swollen joint count (SJC) from a total count of 44 joints for DAS, or 28 joints for DAS28. Also included in calculation of the indices are tender joint count (TJC) from 28 joints for DAS28, or for DAS, Ritchie articular index (RAI) (Ritchie *et al.*, 1968), which grades tenderness from examination of 55 joints; plus a laboratory measure of systemic inflammation (ESR or C-reactive protein (CRP)) and a patient reported measure of disease activity, recorded on a 100 millimetre (mm) visual analogue scale (VAS). These variables are applied to formulae (shown Table 1-3), which are available on the internet: (http://www.das-score.nl/das28/DAScalculators/dasculators.html), or a specific calculator can be used. The DAS28 is quicker to use in clinical practice, because examination of only 28 joints is required, compared to 44

and 55 swollen and tender, respectively, for the DAS. The DAS and DAS28 were also described using formulae with 3 variables (shown in Table 1-3), with omission of the VAS (van der Heijde *et al.*, 1990). A study of 227 RA patients in remission according to American Rheumatism Association (ARA, which later became ACR) preliminary criteria was published in 1996 (Prevoo *et al.*, 1996). The authors found that a DAS of <1.6 represented remission well; however, the preliminary ARA criteria for remission to which DAS was compared were poorly defined. A lower DAS28 definition of remission has been proposed (Sheehy *et al.*, 2014). One of the problems with DAS28 is that it incorporates subjective measures, TJC and VAS, which may be influenced by co-existent conditions such as chronic pain and fibromyalgia, and does not solely reflect inflammation due to RA. An index to reflect pain in RA due to non-inflammatory causes was described by McWilliams and colleagues (2012), who used all components of the 4 variable DAS28, to produce DAS28-P, which was weighted in favour of the patient-reported measures. Higher DAS28-P at baseline predicted less reduction in pain (measured using the short form 36 bodily pain score) after 1 year, independent of DAS28 score, indicating that DAS28-P measured non inflammatory causes of pain in these patients from the Early RA Network (ERAN, described in Table 1-2).

Newer and more simple composite measures of disease activity include the simplified disease activity index (SDAI) (Smolen *et al.*, 2003), and the clinical disease activity index (CDAI) (Aletaha *et al.*, 2005). The SDAI is calculated using the sum of: SJC (out of 28), TJC (out of 28), VAS representing patient's own assessment of global health, VAS representing physician's assessment of patient's global health (both measured in centimetres, cm, from a total possible score of 10 cm), and CRP value (measured in milligrams per decilitre, mg/dl). The CDAI uses the same parameters as the SDAI, but excludes CRP. The obvious advantage of these two measures is that they are easy to calculate; however, they are not normally distributed, which can add complexity to statistical analyses. Both SDAI and CDAI are more stringent than DAS28 when used to define remission (Klarenbeek *et*

al., 2011). The different measures of disease activity are compared in Table 1-3.

Table 1-3 Characteristics of composite measures of rheumatoid arthritis disease activity

	DAS	DAS28	SDAI	CDAI
Formula	0.54x√(RAI) + 0.065 (SJC) + 0.33x Ln(ESR) +0.00722 x (VASmm) Or (3 variable): 0.54x√(RAI) + 0.065 (SJC) + 0.33x Ln(ESR)+0.22 Or (4 variable, CRP): 0.54x√(RAI) + 0.065 (SJC) + 0.17x Ln(CRP+1)+0.0072*(VASmm)+0.45 Or (3 variable, CRP): 0.54x√(RAI) + 0.065 (SJC) + 0.17x Ln(CRP+1)+0.65	0.56√(TJC)+0.28√(SJC) +0.7*ln(ESR)+0.014(VASmm)+0.96 Or (3 variable): [0.56√(TJC)+0.28√(SJC) +0.7*ln(ESR)]*1.08+0.16 Or (4 variable, CRP): 0.56√(TJC)+0.28√(SJC) +0.36*ln(CRP+1)+0.014(VASmm)+0.96 Or (3 variable, CRP): [0.56√(TJC)+0.28√(SJC) +0.36*ln(CRP+1)]*1.10+1.15	TJC+SJC+$VAS_{patient}$cm +$VAS_{physician}$cm +CRP	TJC+SJC+$VAS_{patient}$cm +$VAS_{physician}$cm
Advantages	Normally distributed variable	Only 28 joints are assessed Widely applied and understood Normally distributed variable	Only 28 joints are assessed Simple to apply	Only 28 joints are assessed Simple to apply No need for blood tests
Disadvantages	Complicated formula. Requires assessment of 44 joints for swelling, plus RAI	Complicated formula	Not normally distributed	Not normally distributed
Applications	EULAR response criteria	Applied in NICE criteria for use of biologics Applied as an outcome measure in clinical trials	Used in the ACR/EULAR definition of remission for clinical trials	Outcome measure in clinical trials
Range of values	0.23-9.87	0.49-9.07	0-86	0-76

Table 1-3, continued

	DAS	DAS28	SDAI	CDAI
Definitions of:				
Remission	<1.6	≤2.6	≤3.3	≤2.8
Low disease activity	1.7-2.4	2.6-3.2	3.4-11	2.9-10
Moderate disease activity	2.5-3.7	3.2-5.1	12-26	11-22
High disease activity	>3.7	>5.1	>26	>22

ACR, American College of Rheumatology; CDAI, clinical disease activity index; cm, centimetres; CRP, C-reactive protein; DAS, disease activity score; DAS28, disease activity score using counts of 28 joints; ESR, erythrocyte sedimentation rate; EULAR, EUropean League Against Rheumatism; mm, millimetres; NICE, National Institute of health and Care Excellence; RAI, Ritchie articular index; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue score.

1.8.1.1 Definitions of response for rheumatoid arthritis clinical trials

In 1995, in order to define response to treatment in RA clinical trials, the ACR published criteria that allowed researchers to categorise patients according to whether 'ACR20' response was achieved or not (Felson *et al.*, 1995). An ACR20 response was defined as a 20% improvement in TJC, SJC, and 3 of the 5 remaining core outcome measures: physician assessment of disease activity, patient assessment of global disease activity (both measured using either VAS or Likert scale), patient assessment of pain (VAS or Likert scale), a validated measure of physical function and either ESR or CRP. ACR response criteria are commonly reported in clinical trials, and are easily interpreted as 20%, 50% or 70% improvement, for ACR20, ACR50, and ACR70 responses, respectively. As well as the ACR definition of response in RA, EULAR defined disease activity in RA as either low, moderate or high according to DAS as follows: ≤2.4 is low disease activity, >2.4 and ≤3.7 is moderate disease activity and >3.7 is high disease activity (van Gestel *et al.*, 1996). The 'EULAR response', a classification of response to treatment using 'simplified' disease activity measures (that is, using counts of 28 joints) is now widely applied in research (van Gestel *et al.*, 1998). It is summarised in Table 1-4.

Table 1-4 Definitions of response according to European League Against Rheumatism criteria using simplified joint counts (adapted from van Gestel *et al.*, 1998)

	Good	Moderate		Non
DAS/DAS28 change	≥1.2	≥1.2	>0.6, but <1.2,	<0.6
	and	*and*	*and*	*and*
Disease activity	Low DAS ≤ 2.4 DAS28 ≤ 3.2	Moderate or high DAS >2.4 DAS28 >3.2	Low or moderate DAS ≤3.7 DAS28 ≤5.1	High DAS>3.7 DAS28 >5.1

DAS, disease activity score: DAS28, disease activity score based upon counts of 28 joints.

Once remission in RA became a realistic goal owing to newer therapies, ACR and EULAR jointly proposed a definition of remission of SDAI ≤ 3.3, or when SJC, TJC (both from 28 joints), CRP (in mg/dl) and patient global assessment (measured in cm, using a 10cm VAS) are all ≤ 1 (Felson *et al.*, 2011).

One drawback of these criteria is that they dichotomise (into responders vs. non-responders in the case of ACR or remission criteria) or categorise outcome (in terms of low / medium / high disease activity in the case of EULAR response criteria), which is associated with loss of statistical power and loss of information about change in outcome measures for individual patients (Felson and Lavalley, 2014).

1.8.2 Factors influencing disease activity in rheumatoid arthritis

Information on predictors of disease activity in RA comes from both observational studies, which are more likely to reflect true clinical practice and also clinical trials. DAS28 is often reported from clinical trials and EULAR response, which uses DAS28, is one of the most commonly reported measures of outcome (Fransen and van Riel, 2009). The different factors impacting upon disease activity in RA are discussed below, in sections 1.8.2.1 to 1.8.2.7 and summarised in Table 1-5, which is divided according to risk factors. As shown in Table 1-5, outcome measures used differed between studies. Although remission has been defined in terms of values of composite indices, the context in which remission was declared also varied between studies. Some authors have included patients who have achieved remission only if they are DMARD-free for a given time-period, whilst others have included patients on DMARDs within this category. Furthermore, the duration for which a patient is required to be 'in remission' in order to have reached the desired outcome has varied. Some studies have used sustained remission for a specified duration as an outcome, whilst others have observed whether there is incident remission at a specified time point.

1.8.2.1 Age and gender

The effect of age and gender on disease activity in RA has been well documented, with female gender and increased age at onset of disease associated with lesser improvement in disease activity. In the UK based

Early RA Study (ERAS, described in Table 1-2) remission (defined by DAS<1.6) in 704 patients followed for a minimum of 5 years was associated with male gender (odds ratio, OR 2.64; 95% CI: 1.54, 4.54; p<0.001) (Jayakumar *et al.*, 2012). Using data from 378 patients recruited to the CARDERA (combination of anti-rheumatic drugs in RA) trial, Ma and colleagues (2012) formulated a prediction model for remission at 24 months from baseline and then validated their model using data from ERAN. They found that significant predictors of remission (DAS28<2.6) were lower age (OR for age in years: 0.98; 95% CI 0.95, 0.99), male gender (OR 3.14; 95%, CI 1.80, 5.46) and lower TJC at baseline (OR 0.94; 95% CI 0.90, 0.98). Their prediction model for remission at 24 months was specific (98%), but not sensitive (13%), suggesting that other factors influencing disease activity were unaccounted for. A recent study of Canadian patients with suspected early RA investigated how DAS28 was influenced by gender and age (Arnold *et al.*, 2014). After one year, mean change in DAS28 was significantly lower in women (a decrease of 1.8 units, versus 2.5 for males, p < 0.008) and remission at 12 months, defined by DAS28 ≤2.6, was less likely in older patients (OR 0.97, 95% CI 0.96, 0.98, p= 0.001), females (OR 0.39, 95% CI 0.28, 0.54, p = 0.001) and those with higher baseline DAS28 (OR 0.75, 95% CI 0.68, 0.83, p = 0.001).

1.8.2.2 Genetics

The most significant genetic risk factor for RA lies within the Major Histocompatibility Complex (MHC) centred on the *HLA-DRB1* locus, representing about 30% of the genetic risk for RA (reviewed by Raychaudhuri, 2010). The *HLA-DRB1* alleles associated with RA encode a common a peptide sequence within the third hypervariable region at positions 70 to 74, which is commonly referred to as the shared epitope. As well as increasing the risk of development of RA, there is also evidence to suggest that the shared epitope is associated with worse prognosis in terms of increased risk of erosions and poorer response to therapy. In an analysis involving 178 Spanish patients with RA meeting 1987 ACR criteria, possession of 2 *HLA-DRB1* shared epitope alleles was associated with increased likelihood of ‘severe disease’, which was classified as requiring

treatment with cyclosporine in addition to MTX and HCQ (Gonzalez-Gay *et al.*, 2002). In a logistic regression analysis that controlled for age, gender and disease duration, but not antibody status, OR of requiring cyclosporine for patients with 2 *HLA-DRB1* shared epitope alleles was 2.4 (95% CI; 1.03, 5.7; p= 0.025). In another study of 124 Japanese patients with RA, where the outcome was DMARD resistance defined as indication for biologics within 2 years of DMARD initiation (excluding those who discontinued DMARDs because of adverse effects), DMARD resistance was predicted by the presence of *HLA-DRB1* *0404 shared epitope alleles (OR 2.89; 95% CI 1.28, 6.5; p=0.011) and ACPA (OR 6.31; 95%CI 1.23, 32.34; p=0.027) (Mori *et al.*, 2010). Further evidence was presented from the NOAR cohort in a study to determine whether it was possible to predict failure of MTX monotherapy due to inefficacy or side effects (Hider *et al.*, 2009). In a logistic regression model of inefficacy of the drug that controlled for age, gender, duration of symptoms and use of steroid, *HLA-DRB1* shared epitope positivity was a significant predictor after 1 year (OR 5.88; 95% CI 1.32 to 26.25; p=0.02) and 2 years (OR 3.04; 95% CI 1.21, 7.62, p= 0.02), but was not a significant predictor in the model to predict adverse events due to MTX. There was no significant difference in the numbers of RF positive cases in whom MTX monotherapy was successful or not; however, ACPA were not reported. It is possible that the reported associations of shared epitope alleles and treatment failure are mediated by ACPA, the influence of which are discussed in 1.8.2.3.

1.8.2.3 Antibody status

Seropositivity for either RF or ACPA is associated with reduced likelihood of remission in RA, as demonstrated in two studies involving cases from the Leiden early arthritis clinic (described in Table 1-2). The first study, published in 2009, examined factors predictive of remission in patients with RA according to ACR 1987 classification criteria from both the Leiden clinic in the Netherlands and the UK based ERAS, in which remission was declared by the rheumatologist if there were no swollen joints in a patient not taking DMARD therapy for ≥12 months (van der Woude *et al.*, 2009). Predictors of remission in the 454 cases from the Leiden clinic included

ACPA (hazard ratio, HR, 0.09; 95% CI 0.04, 0.20; p<0.001). The results were strengthened by replication of the findings using data from ERAS: ACPA data were not available for ERAS cases, but RF was associated with reduced chance of remission (HR 0.28; 95% CI 0.16, 0.49; p<0.001). These findings were further supported by the second study, published in 2012, aimed at comparing remission in those treated according to the standard treatment of the Leiden cohort with remission in cases who received treatment adjusted according to DAS in the Dutch Behandel Straregieen study (best treatment strategy in RA, BeSt) (van der Woude *et al.*, 2012). The 508 BeSt study participants also had RA according to 1987 ACR classification criteria and a symptom duration of less than 2 years at baseline and predictors of remission in both cohorts included lack of antibodies to citrullinated proteins, or RF. Other significant predictors of remission in both of these cohorts were male gender and shorter symptom duration at baseline.

1.8.2.4 Periodontal disease

Factors known to increase the risk of developing RA have attracted attention as possible drivers of disease activity. Periodontal disease is commonly seen in patients with RA and the bacterium *Porphyromonas gingivalis*, a key pathogen in periodontal disease, produces peptidyl arginine deaminase (PAD) enzymes that facilitate citrullination (reviewed by Koziel *et al.*, 2014).

In a randomised study of the effect of treatment for periodontal disease on DAS28, Al-Katma and colleagues (2007) examined the difference in DAS28 between 19 patients randomly assigned to receive either no intervention, or instruction on oral hygiene together with scaling of the teeth to remove plaque. They found that disease activity improved more often in the treatment group and that mean DAS28 was significantly different between the 2 groups after the intervention: 4.3 in the treatment group versus 5.1 in the non treatment group (p<0.05). The small number of cases included in this study was a significant limitation and was due to poor uptake: initially, 319 cases were invited to participate; and also drop-out: of 38 cases randomised, 7 from the control group dropped out as they failed to attend their appointments (4) or changed treatment for RA (3) and 2 from the

treatment group were lost, one of whom failed to attend follow up and the other was excluded for not complying with the intervention. Sampling bias could have affected the results of this trial, which due to the nature of the intervention, could not be blinded. Further bias may have been introduced when the results were analysed, which was not on an intention to treat basis. However, these results are interesting because they imply that interventions in oral hygiene may have a positive impact on disease activity in RA and furthermore, there have been consistent results from other small studies.

Further work from the same research group showed that periodontal intervention resulted in improved DAS28 after 6 weeks, regardless of whether RA treatment was with or without anti-TNF agents, and that anti-TNF agents did not improve periodontal disease (Ortiz *et al.*, 2009). However, this study was also limited by a small number of cases (40 cases in total, 10 in each treatment group, divided according to whether they received the intervention, and whether they were receiving anti-TNF treatment) and furthermore, DAS28 was higher in the 2 groups receiving periodontal treatment, which may have confounded the results. In the periodontal treatment groups mean DAS28 were 4.96 and 5.01 for those receiving and not receiving anti-TNF, respectively, compared to 4.34 and 4.29 in the non-periodontal treatment groups taking and not taking anti-TNF treatments, respectively. Although the authors reported no statistically significant difference between DAS28 in the treatment groups at baseline, this appears to have been in reference to an analysis of DAS28 dichotomised into ‘severe’ and ‘moderate’ categories and as there were only 10 cases in each group, there may not have been sufficient power for this analysis. Stable treatment throughout the study was not specified and it is possible that the patients with higher DAS28 scores used more medication, such as steroid, for example, which may also have accounted for the reported findings.

A Brazilian study investigated outcome at 3 and 6 months after randomisation to receive either treatment for periodontal disease or no treatment. A further group of patients had no native dentition (used full dentures). Again, the number of cases in each treatment group were small

(15 in each), but there was no difference in DAS28 between the RA cases receiving periodontal treatment compared to those with no intervention (Pinho Mde *et al.*, 2009). In addition, the authors of this study found no difference in ESR with treatment of periodontal disease, which is in contrast to findings reported by Ribeiro et al (2005) who found significantly fewer patients with high ESR (> 28) in 26 of 42 cases randomised to receive intensive treatment for periodontal disease (54% versus. 75% of those not receiving treatment for periodontal disease, $p<0.05$).

The conflicting results of these studies means that the effect of periodontal disease on RA disease activity remains uncertain. It may be that the benefit of periodontal treatment is short-term, with a positive impact on DAS28 that only lasts for a few weeks. A French open–label randomised control trial that has been recruiting patients since 2012 will examine the difference in DAS28 at 3 months in 40 RA patients with and without treatment for periodontal disease and will hopefully add further information (the ESPERA trial, Monsarrat *et al.*, 2013). In this study, rheumatologists assessing and recording DAS28 will be blinded to the treatment group, which was not a condition specified by the other papers mentioned here. Due to the nature of interventions for periodontal disease, it is not possible for these studies to be double-blinded and as there is no suitable placebo or sham treatment, these investigations are vulnerable to placebo effect.

1.8.2.5 Socioeconomic status

Socioeconomic status (SES) can be measured by numerous different methods and indices, which are broadly categorised into person-level, reflecting the education and income level of an individual, and area-level, which reflects the affluence or deprivation of the geographical area in which a person lives. There is a well-recognised association between lower SES and adverse health outcomes in general, and RA is no exception to this rule (reviewed by Calixto and Anaya, 2014). This phenomenon, which occurs internationally and within individual countries, may exist because healthcare is less accessible in poorer communities. The use of non-conventional or cultural treatments for health conditions is more common amongst ethnic minorities from deprived areas and furthermore, less education presents a

barrier to early recognition of ailments, understanding optimal management of chronic conditions, adherence to therapy, and maintenance of a healthy lifestyle. However, the relationship between lower SES and poor outcome may be the other way around: low SES can occur as a consequence of lower income after loss of function and work capacity due to RA . Evidence that disease activity in RA is influenced by economic status on an international level was presented by investigators from the quantitative standard monitoring of patients with RA (QUESTRA) study, who found an association of DAS28 with gross domestic product (GDP, measured in 1000 USA dollars per capita) (Sokka *et al.*, 2009). The QUESTRA study collected data from consecutive, unselected patients with RA from 71 individual centres spanning 25 different counties from 2005 to 2006. Data from a total of 6004 cases were included in a regression model that confirmed the observed relationship between GDP and DAS28 and explained 61% of the variation in DAS28. Each additional 1000 euro in GDP was associated with a reduction in DAS28 of 0.10 units (95% CI 0.06, 0.13). Although there was no difference in use of DMARDs between countries, the authors were concerned that (unavoidable) bias may have occurred due to preferable presentation of severe cases compared to mild cases in countries with lower GDP. They also found that mean DAS28 in patients not using biologic agents was higher in countries with low GDP (mean DAS28 for non-biologic cases low GDP countries 5.2, compared to 3.7 in high GDP countries), which implied there was a higher threshold for the use of biologics in poorer countries, possibly related to their financial cost. The authors also commented that psychological distress appeared to be greater in patients from countries with lower GDP, which in turn may have influenced disease activity and mediated the relationship between GDP and DAS28. International inequality in the treatment of RA was recently confirmed in a study involving 46 European countries which found that responsibility for the cost of treatment was more likely to fall to individual patients in countries with lower GDP and furthermore, there was an inverse relationship between drug costs and GDP which was more pronounced for biological therapies, and reduced the cost effectiveness of these agents (Putrik *et al.*, 2014).

Area-level deprivation was associated with increased baseline DAS28 in a randomised control trial of patients with longstanding RA (Harrison *et al.*, 2005). At baseline, patients from the British rheumatoid outcome study group (BROSG), which recruited 446 patients from 1998 to 2001 and studied outcome after 3 years of either symptomatic or aggressive treatment for RA, had a greater DAS28 if they resided in more deprived areas: mean DAS28 was 4.8 in 'most deprived', compared to 4.0 in least deprived areas ($p=0.002$). This finding was attributed to the TJC, which was only component of DAS28 significantly different between the SES groups: mean TJC 6 in most deprived, compared to 3 in least deprived ($p<0.001$). Differences in baseline DAS28 and TJC were confirmed after controlling for age, gender, smoking status, treatment centre, disease duration, and treatment. Interestingly, there was no difference in DAS28 at 3 years between levels of SES and this could have been because all participants were followed up in line with the trial protocol and more closely monitored than in routine clinical care (participants from the more deprived areas were more likely to drop out, but this was controlled for in the analysis). This study also found that greater deprivation was associated with more pain, loss of function, co-morbidities and poorer quality of life.

Person-level SES has also been shown to affect disease activity in RA. In a Dutch observational study of 869 RA cases from rheumatology clinics with median disease duration of 8.7 years, who completed postal questionnaires to measure disability, depression and quality of life, low SES (measured according to level of education) was associated with higher DAS28 at baseline (OR =2.8; 95% CI 1.2, 6.4), where DAS28 >3.3 was considered high (Jacobi *et al.*, 2003). A second questionnaire was completed 2 years later by 674 cases and differences in those who achieved a reduction in DAS28 of ≥1.2 from baseline and those who did not were examined. Although there were more cases with low SES who had high DAS28 after 2 years (62 % of those with low SES compared to 37% with high SES), there were no statistically significant differences in those who improved and those who did not between the SES groups. The authors did not report the absolute change in DAS28 within the groups of this study and concluded

that SES influenced disease activity, but the difference between SES groups reduced with time. What is not clear from this cohort is whether DAS28 was significantly different between the groups at 2 years, nor why the discrepancies in disease activity should reduce between the 2 time points in this cohort of patients with different disease durations in whom no changes to therapy were initiated as part of the study. An additional finding was that patients with low levels of education were less likely to access care delivered by allied health professionals, such as physiotherapists, occupational therapists and chiropodists, despite no additional financial costs for patients using these services. This may reflect more active coping mechanisms in those with higher levels of education, more awareness of available therapies, or perhaps that such individuals are more able to articulate their medical needs. Area level deprivation has been associated with RF, but not ACPA positivity in an analysis of 6298 patients with RA (Mackie *et al.*, 2012). In this analysis, Townsend index was used as a measure of deprivation and the OR for RF positivity was 1.14 (95% CI 1.01, 1.29) per Townsend index tertile. This effect was independent of smoking and gender.

There are relatively few observational studies examining the impact of SES on disease activity after initial presentation in RA and most studies have focused on the effect of social deprivation on disability or joint erosion. However, data from ERAS suggested that 'joint scores' (both RAI and counts of the numbers of swollen and tender joints) were worse with increasing area level deprivation at presentation and also after 3 years follow up (ERAS Study Group, 2000). Furthermore, in a subset of individuals for whom data on education level were available, lower person-level SES was also associated with less favourable joint score (although ESR was not). In contrast, the Swedish Better Anti-Rheumatic FarmacOtherapy (BARFOT) observational study of early RA found no association between SES and EULAR response at 3 and 6 months, and 1, 2, 5 and 8 years (Andersson *et al.*, 2013). The study recruited 2800 patients between 1992 and 2006 and collected data on SES retrospectively, in 2010, via a postal questionnaire sent to all living participants, and data from the 1460 respondents were analysed. Confounding by indication may have biased the results of this

study, as participant death could have been related to more severe disease and data from those who died were not included in the analysis. Further bias was also introduced because the 579 cases who did not respond to the questionnaire had higher baseline parameters including: mean DAS28, general health VAS, pain VAS, and SJC, and more were smokers at baseline. It is quite possible that non responders to the postal questionnaire had lower SES. Person-level SES was used in this study and was categorised according to the Swedish classification of occupation: self-employed, upper-white collar workers, lower white collar workers, blue collar workers and 'other', which included non-working individuals such as housewives and students. It is not clear whether the 'other' category could also have included cases not working due to ill health, but although it only encompassed 24 individuals, the 'other' category was significantly associated with non-achievement of good EULAR response at 5 years: OR of good EULAR response 0.15 (95% CI 0.04, 0.67). Furthermore, there were 302 cases who did not complete the question on employment and who were therefore excluded from this analysis. The authors concluded that their findings were due to better health equality in Sweden than in the UK or USA; however, there were several sources of bias that may have influenced the results.

Although there is consistent evidence that disease activity is worse with lower area and person level SES at disease onset, the influence of SES on disease activity in the longer term during routine clinical care is less clear. Data from ERAS suggest that the disparity continues after at least 3 years of follow up, but other studies have not yet confirmed this.

1.8.2.6 Smoking

Cigarette smoking has been proposed as a driver disease activity in RA and evidence for this is discussed within this section. Most studies have found that smokers tend to respond less well to treatment; however, the evidence should be interpreted with caution as potential confounders such as SES and antibody status were not controlled for in every analysis.

A prospective study of the effect of smoking and RF on disease activity in 100 consecutive patients 'recently' (recent was not defined) diagnosed with

RA and ultimately meeting 1987 ACR criteria (described in Section 1.3) used multifactorial ANOVA to analyse differences in SJC, TJC and pain VAS across 3 different categories of smoking: current, previous and never (CRP was not different between the groups at any time point and results of individual analyses of CRP were not reported) (Manfredsdottir *et al.*, 2006). Using data from 3 time points: baseline, 6 and 24 months and 100, 89 and 85 cases, respectively, the authors found a significant difference between smoking groups with highest values for current, then previous, then never smokers: $p<0.001$, 0.02 and 0.005 for SJC, TJC and VAS, respectively. They also performed an ordinary least square regression analysis of predictors of SJC at 6 months, which included potential confounders age, gender, caffeine intake and RF positivity, and there were no statistically significant predictors at the 5% level when all predictors were included in the model, but smoking and a past history of smoking were both significant predictors in a model that excluded other covariates through backwards elimination. This difference may reflect a lack of statistical power in the earlier model. It is not clear why SJC was chosen as an indicator of disease activity for this analysis, although it may have been preferred as a more objective measure than TJC and pain VAS. This study was possibly under-powered and did not use a composite measure of disease activity, so although the results pointed towards a significant effect of smoking on disease activity, further evidence was required to confirm this effect.

Investigators from the BARFOT study analysed data from 1787 cases with early RA and found an association of smoking at the time of study entry with less improvement in DAS28 (Soderlin *et al.*, 2011). At 12 months, the mean reduction in DAS28 from study entry was 1.71 units in those who reported current smoking at study entry, compared to 1.99 in never smokers and 2.14 in previous smokers ($p=0.0001$). Furthermore, current smoking at baseline predicted lack of EULAR response (as described in 1.8.1.1) at 12 months (OR for achieving EULAR response 0.69; 95% CI 0.50-0.93; $p=0.02$), 6 months (OR 0.66; 95% CI 0.48, 0.91; $p=0.011$) and 3 months (OR 0.64; 95% CI 0.47-0.87; $p=0.004$). These results were from logistic regression models that included potential confounders such as symptom duration, age at

baseline, gender, RF, baseline HAQ and DAS28, and treatment, but not SES.

Evidence of a relationship between 'dose' of smoking and reduced response to TNF inhibitors was presented from an observational study of 154 cases starting treatment at Staffordshire (UK) hospital (Mattey *et al.*, 2009). In this study, where 103 cases had a history of smoking and 38 cases were current smokers, change in DAS28 at 3 months was less marked in those with a history of smoking (a reduction of 2.07 in smokers, compared to 2.64 in non-smokers, p=0.01). There was also a correlation between number of pack years smoked and improvement in DAS28 at 3 months: Spearman correlation was -0.28, p=0.002, and reduced likelihood of achieving EULAR response in cases with >30 pack years of smoking. After controlling for age, gender, baseline DAS28, baseline disability, disease duration, presence of nodules, RF positivity, number of previous DMARDs and current smoking (but not SES), the OR for failure of anti-TNF therapy after 3 months was 1.95 (95% CI 1.11, 3.46) per additional pack year category, which were 0, 1-15, 15-30 and >30, where one pack year was quantified as 20 cigarettes per day for a year. Current smoking as a binary variable was not a significant predictor in the model of response at 3 months, but was significant in the model of response at 12 months (OR for non-response 2.7; 95% CI 1.2-5.9; p=0.01); however, current smokers were also more likely to have a smoking history of >30 pack years, which may explain this observation. Whilst lack of response to both etanercept and infliximab after 12 months was more likely with increasing quantity of cigarettes smoked, this trend was significant at 3 months in the group treated with infliximab, but not etanercept.

These findings were in keeping with results from a study of 1267 cases taking etanercept and 1612 cases taking infliximab, registered with the British Society for Rheumatology Biologics Register, BSRBR (Hyrich *et al.*, 2006). In this investigation of factors predictive of response to TNF inhibitors, current smoking at baseline was associated with reduced likelihood of good EULAR response (OR 0.77; 95% CI 0.60 to 0.99), although the influence of quantity smoked was not assessed, and furthermore, SES was not controlled for, so may have confounded the

results. Other predictors of poorer response included female gender and number of previous DMARDs used, whilst lower baseline disability, measured by HAQ, and concurrent use of NSAIDs and MTX were associated with better response.

There is also evidence that smoking has an adverse effect on response to treatment with MTX when used as monotherapy and in combination with SSA. In an investigation of 405 patients taking MTX monotherapy for 3-4 months as part of the Swedish FarmacOtherapy (SWEFOT) study in early RA, predictors of EULAR non-response included current smoking at study entry (OR for good response 0.35; 95% CI 0.20, 0.63), but not previous smoking (Saevarsdottir *et al.*, 2011). Additional factors that predicted poorer outcome in this study included female gender, increased symptom duration, and DAS28, and disability at baseline, but SES was not controlled for in this analysis. In a cohort of Mexican patients with early RA (<12 months) treated with a combination of MTX and SSA, plus oral Prednisolone if clinically indicated, current smoking at baseline predicted lack of ACR50 response at 6 months (OR 3.91, 95% CI 1.41, 10.81) (Rojas-Serrano *et al.*, 2011).

In contrast to the evidence presented so far, recently published results from BRASS indicated no significant association with smoking and DAS28 measured 1 year later and a weak association of moderate alcohol consumption and lower DAS28 (Lu *et al.*, 2014). The authors used data from 662 cases with RA, recruited to the register and followed up annually from 2003 for up to 7 years, with a median follow up time of 4 years. There are several possible reasons for the different smoking related result from this study. Unlike other papers reviewed in the present section, this analysis was adjusted for education level (a dichotomous variable separating those with an education level of high school graduate or higher from lower levels), which is an indicator of SES, and lower education level was associated with past or current smoking. Furthermore, the analysis in this paper was longitudinal and used general linear mixed models to determine how smoking and alcohol consumption influenced DAS28 a year later, so that data from all time points were used with adjustment for repeated measures. This approach is different to the cross sectional approaches reported in most

of the other papers presented here, where outcome at one or more time points were analysed and variations between these points were not accounted for. Furthermore, the BRASS cohort was more heterogeneous, owing to differences in the selection and treatment of patients. Most of the other studies focused on early RA, whereas mean disease duration in BRASS was 15 years with a standard deviation of 12 years, so some cases will have been treated in line with modern management principles, whilst others with a longer disease duration will have been treated according the older 'step up' approach (described in Section 1.6). Additionally, cases in this study were taking various different DMARDs and / or biologic agents, whereas other studies have involved patients treated with similar therapies, for example, MTX monotherapy in the SWEFOT trial and TNF inhibitors in the BSRBR.

In summary, the evidence points towards a deleterious effect of smoking on disease activity in RA, but this effect may have been confounded by SES in some studies. The BRASS study did control for SES, but due to differences in study design, its results are difficult to compare to those of other studies. The strength of association between smoking and ACPA in patients with the *HLA-DRB1* shared epitope (discussed Section 1.4.1), together with the immune-modulatory effects of cigarette smoke (reviewed by Baka *et al.*, 2009), provide a reasonable biological basis for increased disease activity in smokers with RA. The effects of smoking on disease activity seem to be important in early disease and following initiation of MTX or TNF inhibitors, particularly infliximab, although the strength of association here may not be strong. This effect has been observed in current smokers and is probably also pertinent for those with a past history of smoking. In addition, the total cumulative exposure to cigarette smoke may be an important influence of disease activity, with heavier smoking associated with worse outcome.

1.8.2.7 Obesity

Obesity has been linked to poor response to treatment with biological agents in RA. A study of 641 cases with RA according to 1987 ACR criteria recruited to an Italian arthritis register found that remission, defined as

DAS28 < 2.6 for at least 3 months, was less likely in obese individuals, where obesity was defined as BMI>30 kilograms per metre squared (kg/m^2) (Gremese *et al.*, 2013). In a multivariate analysis, the OR of achieving remission in obese subjects was 0.89 (95% CI 0.81,0.99, p=0.02). In this study, remission was also less likely with greater baseline DAS28. A later study by Rodrigues and colleagues (2014), which involved cases from a Portuguese register of RA patients, did not confirm this association with remission (possibly due to reduced power in this study, which included 317 patients), however DAS28 measured 6 months after the initiation of biological treatment was significantly greater in obese patients (obesity defined as body mass index, BMI >30kg/m^2): the regression coefficient from a multivariable analysis was 0.412; p=0.028.

Obesity is associated with elevated levels of CRP and a recent meta-analysis found a Pearson correlation of 0.36 (95% CI 0.30, 0.42) between CRP and BMI (Choi *et al.*, 2013). This association is likely to be related to the higher levels of inflammatory cytokines such as IL-6 and TNF in the serum and adipose tissue of obese, compared to non-obese, individuals (Bastard *et al.*, 2000). Although it is difficult to determine the magnitude of the effect of obesity on CRP, one study found that obesity was associated with both detectable levels of CRP, compared to undetectable (with a cut-off of 0.22 miligrams per decilitre, mg/dL) and clinically significant levels of elevated CRP, defined as 1.00 mg/dL (Visser *et al.*, 1999). Thus, as the DAS28 uses a measurement of CRP measured in miligrams per litre (mg/L), the CRP could possibly vary by as much as 10mg/L between an obese and non-obese subject, resulting in a hypothetical difference in DAS28 of 0.95 units. There is also a reported association between obesity and ESR (Leff and Akre, 1986, Pasulka *et al.*, 1985) and this may be partially explained by the association of obesity and hypercholesterolemia, which in turn can elevate the ESR (Sox and Liang, 1986). Although Gremese and colleagues did not specify which variables were used to calculate DAS28, ESR was mentioned as the inflammatory marker used in a separate analysis, so was possibly included in the DAS28 calculation. Whichever inflammatory marker was used, elevation of its value as a result of obesity may have effected

DAS28 and therefore confounded the results. Similarly, Rodrigues (2014) also did not specify which parameters were used to calculate DAS28 in this article, which was published as an abstract of the European Workshop for Rheumatology Research in 2014. Another possible reason for the lack of response seen in obese individuals could be reduced bioavailability of DMARDS in patients with greater volumes of adipose tissue, although there is no published evidence to confirm this for MTX in RA.

Table 1-5 Evidence for factors influencing disease activity in rheumatoid arthritis

Authors	Year	Subjects	Outcome measure	Outcome time point	Baseline predictors of greater disease activity
Age and gender					
(Jayakumar *et al.*)	2012	704 cases from ERAS, with RA, DMARD naïve and with less than 2 years' symptom duration at baseline, followed for at least 5 years	DAS remission (<1.6) whilst on DMARDs	Incident remission and sustained remission present at 3,4 and 5 years	Female gender Longer symptom duration Higher TJC
(Ma *et al.*)	2012	379 cases with RA, < 2 years duration from CARDERA trial (initial analysis) 194 cases of newly diagnosed RA from ERAN (validation cohort)	DAS28 remission (<2.6) whilst on DMARDs	Incident remission at 2 years	Increasing age Female gender Higher TJC
(Arnold *et al.*)	2014	1144 patients with early inflammatory arthritis (CATCH cohort).	Change in DAS28	12 months	Mean change in DAS28 less in females (Age had no significant effect)
			DAS28 remission (≤2.6)	Incident remission at 12 months	Increasing age Female gender (Baseline) DAS28

Table 1-5 continued

Authors	Year	Subjects	Outcome measure	Outcome time	Baseline predictors of greater disease activity
***HLA-DRB1* shared epitope**					
(Gonzalez-Gay *et al.*)	2002	178 unselected Spanish cases with RA according to 1987 ACR criteria	Severe RA, defined as disease requiring treatment with Cyclosporine in addition to MTX and HCQ.	Variable (cross sectional study)	Possession of 2 *HLA-DRB1* shared epitope alleles
(Hider *et al.*)	2009	309 cases with inflammatory polyarthritis (NOAR cohort)	Failure of MTX monotherapy due to inefficacy	1 and 2 years	*HLA-DRB1* shared epitope
(Mori *et al.*)	2010	124 Japanese cases with RA, meeting 1987 ACR criteria	DMARD failure (need for biological therapy)	2 years	*HLA-DRB1*04* alleles ACPA
Autoantibody status					
(van der Woude *et al.*)	2009	454 cases from the Leiden clinic with RA according to 1987 ACR criteria and	Remission defined by rheumatologist in cases with no swollen joints and free from DMARD for ≥ 12 months	Variable	ACPA positive RF positive Higher symptom duration
(van der Woude *et al.*)	2012	508 cases from the BeSt study with RA according to 1987 ACR criteria and 424 cases from the Leiden clinic (as above).		Cases followed for up to 5 years	

Table 1-5 continued

Authors	Year	Subjects	Outcome measure	Outcome time	Baseline predictors of greater disease activity
The influence of periodontal disease					
(Ribeiro *et al.*)	2005	42 RA cases, aged >40. After randomisation, 16 received professional tooth cleaning and instructions on oral hygiene, whilst the remainder received the same treatment, plus additional full mouth scaling and root planing (i.e. more intensive treatment for periodontal disease).	ESR	3 months	ESR fell more with more intensive treatment for periodontal disease
(Al-Katma *et al.*)	2007	29 cases with established RA according to 1987 ACR criteria, randomised to receive oral hygiene intervention or no intervention	DAS28	8 weeks	Reduction in DAS28 significantly lower in non-treatment group, who did not receive periodontal therapy
(Ortiz *et al.*)	2009	40 non smoking cases aged >30 with active RA, of whom 20 were receiving DMARDS plus anti-TNF and 20 DMARDS alone. Cases were randomised within the TNF/ non-TNF groups to receive treatment for periodontal disease or not. A total of 4 groups of 10 cases.	DAS28	6 weeks	Treatment of periodontal disease improved DAS28 in those taking anti-TNF and not taking anti-TNF.

Table 1-5 continued

Authors	Year	Subjects	Outcome measure	Outcome time point	Baseline predictors of greater disease activity
(Pinho Mde *et al.*)	2009	45 non smoking RA cases from Brazil with periodontal disease, 15 controls without RA and with periodontal disease and 15 controls without either condition. Of the RA cases, 15 received treatment for periodontal disease, 15 received no treatment and 15 had dental extractions and dentures.	DAS28	3 months	Improved DAS28 in treatment group
				6 months	No difference in DAS28 between treatment and non treatment groups
Socioeconomic status					
(ERAS study Group)	2000	869 cases from ERAS (newly diagnosed RA with symptoms for <2 years, DMARD naïve)	Joint count (explained in section 1.8.2.5) and RAI, ESR	Baseline	Lower SES
				3 years	Lower SES influenced joint scores, but not ESR.
(Jacobi *et al.*)	2003	869 questionnaire respondents from the Netherlands, median disease duration 8.7 years.	DAS28	Baseline	Low SES (measured by education level)
			Fall in DAS28 of ≥1.2	2 years	No difference across SES categories
(Harrison *et al*)	2005	446 patients recruited to a RCT (BROSG)	DAS28	Baseline	Area level social deprivation (at baseline)
				3 years	No difference between levels of deprivation (after 3 years)

Table 1-5 continued

Authors	Year	Subjects	Outcome measure	Outcome time	Baseline predictors of greater disease activity
(Sokka *et al.*)	2009	6004 unselected RA cases from 71 centres, across 25 countries (QUESTRA)	DAS28	Cross sectional	Low GDP of country of residence Unemployment (in 2010)
(Andersson *et al.*)	2013	1460 cases with early RA, recruited to BARFOT between 1992 and 2006 and completed questionnaire in 2010	EULAR response	5 years	Female gender Longer disease duration Smoking (baseline) More treatment
				8 years	Older age Female gender More treatment RF positivity Smoking (baseline)
Smoking					
(Hyrich *et al.*)	2006	2879 RA cases prescribed anti-TNF treatment (BSRBR)	EULAR response	6 months	Current smoking Female gender Number of previous DMARDs Higher baseline disability
(Mattey *et al.*)	2009	147 cases with RA, starting anti-TNF treatment for the first time, having met NICE criteria for this treatment.	DAS28 EULAR response	3 months	DAS28 higher in smokers Response less likely with greater amount of cigarettes smoked
				12 months	Response less likely with greater amount of cigarettes smoked and in current smokers

Table 1-5 continued

Authors	Year	Subjects	Outcome measure	Outcome time point	Baseline predictors of greater disease activity
(Saevarsdottir *et al.*)	2011	405 early RA cases taking MTX monotherapry from SWEFOT study.	EULAR response	3-4 months	Current smoking Female gender Increased symptom duration (baseline) DAS28 HAQ
(Soderlin *et al.*)	2011	1787 cases with early RA fulfilling 1987 ACR criteria from the Swedish BARFOT study	DAS28 EULAR response	12 months	Current smoking
(Rojas-Serrano *et al.*)	2011	144 patients with early RA (<12 months) attending a Mexican rheumatology clinic.	ACR50	6 months	Current smoking (low level of education was almost significant)
(Lu *et al.*)	2014	662 cases with RA from BRASS, mean disease duration 15 years.	DAS28	Mean follow up 4 years Outcome was DAS28 12 months after smoking data collected.	No association with smoking Weak 'J-shaped' relationship with alcohol.
Obesity					
(Gremese *et al.*)	2013	641 cases with RA according to 1987 ACR criteria, failed MTX and taking anti-TNF agents	DAS28 remission (<2.6) for at least 3 months	6, 9 and 12 months	Obesity (BMI >30) Higher baseline DAS28
(Rodrigues *et al.*)	2014	317 cases with RA using biological treatment after failure of DMARD	DAS28	6 months	Obesity (BMI >30) No significant relationship between obesity and remission (DAS28<2.6)

ACPA, anti citrullinated peptide antibody; ACR, American College of Rheumatology; BMI, body mass index; BARFOT, Better Anti-Rheumatic FarmacOTherapy; BRASS, Brigham and women's hospital Rheumatoid Arthritis Sequential Study; BROSG, British Rheumatoid Outcome Study Group;

BSRBR, British Society for Rheumatology Biologics Register; CARDERA, Combination of Anti Rheumatic Drugs in Rheumatoid Arthritis; CATCH, Canadian Early Arthritis Cohort; DAS28, disease activity score based upon counts from 28 joints; DMARD, disease modifying anti rheumatic drug; ERAN, Early Rheumatoid Arthritis Network; ERAS, Early Rheumatoid Arthritis Study; EULAR, European League Against Rheumatism; HCQ, Hydroxychloroquine; MTX, methotrexate; NICE, National Institute for Health and Care Excellence; NOAR, NOrfolk Arthritis Register; QUESTRA, QUantitative STandard monitoring of patients with RA; RA, rheumatoid arthritis; RCT, randomised controlled trial; RF, rheumatoid factor; SWEFOT, Swedish FarmacOtherapy; TNF, tumour necrosis factor.

1.8.3 Measurement of disability in rheumatoid arthritis

The Stanford Health Assessment Questionnaire (HAQ) (Fries *et al.*, 1980) was formulated in order to assess outcome, including functional impairment, in patients with arthritis and was later modified so that the questions were more readily interpreted by British patients (Kirwan and Reeback, 1986). It is now a validated and widely used tool for the measurement of outcome in RA that is easily reproducible and sensitive to change (reviewed by Bruce and Fries, 2003). Furthermore, it is recommended by OMERACT as a method of obtaining a patient reported measure of functional ability (Felson *et al.*, 1993). The full HAQ, which was designed to assess 5 aspects of outcome (disability, discomfort, drug side effects, financial cost and death), assesses disability and also includes a pain VAS, details of drug side effects measured using a toxicity index, details of hospital admissions, drugs used and procedures (so that financial cost can be calculated), and time and cause of death if applicable. The disability component of the questionnaire is easy and quick to complete, consisting of 2 or 3 questions within 8 categories of daily activity: dressing and grooming, rising, eating, walking, hygiene, reach, grip and activities. There are 4 possible responses to each question (0 to 3), so that the patient can indicate how difficult they find a given activity. The highest score from each category is used to calculate the total score, (unless devices or personal assistance are used for one of the categories, in which case category scores of 0 or 1 are increased to 2 in order to better represent the level of disability), so the highest possible value is 24 and the lowest is zero. These questions comprise the disability index component of the HAQ, sometimes abbreviated to HAQ-DI, and the total score is usually divided by 8 to give the average response over all categories, with 25 possible scores ranging from 0-3. One difficulty relating to the use of HAQ-DI as an outcome is that it is an ordinal variable (Tennant *et al.*, 1996). That is, a change in value at either end of the scale does not represent the same difference in disability as a numerically equivalent change in the middle of the scale. In order to overcome this, many authors categorise or dichotomise HAQ-DI, resulting in loss of information and statistical power. A further problem of HAQ-DI is that it does not detect low

levels of disability well and may score some patients as having no functional impairment when in fact some is present. One of several versions of the HAQ, formulated 24 years after its original description, overcomes these issues. The 10 item 'HAQ-II', produced by Wolfe and colleagues (2004), involves fewer questions and is therefore faster to complete than the original. In addition, it was developed using a Rasch model so that its scores represent a linear scale more closely and furthermore, it is more sensitive at detecting lesser degrees of disability. With these advantages over HAQ-DI, the HAQ-II can be used as an outcome variable for parametric analyses.

Numerous other methods of measuring functional outcome have been validated for use in RA research including: the arthritis impact measurement scale (Meenan *et al.*, 1980), which is also recommended by OMERACT to assess disability in clinical trials, short form-36 health survey (Weinberger *et al.*, 1991), Barthel index (Mahoney and Barthel, 1965), and the recent onset arthritis disability questionnaire (ROAD) (Salaffi *et al.*, 2005). Despite the plethora of indices available to quantify disability in RA, the HAQ and its modified versions are the most widely reported. A systematic review of the measurement properties of different tools to measure patient reported disability in RA concluded that the HAQ was one of the most reliable in terms of validity, internal consistency, reproducibility, responsiveness and interpretability (Oude Voshaar *et al.*, 2011). However, in this review, the HAQ was also one of the most comprehensively investigated scales. This possibly reflects its popularity as well as its suitability as an outcome measure, and in time, there may be more evidence in favour of the newer scales such as the HAQ-II and ROAD.

1.8.4 Factors influencing disability in rheumatoid arthritis

Disability due to RA contributes a significant financial burden incurred through both direct health care costs and indirect costs due to loss of workforce (Hallert *et al.*, 2004, Puolakka *et al.*, 2005, Bansback *et al.*, 2012), and also has an adverse impact upon the overall wellbeing and mental health of individuals (Nicassio, 2010). Loss of physical function due to RA has been the focus of much research and longitudinal studies have explored

factors influencing functional impairment, both in the short-term and long term following an initial diagnosis of RA. However, it is difficult to compare the results of such studies, owing to significant differences in their design, including length of follow up, measures of disability used, statistical analysis and even patient population. There is considerable inter-individual variation in HAQ over time (Drossaers-Bakker *et al.*, 1999), with age and gender affecting outcome such that female patients and those whose onset of RA is at an older age seem to do worse. In a study of 732 cases with RA according to 1987 ACR criteria who were recruited to ERAS, females were more likely than males to have worse function after 5 years' follow-up (OR, 1.6, 95% CI 1.3-2.9) (Young *et al.*, 2000). In a 15 year longitudinal study of HAQ over time in an inception cohort of patients presenting to their general practitioner with early inflammatory polyarthritis, women had higher HAQ scores at each measurement point (mean difference 0.29, 95% CI 0.25-0.34) and furthermore, although baseline HAQ scores were lower in males over 75 than younger males (mean difference 0.14, 95% CI 0.29, 0.001), HAQ deteriorated at a greater rate in all patients whose arthritis presented at an age over 75 years (Camacho *et al.*, 2011). These findings were confirmed by results from a French cohort of patients with possible early RA, in which HAQ at 5 years was more likely to be greater than the median value of HAQ, in older patients (OR 1.91, 95% CI 1.32-1.77) or females (OR 1.02, 95% CI 1.02-2.50) (Combe *et al.*, 2013).

With respect to the change in level of disability over time, an initial fall followed by a gradual increase with time: a 'J-shaped curve', has been described (reviewed by Toussirot, 2010). This pattern of change, or trajectory, was recently confirmed in a comprehensive analysis of change in HAQ over 10 years using data from patients recruited to ERAS (Norton *et al.*, 2013). In this study, growth mixture modelling was used to describe 4 distinct trajectories or classes of change in HAQ over 10 years. Whilst the largest of the 4 trajectories (including 46% of cases) described a J shape, with a greater rate of decline in function compared that associated with normal ageing, there were 2 classes with more stable progression: 'low stable', representing 6% of cases and 'moderate stable', representing 28%

of cases. The fourth class described a less favourable change in HAQ over time (the 'high stable' class), in which the patients were more likely to be female, have lower level of education, higher ESR at baseline and more evidence of radiographic erosion at 3 years. There was also greater co-morbidity at 3-5 years within this group (but not at baseline) and an increased mortality amongst patients in this category, highlighting once again the importance of function as an outcome measure in RA. Table 1-6 summarises the evidence for predictors of disability in RA and is divided according to whether disability was a short term outcome (within 2 years of study entry) or a long term outcome, after 2 years.

1.8.4.1 Disease activity and disability

Disease activity, with inflammation and pain in the joints, contributes significantly towards disability throughout follow up, whereas joint damage indicated by radiographic change influences disability in established RA (reviewed by Bombardier *et al.*, 2012). At baseline, disability measured by HAQ was influenced by RA disease activity and inflammation measured by CRP in a study of 133 cases with RA and less than 3 years symptom duration (Jansen *et al.*, 2000). This was in keeping with the findings in a cohort of 112 female patients from the Leiden clinic in the Netherlands in which there was a significant correlation between DAS and HAQ at baseline (Spearman's correlation 0.68, $p<0.001$) (Drossaers-Bakker *et al.*, 1999).

1.8.4.2 Autoantibodies

The effect of autoantibodies on disability is not entirely clear: some studies have concluded RF and ACPA predict worse outcome, whilst others have suggested no effect. One explanation of these different outcomes is that antibodies are associated with worse (more rapid) radiological progression, which in turn is associated with poorer long-term functional status (Figure 1-4). Dirven and colleagues (2012) proposed that predictors of short term HAQ were different to those of rapid radiological damage. They studied 508 cases with RA according to the 1987 ACR criteria from the BeSt study and concluded that RF and ACPA did not predict HAQ ≥1 at 3 months, whilst RAI, baseline HAQ and baseline pain did. These findings were supported when further analysis of the BeSt cohort showed that rapid radiological

progression predicted worse HAQ after 8 years (van den Broek *et al.*, 2012). The BeSt study was a randomised trial of different treatment strategies and patients received either MTX alone; MTX, SSA and prednisolone; or MTX plus Adalimumab. The different treatments received and the fact that the subjects were part of a trial make these results difficult to compare to other studies, as care delivered as part of a rigorous drug-trial protocol is very different to that provided for subjects enrolled in observational studies, which are more representative of 'real life' clinical settings. Furthermore, the HAQ outcome was dichotomised, which could have reduced the study's power to detect a difference in HAQ according to autoantibody status. Despite these limitations, the evidence from the BeSt study provides an attractive and plausible explanation for differences between studies that have investigated the relationship between auto antibodies and functional outcome. Similarly, the change in treatment for RA over time (discussed in Section 1.6) may have also impacted upon results from observational studies: the use of biologic agents and combination therapies should have reduced or slowed radiological progression, which in turn would result in improved functional outcome (Figure 1-4) and therefore, autoantibodies would be expected to predict functional outcome more often in older than modern observational studies.

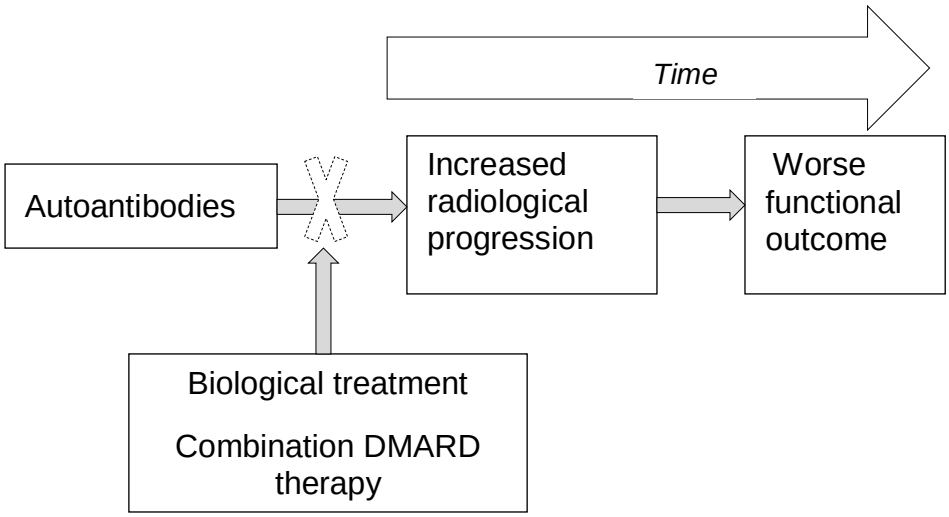

Figure 1-4 Schematic representation of the postulated relationship between auto antibodies and functional outcome in rheumatoid arthritis
DMARD, disease modifying anti rheumatic drug

There have been relatively few studies with HAQ before 12 months as an outcome; however, contrary to the evidence presented from the BeSt trial, other investigators have found an association between auto-antibodies and worse HAQ as early as 12 months from baseline. In a small study that included 182 cases with RA according to 1987 ACR criteria, Quinn *et al* (2006) found that improvement in HAQ from baseline to 12 and 24 months was less likely in RF positive cases and furthermore, in the 67 RF negative cases from this group, high titre of ACPA (>100) was associated with absence of improvement in function. In addition to the differences in timing of the outcome, the difference between this result and that of the BeSt study could also be related to the outcome measures used, which was HAQ ≥1 at 3 months in the Dutch study. Graell and colleagues (2009) also found that RF predicted worse functional outcome after 2 years: OR for modified HAQ (mHAQ) >0 after 2 years was 3.77 in RF positive patients; 95% CI 1.20, 11.81; p = 0.023. The population investigated here were part of an open label study of different treatments for RA, which should be borne in mind when interpreting the results: they may not be as generalizable as those from observational studies which mirror 'real life' more closely. Furthermore, the use of the mHAQ, which is less frequently used as an outcome measure,

has limitations and cannot be directly compared to HAQ. It is limited by a large 'floor' effect, with a relatively large number of cases scoring the lowest possible value (zero), so that gain in function may not be captured in some individuals, despite clinical improvement. Thus, mHAQ is also not as sensitive to change, so small improvements may not be captured (reviewed by Maska *et al.*, 2011).

1.8.4.3 Psychosocial influences on disability

The influences of psychosocial factors on functional impairment have been investigated by researchers working on the NOAR cohort. Recently, Camacho and colleagues (2012) published evidence that 'learned helplessness', a psychological state in which the subject feels unable to control the course of their disease, is associated with worse function in patients with inflammatory polyarthritis. Using data from 447 NOAR cases with available HAQ data, they described a median increase in HAQ score (where the maximum possible score was 3) of 1.12 (95% CI 0.82, 1.41) for those with high, compared to 'normal' learned helplessness. Furthermore, a similar effect was seen in those with low, compared to normal learned helplessness, with a median decrease of 0.39 units (95% CI -0.69, -0.10). The authors proposed that learned helplessness mediated their observed association of social deprivation with poor functional outcome. The impact of psychosocial factors was also considered by Drossaers–Bakker *et. al.* (1999), in the previously mentioned 12 year study involving 112 females with RA. Psychosocial functioning was measured using a combination of assessments including components of the Dutch version of the arthritis impact measurement scale 2 and parts of the RAND-36 measure of health related quality of life. In a multivariable regression model that controlled for the effects of age, disease duration, disease activity, (radiological) joint destruction, pain VAS and comorbidity, psychosocial functioning at 12 years was a significant indicator of HAQ at 12 years.

1.8.4.4 Smoking

The relationship between smoking and susceptibility to RA is well documented, as is the interaction between smoking and *HLA-DRB1* shared epitope alleles, which was discussed in Section 1.4.2. There is some

evidence that smoking is associated with worse functional outcome in RA. Masdottir *et. al.* (2000) reported increased median HAQ values associated with heavy smoking (≥20 pack years) in one study of 63 women with RA: median HAQ in heavy smokers 1.1, compared to 0.5 in smokers of <20 pack years ($p = 0.002$). This effect was also seen in a retrospective analysis of data from BRASS, where current smoking was associated with higher mean mHAQ one year later (Lu *et al.*, 2014). Both of these studies were retrospective, using data from patients with established RA. In Mansdottir's study, the disease duration ranged from 5 to 21 years and in the analysis of the BRASS data, mean disease duration was 15 years. These results may have been confounded by radiological damage, as smokers are more likely to have antibodies to citrullinated peptides, which in turn may increase the risk of erosive damage. Lu *et al*. (2014) also investigated the effects of alcohol consumption on functional outcome in RA and found that compared to cases who consumed no alcohol, mHAQ was significantly lower in cases who consumed 5.0 to 10.0g of alcohol per day. Their analysis controlled for potential confounders, including education level (as a marker of socio-economic status) and autoantibody status.

1.8.4.5 Obesity

Obesity was also investigated by the NOAR team who reported that morbid obesity (BMI ≥35 kg/m^2) was associated with worse HAQ score in their study of 1246 patients with inflammatory polyarthritis, of whom 87 (7%) were morbidly obese (Humphreys *et al.*, 2013b). In an analysis that controlled for the effects of age, gender, DAS28, smoking and treatment, the relationship between morbid obesity and HAQ tertile was described by an OR of 1.94 (95% CI 1.17, 3.24).

Table 1-6 Studies investigating predictors of disability in rheumatoid arthritis

Prospective studies of short-term (≤ 2 years) disability

Authors	Date	Subjects	Outcome measure(s)	Outcome times	Predictors of disability	Limitations
(Jansen *et al.*)	2000	133 untreated prospective outpatients meeting ACR criteria for RA, <3 years symptom duration	HAQ (DI) dichotomised into 'less disabled' (<median value) or 'more disabled' (>median value)	Baseline 1 year	High DAS28 at baseline High CRP at baseline Baseline HAQ Baseline pain VAS	Both predictors and outcomes dichotomised for regression analyses, limiting power
(Quinn *et al.*)	2006	298 cases with either CTD (116) or RA according to ACR criteria (182)	HAQ (DI) -quartiles	1 and 2 years	Baseline HAQ RF positivity ACPA positivity in RF negative RA patients (n=67)	Study population not exclusively RA. Predictors of disability not main study outcome.
(Graell *et al.*)	2009	105 cases enrolled onto an open label study using step-up treatment with Gold and MTX. ACR criteria for RA were met, <24 months' symptom duration at baseline	mHAQ, dichotomised into 0= no disability and >0 = disability	2 years	Older age RF positive Baseline mHAQ>0	Dichotomised outcome variable limited power. Where cases dropped out, they were not included in analysis, which is a potential source of bias. Problems associated with mHAQ include less sensitivity to change and increased floor effect compared to HAQ-DI.

Table 1-6 continued

Authors	Date	Subjects	Outcome measure(s)	Outcome times	Predictors of disability	Limitations
(Camacho *et al.*)	2012	553 consecutive cases with recent onset IP presenting to primary care (NOAR cohort) Symptom duration less than 2 years.	HAQ (DI) - continuous	Baseline	Greater social deprivation and learned helplessness. Learned helpless possibly mediated the relationship between deprivation and HAQ	Area level deprivation used (not person level)
(Dirven *et al.*)	2012	497 patients from the Dutch BeSt study. Treatment naïve, recent onset RA, meeting ACR criteria	HAQ (DI), dichotomised into HAQ ≥1 or HAQ<1	3 months	Baseline HAQ Baseline Pain Baseline RAI Less aggressive study treatment group (Baseline RF, ACPA and presence of erosions were not predictive of disability)	Dichotomised outcome variable and some predictor variables reduced power. This study was a post-hoc analysis from a randomised study of different treatment method for RA.
(Humphreys *et al.*)	2013	1246 consecutive cases with recent onset IP presenting to primary care (NOAR cohort) Symptom duration less than 2 years	HAQ (DI)- divided into tertiles	Baseline	Highest HAQ tertile associated with morbid obesity (BMI ≥35)	

Table 1-6 continued
Prospective studies of long-term (> 2 years) disability

Authors	Date	Subjects	Outcome measure(s)	Outcome times	Predictors of disability	Limitations
(Drossaers-Bakker *et al.*)	1999	112 consecutive female patients diagnosed with RA at the Leiden medical clinic from 1982 to 1986	HAQ (DI) – continuous	Baseline, 3, 6 and 12 years	Concurrent disease activity, Concurrent radiological damage (at 12 years), Psychosocial parameters	Related to problems associated with the use of HAQ-DI as a continuous variable.
(Young *et al.*)	2000	732 consecutive outpatients with RA according to ACR criteria. (ERAS)	Functional grades i-iv Requirement for aids / appliances/ home modifications	5 years 5 years	Female gender HAQ>1 at baseline Female gender HAQ>1 at baseline Age >60 years at presentation	Dichotomised outcome variable limited power. Potential bias as cases who dropped out not included in analysis.
(Combe *et al.*)	2003	191 consecutive outpatients with RA according to ACR criteria, DMARD naïve, diagnosed less than 1 year previously	HAQ (DI) - continuous	5 years	Baseline HAQ, ESR,CRP, RAI and presence of erosions. (Sex, age, RF and HLA class II alleles did not predict disability)	Related to problems associated with the use of HAQ-DI as a continuous variable.
(Harrison *et al*.)	2005	466 cases from the UK BROSG trial. Disease duration >5 years, ACR criteria for RA were met.	HAQ (DI) - continuous	Baseline 3 years	Increased area level social deprivation Increased area level social deprivation	Assumed a linear change in HAQ over time. Treated HAQ as a continuous variable Analysis limited to area-level social deprivation.

Table 1-6 continued

Authors	Date	Subjects	Outcome measure(s)	Outcome times	Predictors of disability	Limitations
(Camacho *et al.*)	2011	3666 consecutive cases with recent onset IP presenting to primary care. (NOAR cohort)	HAQ (DI) - continuous	Baseline, 1,5,10,15 years	Female gender (all time points) Late onset IP (>75 years age compared to <55 years)	Related to problems associated with the use of HAQ-DI as a continuous variable. Attrition, as expected with long term follow up.
(van den Broek *et al.*)	2012	465 patients from the Dutch BeSt study. Treatment naïve, recent onset RA, meeting ACR criteria	HAQ (DI)- continuous	8 years	Rapid radiological progression in the first year.	Related to problems associated with the use of HAQ-DI as a continuous variable
(Combe *et al.*, 2013)	2013	573 patients with possible early RA (ESPOIR cohort)	HAQ (DI) dichotomised according to whether above or below meadian value	5 years	Baseline HAQ Older age Female gender Baseline pain VAS	Dichotomised outcome variable reduced power. Cohort had early inflammatory arthritis rather than RA
(Norton *et al.*)	2013	1460 cases with RA, from ERAS Symptoms <2 years	HAQ-(DI)-continuous	Baseline to 10 years, described as 4 distinct trajectories of change (classes)	Worse prognostic class predicted by: Female gender Lower education level Increased radiographic damage at 3 years (No difference in RF, ANA, SE, year of first visit, or whether biologics used)	Related to problems associated with the use of HAQ-DI as a continuous variable. Attrition, as expected with long term follow up.

ACPA, anti citrullinated peptide antibody; ACR, American College of Rheumatology; ANA, Anti nuclear antibodies; BeSt, Behandel Straregieen; BMI, body mass index; BROSG, British Rheumatoid Outcome Study Group; CRP, C-reactive protein; CTD, connective tissue disease; DAS28, disease activity score based upon counts of 28 joints; DMARD, disease modifying anti- rheumatic drug; ERAN, Early Rheumatoid Arthritis Network; ERAS, Early Rheumatoid Arthritis Study; ESPOIR, Etude et Suivi des POlyarthritis IndiffeRenciees. ESR, erythrocyte sedimentation rate; HAQ (DI), health assessment questionnaire (disability index); HLA, Human leucocyte antigen; IP, inflammatory polyarthritis; mHAQ, modified health assessment questionnaire; MTX, Methotrexate; NOAR, NOrfolk Arthritis Register; RA, rheumatoid arthritis; RAI, Ritchie articular index; RF, rheumatoid factor; SE, *HLA-BRB1* shared epitope; UK, United Kingdom; VAS, visual analogue score.

1.8.5 The relationship between disease activity and disability in rheumatoid arthritis

The evidence presented so far (in Section 1.8.4) suggests that disease activity influences disability in early RA and that with time joint damage, indicated by erosions on radiographs, shows increasing correlation with disability. Although disease activity is likely to impact upon function at any time during the course of RA, the exact relationship between these outcomes is not entirely clear. Disease activity may have less of an influence on disability with increasing age and co-morbidity, or the relationship between these two may be different in men and women. To date, there have been few studies to investigate how DAS28 affects HAQ. In an analysis of cases from Yorkshire Early Arthritis Register (YEAR, the cohort which is the focus of this Thesis), Conaghan and colleagues (2010) showed that moderate DAS28 (that is, where DAS28 was between 3.2 and 5.1 at 12 months from baseline and at least once between baseline and 12 months) was associated with a HAQ at 12 months that was ≥0.49 units worse than at baseline in 10.7% of cases, which was comparable to the rate for cases with a persistently high (>5.1) DAS28 (11.1%). Thus, disease activity between disease onset and 12 months influenced HAQ at 12 months. Data from ERAN confirmed these findings. In a study that analysed DAS28 and HAQ at 1,2 and 3 years, Kiely and colleagues (2011) showed that patients with moderate or high DAS28 at 12 months were less likely to have a HAQ score of <1.25 at 2 and 3 years than cases with a low DAS28 at 12 months. Of those with high, moderate and low DAS28 at 12 months, 25%, 52% and 79% respectively achieved HAQ<1.25 at 2 years and 26%, 47% and 81% at 3 years, respectively. A recent study from a Canadian observational cohort examined correlations between DAS28 and HAQ in early RA (<12 months symptom duration) from baseline to 2 years (Boyd *et al.*, 2013). Over the 2 years of follow up, Pearson correlation ranged from 0.3 to 0.59 and was strongest at baseline and in RF positive patients, where the correlation between mean DAS28 and mean HAQ was 0.63, compared to 0.47 in RF negative patients (significance of difference, $p = 0.004$). The authors also reported that correlations were slightly weaker for those aged >65, although this difference was not statistically significant (overall correlation between DSA28 and HAQ

0.50 in those under 65, vs. 0.48 in those aged over 65, p=0.49). The problem with using Pearson's correlation coefficient to report the relationship between HAQ and DAS28 is that it measures the strength of a linear relationship between the two variables at a given point in time and does not indicate how change in one variable influences the other, and furthermore, it assumes that both are normally distributed interval data, which the HAQ is not (discussed in 1.8.3). However, this analysis does provide evidence of a relationship between disease activity and disability and raises questions such as why there should be a stronger correlation between DAS28 and HAQ in RF positive patients. This result could simply be due to type 1 error: the study included data from 1143 cases at baseline, but this number reduced with time and at 24 months, data from only 214 cases were available. Apparently this was not due to attrition, but because the study was ongoing at the time of publication of the article and therefore many patients had not completed 2 years' follow up.

1.9 Summary

The present chapter has reviewed the history, epidemiology, clinical presentation, treatment, measurement of outcomes and prediction of disease activity and disability in RA. Early, aggressive treatment of RA is essential to prevent irreversible structural damage and disability in the longer term. Therefore, early disease is an important focus for research. The hypotheses under scrutiny in this Thesis relate to outcomes in early RA, specifically to disease activity and disability. Much work has already been completed on factors influencing outcome in RA and so far there is evidence that disease activity and disability over time are less favourable for females than males and people from more socially deprived backgrounds. An additional adverse effect has also been seen for smoking, which is possibly worse with increasing amount smoked, and furthermore, autoantibodies in RA seem to be associated with less chance of remission. Other influences such as periodontal disease and alcohol consumption may also impact upon outcomes in RA, although further studies are necessary to clarify these effects. Much of the research in this area has been 'cross sectional' in nature; that is, the primary outcome is often the absolute change in an outcome measure between two time points.

This approach, although a common technique reported in RA research, does not examine the fluctuation in outcome variable between time points examined. Outcomes in RA vary widely between individuals, which is perhaps another reason why relatively few predictors of RA outcome can be applied in clinical practice. To date, there have been few studies describing how fluctuation in disease activity impacts upon function in RA over time, although some have reported on correlations between function and disease activity at distinct time points. The relationship between DAS28 and HAQ-DI merits further exploration. Current treatment strategies focus on minimising (or eliminating) disease activity in RA and whilst there is strong evidence for the importance of suppressing inflammation in RA, it is not clear whether this is enough to prevent disability. Evidence reviewed in Section 1.8.5 indicates that "moderate DAS28 is not benign" (Conaghan *et al.*, 2010) and although biological therapies are reserved for cases with severe disease activity (DAS28 > 5.1) in the UK, a significant number of patients with 'moderate' disease activity suffer impaired functional outcome. This raises the question of whether present NICE guidelines are adequate and indicates shortcomings specific to certain patients whose DAS28 scores persistently fall between 3.2 and 5.1.

1.10 Hypothesis

The work within this Thesis addresses some of the gaps in present knowledge of outcome in early RA and in particular, the relationship between disease activity and disability. It is anticipated that in early RA, treatment of disease activity will result in less disability. A discrepancy in the relationship between these variables would indicate that influences other than RA disease activity contribute to disability in early disease. In other words, whilst suppression of inflammation in early RA is clearly important, there may be other causes of disability, which may be amenable to intervention within the rheumatology clinic.

Modern statistical techniques may be employed to explore change DAS28 and HAQ-DI and their relationship over time. Current evidence suggests that change in function with time is non- linear and fluctuation in outcome between time points is expected. Therefore, traditional, cross sectional statistical approaches like regression analysis may not accurately represent changes in the outcome under scrutiny. Longitudinal analysis is expected to better describe changes in disease activity and function with time.

Trajectories of change in HAQ have been described, whereby individual patients can be classified according to pattern of change in HAQ over time. Trajectories have also be described for disease activity (Siemons *et al.*, 2013), with some patients falling into a poorer prognostic category of DAS28. The trajectory of DAS28 is likely to influence the HAQ trajectory, with cases from the least favourable DAS28 categories also doing less well in terms of HAQ. Furthermore, cases with persistently moderate DAS28 are also expected to experience significant loss of function over time. Thus, the hypotheses tested are:

- Change in DAS28 and HAQ-DI over the first 24 months in early RA can be described by growth trajectories, with some patients falling into more favourable trajectory groups.
- Those in less favourable trajectory groups of DAS28 and HAQ-DI are more likely to be female, have lower SES, antibodies to RF or ACPA, have a higher BMI, and be heavier smokers.

- Trajectory of change in DAS28 has a direct influence on change in HAQ-DI over the first 24 months of treatment in early RA, with HAQ-DI following a similar trend to DAS28.

Chapter 2 Patients and methods

2.1 Introduction to Yorkshire Early Arthritis Register

A register of patients with RA was established in Yorkshire in 1995, as part of Leeds Early Arthritis Project. A register of this sort continues to the present day, although considerable changes were made as the project evolved with time, reflecting changes in both contemporary understanding of the disease process and treatment of RA. The initial 330 cases recruited to the study between 1995 and 1997 were designated the 'YEAR A cohort'. Drawing on experiences gained through the collection of data for this initial, pilot cohort, YEAR B was established in 1997. This register recruited patients from hospital-based rheumatology centres (Figure 2-1) in Yorkshire from 1997 until 2002. All patients aged 18 years or older, within 12 months of diagnosis of RA (based upon the judgement of the treating consultant) were asked to join the register and consent to data collection at baseline, 3, 6, 12, 18 and 24 months. Further details of data collected are presented in Section 2.2. Treatment was based upon, but not restricted to, a regionally agreed treatment protocol, for which the main DMARD was SSA (described in more detail in Section 2.3). The study was approved by the Northern and Yorkshire Main Research Ethics Committee (Main Research Ethics Committee reference number: MREC99/3/48).

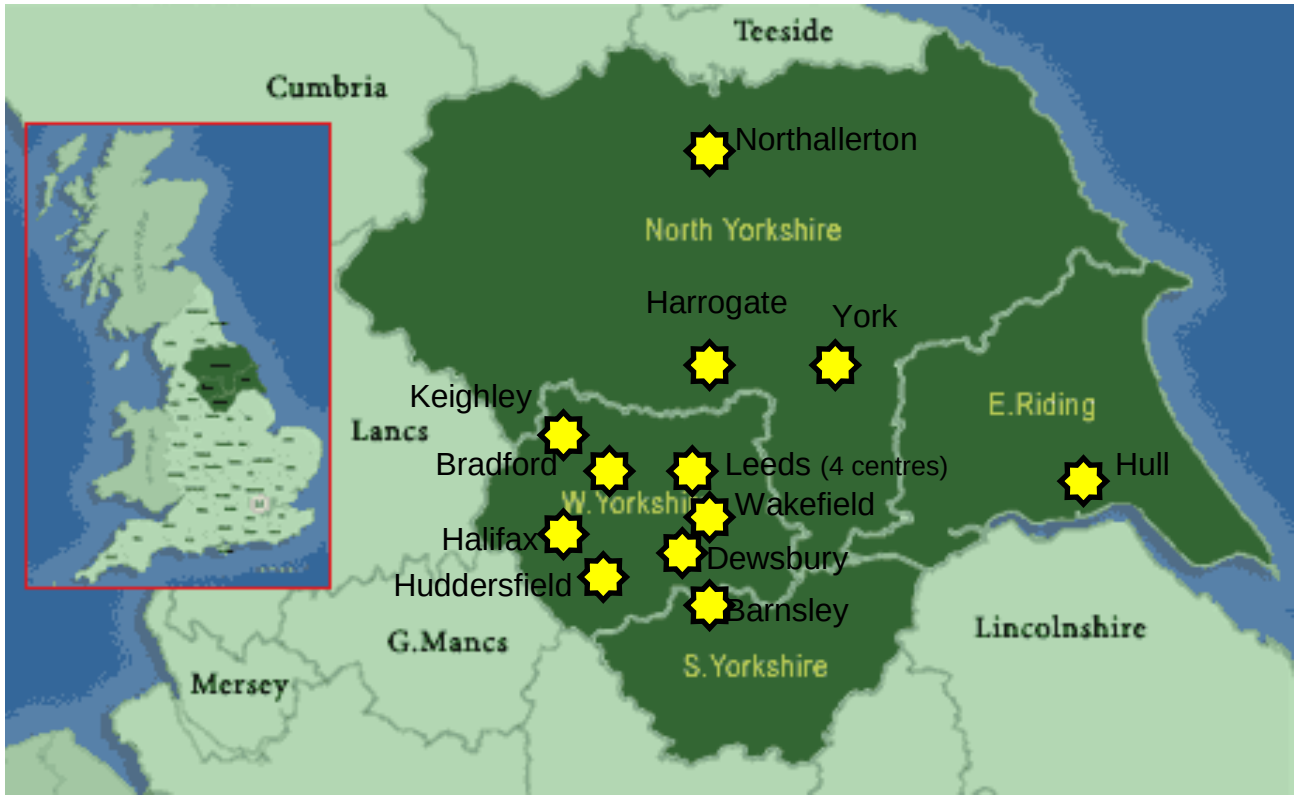

Figure 2-1 Locations of Yorkshire Early Arthritis Register centres

Centres are denoted by this symbol: . Centres included: Airedale hospital, Keighley; Barnsley hospital; Calderdale royal hospital, Halifax; Chapel Allerton hospital, Leeds (YEAR C only); Friarage hospital, Northallerton; Harrogate district hospital; Hull Royal infirmary; Huddersfield royal infirmary; Leeds general infirmary (YEAR B only); Pinderfields hospital, Wakefield; Seacroft hospital, Leeds (YEAR B only); St Luke's hospital, Bradford; St James's hospital, Leeds (YEAR B only); Wharfedale hospital, Otley, Leeds (YEAR B only); York hospital. Image adapted from original with kind permission www.picturesofengland.com

YEAR C was established in 2002 and data collection continued until 2009. Due to re-location of the rheumatology department within Leeds Teaching Hospitals NHS trust, patients from Leeds were recruited from Chapel Allerton Hospital rather than Leeds General Infirmary, St James's University Hospital, Seacroft and Wharfedale hospitals, as for YEAR B. The main difference between YEAR B and C was that for the later cohort, the treatment protocol was based upon MTX (Section 2-3). There were also differences in data collection, with an additional data collection time point at 9 months, and changes to some questions. For example, in YEAR B, data collectors were asked to record whether the patient was a smoker or a non-smoker, but the question was interpreted differently by staff at different centres: some recorded the contemporary smoking habits of individual patients and others asked about previous smoking history. Figure 2-2 demonstrates how the percentage of patients classified as 'smoker' varied according to centre. For example, at Harrogate where 84 cases were recruited and Seacroft where 13 cases were recruited, only 25% from each centre were included in the 'smoker' category, suggesting that ex-smokers from Harrogate and Seacroft were classified in the 'non-smoker' category. This compares to Wakefield (75 cases) and Bradford (24 cases), where 41% and 58% of cases were classified as smokers, respectively, suggesting that staff as these centres included ex-smokers in the 'smoker' category.

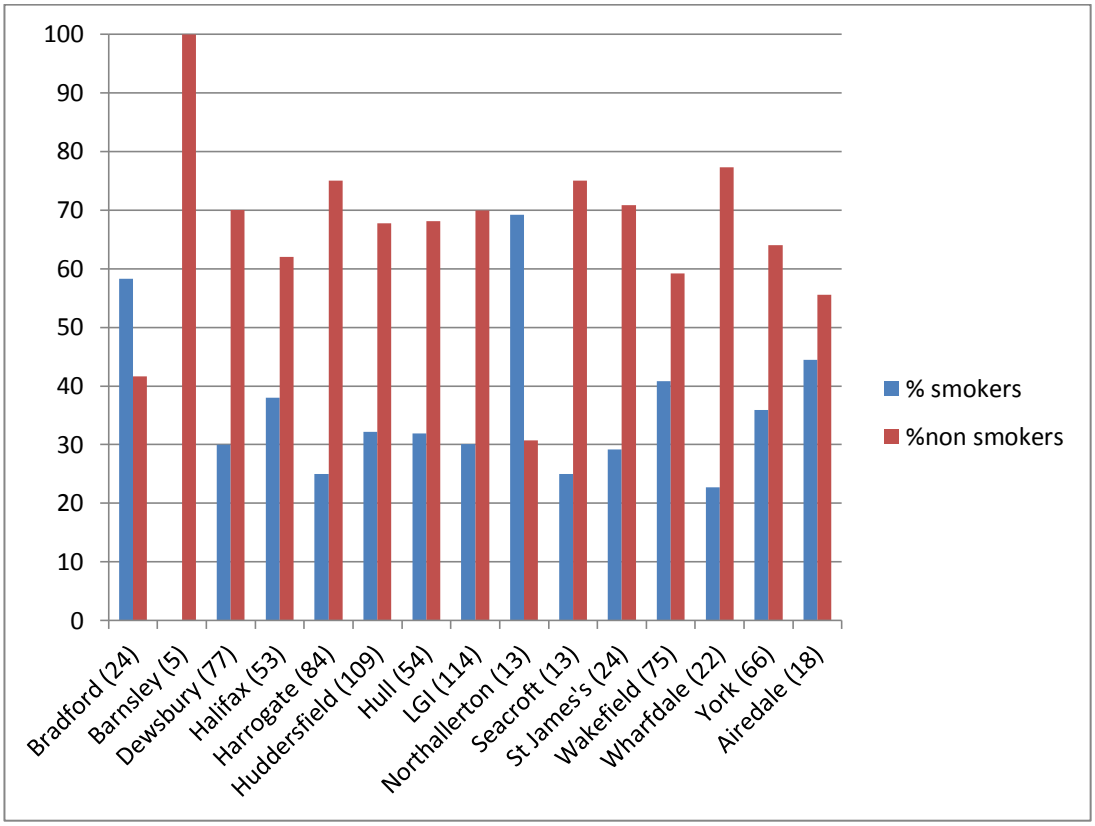

Figure 2-2 Bar chart to show how smoking and non-smoking was captured by individual Yorkshire Early Arthritis Register B centres.
(Numbers in brackets after the centre names represent the total of cases recruited from that centre).

For YEAR C, smoking history was recorded in more detail, including information about past history of smoking and whether patients considered themselves to be smokers at the time of data collection. This change was implemented to avoid ambiguity and to allow information concerning cardiovascular risk factors to be captured in YEAR C. The different YEAR cohorts are compared in Table 2-1. YEAR C was closed in 2009 and replaced by the Inflammatory Arthritis CONtinuum (IACON) register, which is recruiting at the time of writing. This register is based in Leeds and aims to capture patients with early inflammatory arthritis as close as possible to the time of presentation to the arthritis clinic. Data collected from YEAR B and YEAR C were included in the present study and details of methods used in these 2 cohorts will be discussed in further detail.

Table 2-1 Differences between the Yorkshire Early Arthritis Register cohorts.

	YEAR A	YEAR B	YEAR C
Dates of data collection	1995-1997	1997-2002	2002-2009
Inclusion criteria	Considered likely to have RA	Consultant made diagnosis of RA	Consultant made diagnosis of RA
Initial treatment	Not specified	SSA	MTX
Follow up time	12 months	24 months	24 months
Number recruited	330	774	807

MTX, methotrexate; RA, rheumatoid arthritis; SSA, sulphasalazine; YEAR, Yorkshire Early Arthritis Register.

2.2 Data Collection

Informed consent was obtained from each patient at the baseline visit and data were collected by trained research nurses and rheumatology doctors. Details were written onto pre-printed clinical record forms, which were then transferred to a spread sheet by data entry clerks. Although there were no official strategies to promote attendance at each data collection visit, the databases were reviewed periodically, and if an appointment had been missed, the patient was contacted by telephone and asked to attend for the next visit. At the baseline visit demographic details, indicators of lifestyle and past medical history were noted and at every visit details of patient reported outcomes and clinical examination findings were recorded. Blood samples were taken at each visit, to check for markers of inflammation. Samples were also obtained to check for the presence of autoantibodies. Some of the data were applied in other projects; however, the remainder of this Section will discuss the collection of data that was subsequently analysed as part of the present study.

2.2.1 Baseline data: lifestyle and medical history

Details of past medical history were collected for both YEAR B and C cohorts as described in Table 2-2. Smoking data were collected and for YEAR C, alcohol consumption, height and weight were also recorded. The patient was asked to recall the month and year of onset of symptoms of arthritis. Further details of the data collected at the baseline visit of each cohort are provided in Table 2-2, which also highlights the differences in baseline data collection between the two cohorts.

2.2.2 Patient reported outcome measures

At every visit, patients were asked how long their joints were stiff for in the morning (EMS), and if greater than 15 minutes, this duration in minutes was recorded. VAS were used to quantify disease activity, pain and fatigue. For fatigue, YEAR B cases were asked whether they experienced “abnormal fatigue” (further clarification of this question was left to the discretion of the data collector) and in YEAR C, this question was worded thus: “do you feel unusually tired?”. Positive responses to these questions prompted completion of the VAS, whereas negative responses were translated as a score of 0 on the VAS. In YEAR B, all cases were asked to complete the VAS for pain, but in YEAR C, only cases who responded positively to the question: “Do you have pain associated with your rheumatoid arthritis?” were asked to complete the pain VAS. Each VAS was represented by a printed horizontal line, 10 cm in length, where 0 cm represented no disease activity, pain, or fatigue, and 10 cm represented pain or fatigue (tiredness was the word used in YEAR C) “as bad as it could be”, or extremely active disease. Participants were asked to indicate how active they felt their disease was, or how much pain or fatigue they had experienced, over the last 7 days, by placing a mark on the line. At most YEAR visits (listed in Table 2-3), participants were asked to complete a HAQ, which is shown in Appendix 1.

Table 2-2 Data collected at baseline in the Yorkshire Early Arthritis Register B and C cohorts

Variable type	Details of data collection at baseline YEAR B	 YEAR C
Demographic details	Gender defined by patient Date of birth Address including post code Ethnic origin defined by patient: White, Afro-Caribbean or Asian	Gender defined by patient Date of birth Address including post code Ethnicity defined by patient: White, Black, Asian, Asian-eastern, or mixed ethnicity; each category was further defined.
Smoking	Smoker / Non-smoker	Non-smoker/ Ex-smoker / Smoker If ever smoked, how long for and how many cigarettes per day.
Co-existent medical problems: Patients were asked whether they had any of these conditions (Yes/No). Any prompting questions or explanations were at the discretion of the data collector.	Hypertension (Including patients on antihypertensive medication), Ischaemic heart disease, Diabetes (Not further defined), Chronic airways disease requiring medication, Renal disease, Cerebrovascular disease, Peripheral vascular disease, Chronic liver disease, Other (to specify). Alongside each condition, there was space to record comments.	Hypertension, (Including patients on antihypertensive medication), Ischaemic heart disease, Diabetes (Further defined as IDDM/ NIDDM), Chronic airways disease requiring medication, Renal disease, Cerebrovascular disease, Peripheral vascular disease, Chronic liver disease.
Cardiovascular risk factors: Any prompting questions or explanations were at the discretion of the data collector.	Not specifically collected	In addition to above, patients were asked whether they had: hyperlipidaemia (don't know/yes/no)- if prescribed lipid lowering medication, a 'yes' was recorded; a family history of ischaemic heart disease (don't know /yes/no).

Table 2-2 continued

Variable type	Details of data collection at baseline YEAR B	 YEAR C
Height (cm) and weight (Kg)	Not collected	Recorded
Alcohol consumption	Not collected	Quantified* according to gender : Less than 2-3 units per day for women, or more than 2-3 units per day for women. Less than 3-4 units per day for men, or more than 3-4 units per day for men. Or: Weekends only (both men and women): if so, Less than 8 units per day, or More than 8 units per day.
Family history	Not collected	RA: yes /no/ unknown. If yes: child, sibling, parent, grandparent, great grandparent, other (described) Other autoimmune conditions (e.g. MS, CTD, Diabetes): yes/ no/ unknown. Vascular disease (including IHD peripheral vascular disease, stroke): yes/ no/ unknown.

*A guide to the number of units of alcohol within defined measures of beer, cider, wine, champagne, port, sherry, liqueur and spirits was included within the appendix of the clinical record form.

cm, centimetres; CTD, connective tissue disease; IDDM, Insulin Dependent Diabetes Mellitus; IHD, ischaemic heart disease; Kg, Kilograms; MS, multiple sclerosis; NIDDM, Non Insulin Dependent Diabetes Mellitus (No further questions were asked to determine whether the patient had type one or type 2 diabetes mellitus); RA, rheumatoid arthritis; YEAR, Yorkshire Early Arthritis Register.

Table 2-3 Clinical data, patient reported outcomes and laboratory measures acquired at Yorkshire Early Arthritis Register visits

Data captured		Baseline		3 months		6 months		9 months†		12 months		18 months		24 months	
		B	C	B	C	B	C	B	C	B	C	B	C	B	C
Joint counts		✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
Patient VAS:	Pain	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
	Disease Activity	✓	✓	X	✓	✓	✓	X	✓	X	✓	✓	✓	✓	✓
	Fatigue	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
Early morning stiffness (duration in minutes)		✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
HAQ		✓	✓	X	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓
DMARD prescribed this visit		✓	✓	✓	✓	✓	✓	X	✓	✓	✓	X	✓	✓	✓
DMARD prescribed previously		✓	X	X	✓	X	✓	X	✓	✓	✓	X	✓	✓	✓
DMARD side effects		X	X	X	✓	X	✓	X	✓	✓	✓	X	✓	✓	✓
NHS Blood tests	RF	✓	✓	X	X	X	X	X	X	✓	✓	X	X	✓	✓
	CRP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	ESR	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum stored		✓	✓	X	X	X	X	X	X	✓	✓	X	X	✓	✓

† There was no YEAR B visit at 9 months.
CRP, C-reactive protein; DMARD, disease modifying anti rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NHS, National Health Service; RF, rheumatoid factor; VAS, visual analogue score.

2.2.3 Clinical data collection

At the baseline visit, participants were asked to recall the date of onset of RA symptoms. At every visit, the study doctor or nurse recorded the swollen and tender joints diagrammatically. A table was used for this purpose throughout YEAR B, whereas for YEAR C, these details were recorded with the aid of a homunculus diagram (see Appendices 2 and 3). Details of all medications taken by the subject were noted on the clinical record form at baseline, 6 and 12 months for YEAR B. For each visit, there was a prompt in the YEAR C clinical record form to remind the study nurse to complete an appendix detailing any concomitant medication, doses and subsequent changes. The recommended

treatment regimes were different between the 2 cohorts and are detailed in Section 2.3. Whilst the YEAR B clinical record form simply asked for details of reasons behind deviation from this protocol, the medications section of the YEAR C clinical record form (shown in Appendix 4) was more detailed and asked which DMARDs were taken, their doses, and for how long they were taken, together with details of any DMARD side effects experienced by the patient.

2.2.4 Laboratory measures

2.2.4.1 Antibodies and inflammatory markers

On the same day as the patient interview and clinical assessment, blood samples were acquired and analysed within the standard National Health Service (NHS) laboratories of the participating hospitals. These investigations included CRP and ESR, which were later used to calculate DAS28, and IgM RF, measured using standard nephelometric assays.

Samples of serum for storage (minus 20 degrees centigrade, ^{o}C) were also acquired at the baseline, 12 and 24 month YEAR visits. These samples were later defrosted and used for ACPA determination, which was not available as a routine NHS test at the time of data collection. This analysis was performed by a member of the YEAR Consortium and has been described previously (Morgan *et al.*, 2009).

2.2.4.2 Human Leucocyte Antigen-DRB1 genotyping

Stored samples of ethylenediaminetetraacetic acid (EDTA) anti-coagulated blood were used to extract deoxyribonucleic acid (DNA) and a semi-automated polymerase chain reaction (PCR) technique was employed to determine the number of copies of the shared epitope and *HLA–DRB1* subtype, as previously described (Morgan *et al.*, 2009).

2.2.4.3 Absence of stored samples

In cases where no stored blood samples were available, patients were contacted by post and asked to attend a local phlebotomist to have a blood sample taken, which was then returned by post to the research laboratory at Chapel Allerton Hospital. These samples were then processed, as described above, to determine *HLA-DRB1* genotype and ACPA status.

2.2.5 Cases excluded from Yorkshire Early Arthritis Register C

At the time of recruitment to YEAR C, there were three randomised control trials also recruiting Leeds patients with RA who had not taken DMARDs before. The initial intention was to consent suitable patients for inclusion within YEAR as well as the trials and include patient data collected via the randomised trials in the YEAR C database. However, because YEAR was set up to observe the course of early RA in a realistic clinic setting, this decision was later revised and cases eligible for trials were not included in the YEAR database. As these selected cases were excluded, there is a potential impact on the findings of the study: YEAR C did not represent all cases of incident RA in Yorkshire at the time of data collection. The three studies recruiting at the time of YEAR C data collection were:

- PRevention Of Work Disability (PROWD). This study recruited 145 Yorkshire patients between 2003 and 2004. One inclusion criteria for the study was that patients had a 'self-reported work impairment due to RA' (Bejarano *et al.*, 2008).
- Infliximab as inDuction therapy in Early Arthritis (IDEA). This study recruited 112 patients with 'active' RA (defined as disease activity score based upon 44 joints of at least 2.4) from Leeds, Harrogate, Huddersfield and Bradford between 2006 and 2009 (Nam *et al.*, 2014a).
- Etanercept and Methotrexate in Patients to Induce Remission in Early inflammatory arthritis (EMPIRE). This study recruited 110 cases from Leeds, Huddersfield, Harrogate and York between 2006 and 2009 (Nam *et al.*, 2014b).

2.3 Treatment protocols

Consultant rheumatologists from the rheumatology centres agreed upon a 'step-up' treatment approach using DMARDs SSA, MTX and HCQ which was in keeping with contemporary best practice. For YEAR B, the initial drug of choice was SSA, whilst for YEAR C, this was changed to MTX. One other key difference between the treatment protocols of 2 cohorts was the administration of intramuscular steroid in the form of 120 mg of methylprednisolone at the baseline visit in YEAR C. The treatment protocols, which are shown in Figure 2-3, were intended for guidance only and deviations to meet the needs of individual patients were expected. Such changes could be documented in the clinical record forms; no limitations were placed on concomitant treatment with other medication such as anti-inflammatory drugs or oral or parenteral corticosteroids. Whilst YEAR data collection was on-going, the treatment of RA was evolving, owing to the introduction of biological therapies such as TNF inhibitors. If cases met criteria for this treatment, it was initiated in line with UK guidelines.

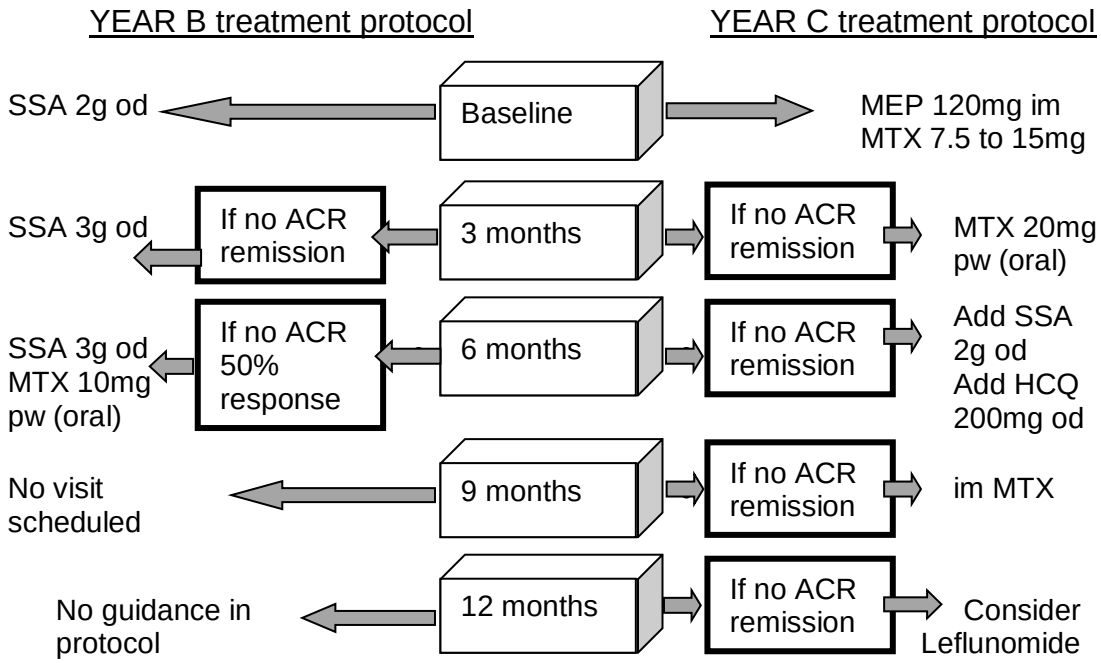

Figure 2-3 Yorkshire Early Arthritis Register treatment protocols
ACR, American College of Rheumatology; g, grams; HCQ, Hydroxychloroquine; i.m., intramuscular; MEP, methylprednisolone; mg, milligrams; MTX, Methotrexate; od, once daily; pw, per week; SSA, Sulphasalazine; YEAR, Yorkshire Early Arthritis Register.

2.4 Data Validation

Following the collection and entry of data onto a database, the information was reviewed to determine:

- How much of the original data were missing
- Whether it was possible to recover any of the missing values retrospectively, using hospital notes or computer systems.
- The error rate associated with transcribing information from clinical record forms to the database for YEAR C.

Validation of the YEAR B data was undertaken by the YEAR data entry team towards the end of the data collection period in 2001 and 2002. On each occasion, a random sample of 10% of cases was selected and the data recorded electronically were compared to data captured on the clinical record forms. Unfortunately, no formal record of the validation process of YEAR B

data was made and the error rate associated with transcribing data from the clinical record forms to the electronic database was not calculated. For validation of the data in the YEAR C database, which was undertaken in 2010 by Dr Hensor, the method of data entry verification described by Mullooly (1990) was applied. A random sample of 10% of patients who had attended at least 6 YEAR visits was selected for comparison of the written and electronic records. As an error rate of 0.71% was discovered, a random sample of 200 of the remaining clinical record forms were selected for further verification of the corresponding electronic records. This number was slightly greater than the 25% of records suggested by Mullooly.

When data in either cohort were missing, the recruiting centres were contacted and efforts were made to recover missing values through inspection of hospital notes, or in the case of blood test results, hospital results servers. If this data could not be captured, the reason for this was noted. For YEAR B, I undertook a second-wave validation in 2010 to specifically address inaccuracies in recorded age, symptom duration and clinical data. This involved checking data entered onto the database against clinical record forms where entries were ambiguous or missing. If the clinical record form did not contain the desired information, hospital records or electronic records (for blood test results) were inspected, where available. For the analyses presented in this Thesis, where the focus is on early RA, it was especially important to check that symptom duration was accurately recorded. In some cases, it appeared that the symptom duration was far longer than the study protocol had indicated for inclusion in the cohort (12 months or less). In other cases, recorded symptom durations were improbable: the date of onset of symptoms appeared to be after the date of the baseline visit. Wherever medical records were available, these inaccuracies were checked. Patient age was usually accurate, however in some cases the year of birth was entered inaccurately. This problem was overcome by using hospital records to check actual date of birth.

2.5 Statistical analysis

The hypotheses tested in this Thesis concerned early RA, so patients with symptoms for over 24 months were excluded from the analyses. The pragmatic

decision to use 24 months as a cut-off meant that whilst a large number of cases were retained for analysis, the focus of the study was early RA. Similarly, cases were also excluded if symptom duration was missing. In cases of missing or long symptom duration, efforts were made to capture this data or confirm that the recorded symptom duration was accurate (as described in 2.4). In total, 98 cases were excluded due to missing symptom duration and 51 were excluded due to excessive symptom duration (detailed in Chapter 3, Paragraph 3.4 and Figure 3-1). Although patients recruited to the cohort were from a diverse population and included individuals from different ethnic backgrounds, the majority considered themselves to be 'white Caucasian' and numbers of individuals from other ethnicities were small (detailed in Chapter 3, Table 3-1). All subjects were included in the analyses within this Thesis, regardless of ethnicity, in order to maximise the number of cases included.

2.5.1 Outcome variables

As mentioned above, the YEAR cohort was established in order to answer the question: *"Do conventional prognostic factors predict the clinical outcome as measured by the response criteria of early RA patients treated in a standardised 'step-up' fashion?"* Therefore outcome and predictor variables were selected for inclusion in statistical analyses if they were considered pertinent to answering this question. Clinical outcome can be measured using a variety of methods (Chapter 1, Section 1.8), some of which were included in the YEAR clinical record forms. In the UK, DAS28 is currently used to guide treatment with biologic therapy such as TNF inhibitors, as outlined in Chapter 1, Section 1.6 and Figure 1-2. Capture of DAS28 was a target for data collection in the YEAR cohort and has been used as the primary outcome measure in the statistical analyses. To minimise the impact of missing variables disease activity VAS and ESR, the 3 variable DAS28, using CRP was calculated for the analyses in this Thesis (described in Section 1.8.1 and Table 1-5).

Disability was also selected for analysis and was captured using HAQ-DI (Chapter 1, 1.8.3). The questionnaire completed by YEAR participants is shown in Appendix 1. As HAQ-DI represents an ordinal scale, Rasch analysis was applied (as discussed by Tennant and Conaghan, 2007), so that the transformed HAQ-DI could be analysed as an interval variable. This

transformation was performed by the data analyst from the YEAR Consortium, Dr Elizabeth Hensor, and is described in detail in Appendix 5. Where HAQ-DI was only partially completed by the patient (item non response), the whole score was treated as missing (handling of missing values is described in 2.5.5).

Predictors of DAS28 and HAQ-DI at 6 and 12 months were analysed. These 2 time points were selected because they were both within the 'window of opportunity' for RA treatment (described in Section 1.6) and furthermore, disease activity at these time points have been demonstrated to predict future joint damage (Combe *et al.*, 2014). Therefore, predictors of outcome at 6 and 12 months are of interest as they may be useful to inform management decisions in RA.

2.5.2 Predictor variables

Predictor variables are summarised in Table 2-4. Known predictors of outcome in RA were selected for inclusion in the statistical models, based upon the evidence presented in Chapter 1, 1.8.2 and 1.8.4, and dependent upon baseline data collected. In addition, patient reported outcomes at baseline were included in the cross-sectional analyses of change in DAS28 and HAQ-DI at 6 and 12 months to investigate their suitability as predictors of outcome. These included duration of EMS (measured in minutes), VAS pain and VAS fatigue (both VAS were measured in cm). As duration of EMS was not a continuous variable (patients tended to report EMS in terms of 10, or 30 minute intervals), it was collapsed into categories, using the 'Xtile' Stata command. Four categories were selected so that each represented a suitable proportion of cases (an unusually small category could result in skewing of the results when entered into the regression model). The categories were 0-35 minutes, 40-75 minutes, 90-210 minutes and 220 minutes or more. The postal codes of participants' home addresses, supplied at the baseline visit, were used to derive their corresponding index of multiple deprivation (IMD), an indicator of area-level SES. The IMD was developed to enable the targeting of resources towards deprived areas, but has been adopted for use in research. Geographically determined areas, called lower layer super output areas (LSOA), are allocated

IMD scores based upon information from seven different domains, which contribute to the final score as follows:

- Income 22.5%
- Employment 22.5%
- Health and disability 13.5%
- Education, training and skills 13.5%
- Barriers to housing and services 9.3%
- Living environment 9.3%
- Crime 9.3%

In England there are 32,482 LSOAs, which are ranked according to IMD, where rank 1 is most deprived and rank 32,482 is least deprived. For the present study, the English index of deprivation (Department For Communities and Local Government, 2004) was utilised. This version of the IMD used data collected during 2001, and included data from the national census. For the present study, the IMD rank was divided into quartiles for application in regression analyses.

It was not possible to apply the smoking variable to all analyses as patients included in YEAR B were not explicitly asked about a past history of smoking (explained in Section 2.1). Similarly, data on BMI were not collected at all for YEAR B and furthermore, data on comorbidities were incomplete in many more cases from YEAR B than YEAR C (detailed in Chapter 3, Section 3.4). Therefore, a YEAR C sub analysis was carried out that included these variables as predictors of outcome, which is described in 2.5.4.3.1. Smoking was added to regression models as a continuous variable, which was an estimate of the quantity of cigarettes smoked by the participant, measured as pack years, where one pack year is the equivalent of having smoked 20 cigarettes every day for one year. As data on comorbidities was limited to the presence or absence of the ailments listed in Table 2-2, and severity of these conditions were not considered, the 'comorbidity' variable was simplified and included as a binary variable (comorbidities present / absent) in the regression models.

Table 2-4 Predictor variables included in statistical models

Type of variable known to influence outcome in RA	Predictor variables included in statistical models		Type of variable
Genetic	*HLA-DRB1* "shared epitope"		Dichotomous (present / absent)
Environmental	Smoking		Continuous (pack years)
Biological	Age		Interval (years)
	Gender		Dichotomous (male / female)
	Antibody	RF (IgM)	Dichotomous (Present / absent)
	Antibody	ACPA	Dichotomous (present / absent)
Patient reported	EMS Fatigue VAS Pain VAS		Categorical Interval (cm) Interval (cm)
Social	Socioeconomic status, measured by index of multiple deprivation		Categorical (quartiles)
Multifactorial	Body mass index		Continuous
	Comorbidities		Dichotomous (present / absent)

ACPA, anti-citrullinated peptide antibodies, cyclic citrullinated peptide; cm, centimetres; EMS early morning stiffness; IgM, Immunoglobulin M; *HLA-DRB1*, *human leucocyte antigen DRB1*; RA, rheumatoid arthritis; RF, rheumatoid factor; VAS, visual analogue score.

2.5.3 Summary statistics and missing values

The data were summarised using means and standard deviations for normally distributed variables and percentages for dichotomous or categorical data. The software used was IBM SPSS statistics version 20.0.0.1, (SPSS Inc. Chicago, Illinois, 2011). Differences between the 2 cohorts were anticipated, as advances in contemporary treatment strategies were expected to have improved outcome with time, and therefore, the summary statistics were compared across YEAR B and YEAR C. Although data from YEAR B and C were analysed together, differences between the cohorts were accounted for in the analysis, as described in section 2.5.4.1. The quantity of missing data was

summarised as percentage of values missing overall and then percentage of values missing per variable. The number and percentage of patients who dropped out of the study were also reported, together with reasons for dropping out. Handling of missing values for the analysis of these data is discussed in 2.5.5

2.5.4 Statistical models

2.5.4.1 Cross sectional analysis: linear regression

Change in DAS28 and HAQ-DI were determined by subtracting these values at baseline from those at 6 and 12 months. Predictor variables were all added to the model simultaneously and included: age, gender, symptom duration, RF, duration of EMS, pain VAS, fatigue VAS, baseline DAS28, and for the analyses of change in HAQ-DI, baseline HAQ-DI was also included. Due to differences between cohorts, YEAR cohort (B or C) was also included as a covariate in the regression models and furthermore, in order determine whether the effects of the covariates in the models were different between the cohorts, interaction terms between cohort and each covariate were also included. The interaction terms were sequentially discarded if not statistically significant (the least significant terms were removed first, using a statistical significance, $p \leq 0.100$), until only significant interactions remained in the model. For EMS duration, which represented more than one category, a Wald test was used to determine whether the group effect of EMS category differed according to YEAR cohort and the interaction terms between cohort and EMS categories were discarded if $p>0.100$. Missing data within the outcome and predictor variables were handled using multiple imputation, which is described in detail in 2.5.5. Analysis of the data with complete cases was also reported, for comparison.

Several measures were taken to confirm that the assumptions of linear regression were not violated. Correlations between the variables were checked and correlation of >0.7 was considered too high for the assumption of multicollinearity. Histograms of the residual values, (where residuals were calculated by subtracting the value of the dependent variable predicted by the model from the actual value of the dependent variable) were used to judge adherence to the assumption of multivariate normality. For good model fit, residuals should be normally distributed with equal variance (homoscedasticity).

The latter was judged by examining plots of the residual versus fitted values, whereby no discernible pattern indicated homoscedasticity. The presence of outliers was detected by obtaining the standardised residual values, which were calculated by dividing the value of each residual by its standard error (SE) Observations with standardised residual values less than -3.3 or greater than 3.3 were considered to be outliers, as suggested by Pallant (2010).

Where available, R square values were determined in order to judge how much of the variance of the outcome parameter was explained by the models. Regression coefficients were recorded, along with SE and statistical significance, p, where $p<0.05$ was considered to be statistically significant. This analysis was performed using Stata, version 11.1, (Stata Corporation, College Station, Texas, USA 2009).

2.5.4.2 Longitudinal analysis: latent growth curve analysis

In structural equation modelling, path analysis and regression modelling are combined to test hypotheses relating to the 'causal' relationships between variables (Byrne, 2010). From this statistical technique latent growth analysis was developed, which facilitates analysis of change in a variable over time. Time is included in the model as a latent variable (a latent variable is one that is not directly measured) and the effect of time on the outcome variable is estimated. In its simplest, linear, form the latent growth curve describes the trajectory of a variable, y in terms of its intercept (value at baseline) and slope (rate of change). Thus:

$$y = a + bx$$

Where a is the value of the dependent variable, y at baseline (that is, when time, x =0) and b is the change in y per unit of time (x). In this example, a negative value of b indicates that y decreases with time, whilst a positive value indicates an increase.

The complexity of the model can be increased if necessary to include polynomial functions which describe non-linear change in a variable. For example, a quadratic growth curve is described as:

$$y = a + bx + cx^2$$

Here, the value of c indicates how the rate of change, b, alters with time. A negative value of c suggests that the rate of change of y slows with time, whereas a positive value indicates that the rate increases with time. Addition of further polynomial growth factors is possible, (x^3, x^4, x^5given an adequate number recorded values of variable y, but interpretation of the resulting model becomes complex.

Another type of longitudinal analysis is multilevel modelling (MLM). MLM is similar in many respects to the latent growth curve method and analysis of the same data in a multilevel regression model would yield similar estimates. Differences between multilevel models and latent growth curve models exist due to historical differences in the application of both techniques and the capabilities of each method within statistical packages. However, such differences and the distinction between the 2 methods are becoming less apparent with time (Hox and Stoel, 2005, Preacher *et al.*, 2008).

For the present study, three separate latent growth curve models were considered:

- A latent growth curve model of change in DAS28 over 24 months.
- A latent growth curve model of change in HAQ-DI over 24 months.
- A parallel process latent growth curve model to observe how HAQ-DI varies with DAS28 over 24 months.

Linear models were tested initially and then, in order to improve model fit, quadratic and then 'freed loading' models were tested. In the freed loading model, two of the factor loadings relating to linear slope were constrained and the remainder were freely estimated by the model. The effect of time on the outcome was fixed at zero for baseline measurement (0% of the change has occurred) and 1 for the outcome at 24 months (100% of the change has occurred). The other factor loadings were estimated by the model and represented a proportion of the total change; for example, a factor loading of 0.5 at 12 months would imply that half of the total change has occurred at this point. The final models were selected based upon indices of model fit (described in Section 2.5.4.2.1), whether the model was in keeping with expectations from published evidence, and with preference for a parsimonious model. The results

of the analyses were reported in terms of the intercepts, which represented the mean baseline DAS28 and HAQ-DI for the population, and the linear and quadratic slope parameters, which represented the changes in the outcome variable with time. The resulting model-implied growth curves were then plotted and compared to the observed mean values from the sample population. The variances of the latent variables were also noted, together with the indices of model fit.

Next, latent growth curves of DAS28 and HAQ-DI were applied to the data simultaneously and co-variances between the latent time variables (intercepts and slopes) were estimated. Thus, it was possible to determine how change in DAS28 affected change in HAQ-DI. The three linear models are shown in Figures 2-4 to 2-6.

The latent growth analysis was carried out using Mplus version 6.1 [Muthén, L. K., & Muthén, B. O. (1998-2011). Mplus User's Guide. Sixth Edition. Los Angeles, CA: Muthén & Muthén.]

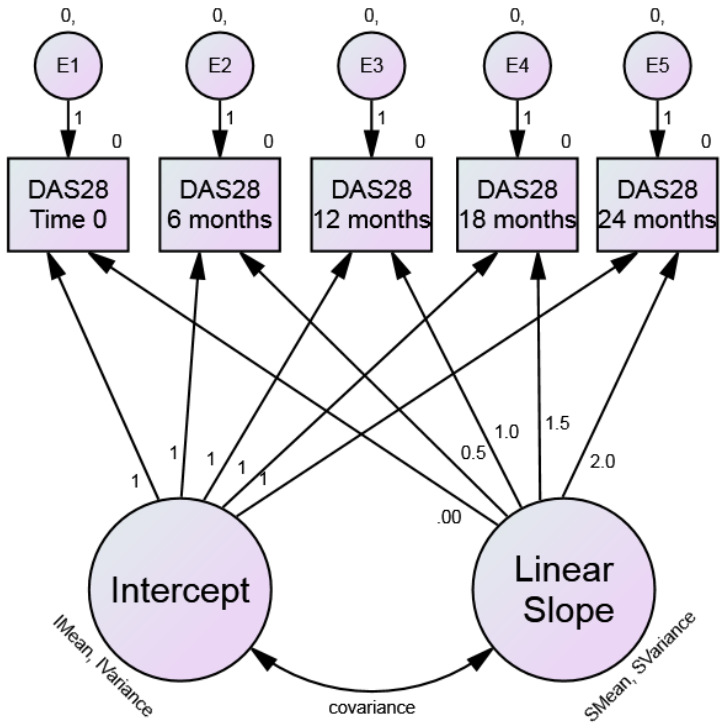

Figure 2-4 Latent growth curve model of change in Disease Activity Score from 28 joints (DAS28) over 24 months

See next paragraph for explanation of the model

DAS28, disease activity score from 28 joints; E1 to E5, error terms; IMean, mean intercept; IVariance, variance of intercept; SMean, slope mean; SVariance, slope variance.

Figure 2-4 is a path diagram representing the latent growth curve analysis of change in DAS28. Variables in rectangles are directly measured, whereas those in circles are latent variables (not directly observed). The influence of time on DAS28 is represented by the intercept (value of DAS28 at baseline) and linear slope (linear change in DAS28 per unit time). E1 to E5 represent the measurement error associated with DAS28 from baseline to 24 months, respectively. Parameters estimated by the model include the means and variances of the latent variables, plus the covariance of these. The numbers above the arrows from linear slope to DAS28 represent units of time elapsed since baseline: that is, 0, 0.5, 1, 1.5, 2 for baseline, 6 months, 12 months, 18 months, 24 months, respectively. The numbers above the arrows from the intercept to DAS28 are all set at 1.

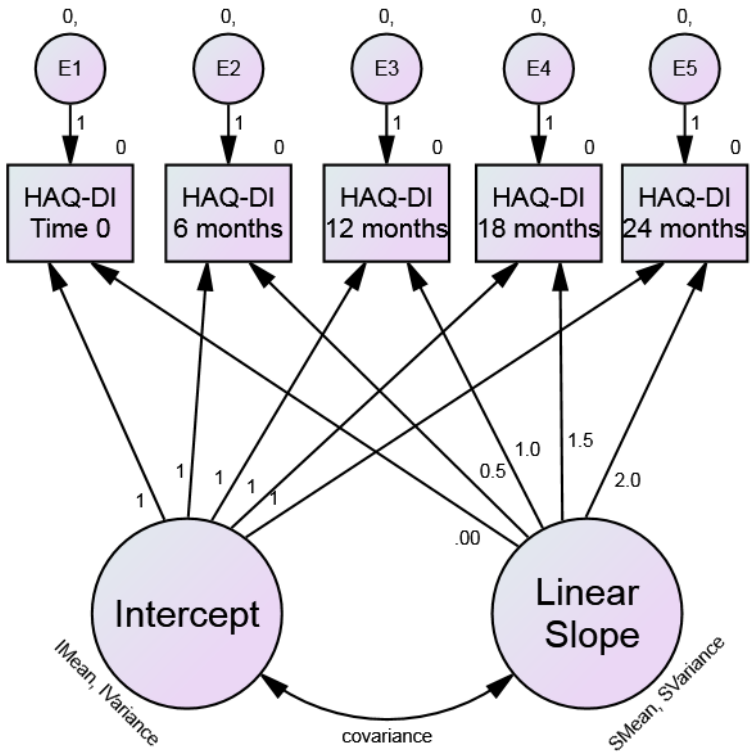

Figure 2-5 Latent growth curve of change in Disability Index of the Health Assessment Questionnaire (HAQ-DI) over 24 months
E1 to E5, error terms; HAQ-DI, disability index component of the health assessment questionnaire; IMean, mean intercept; IVariance, variance of intercept; SMean, slope mean; SVariance, slope variance.

Figure 2-5 is a path diagram of the latent growth curve analysis of change in HAQ-DI over 24 months and is similar to that of change in DAS28 shown in Figure 2-4. An amalgamation of these 2 models, illustrated in Figure 2-6, determined the effect of change in disease activity on change in disability. The co-variances between intercepts and slopes, as shown in the above diagram, reflect how change in one variable is affected by the other.

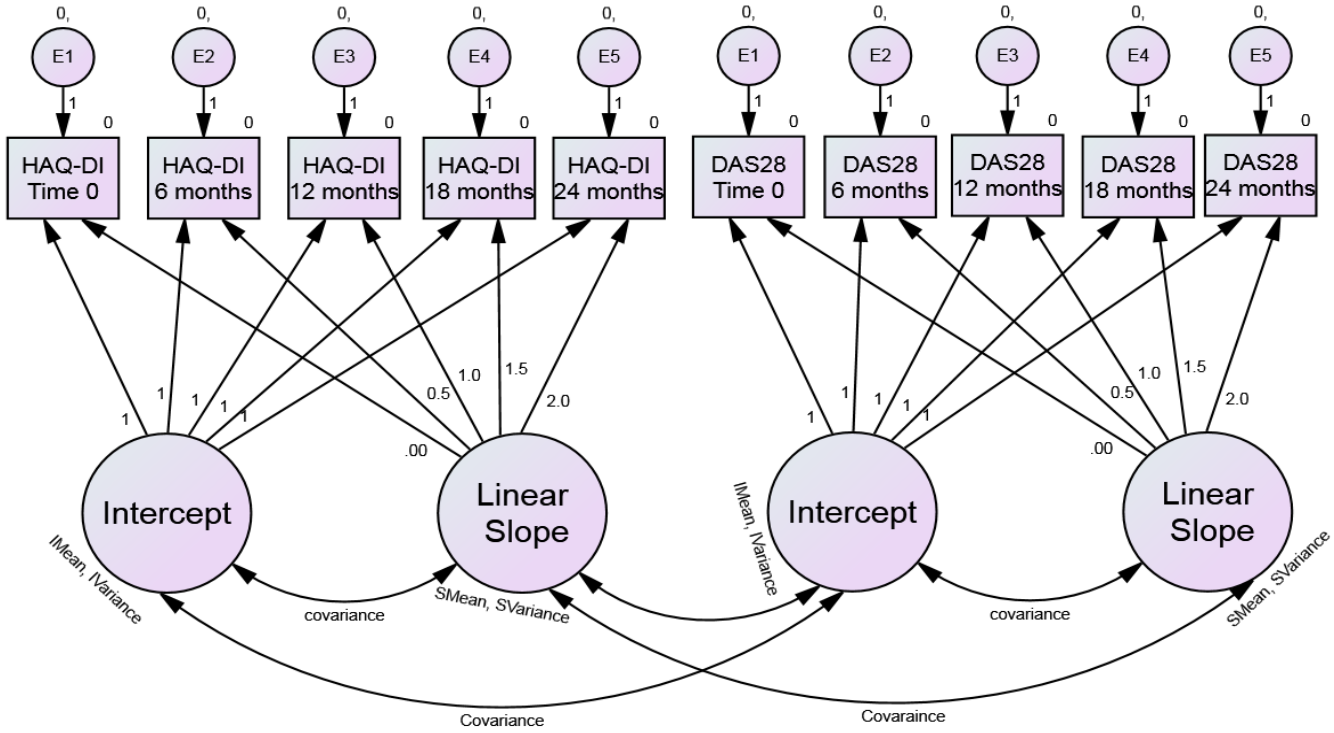

Figure 2-6 Parallel process growth model of change in Disease Activity Score from 28 joints (DAS28) and Disability Index of the Health Assessment Questionnaire (HAQ-DI) over 24 months

DAS28, disease activity score from 28 joints; E1 to E5, error terms; HAQ-DI, disability index component of the health assessment questionnaire; IMean, mean intercept; IVariance, variance of intercept; SMean, slope mean; SVariance, slope variance

2.5.4.2.1 Measures of model fit.

The fit of a structural equation model to the data to which it is applied can be judged using indices of fit, although there is much debate surrounding which are the best to use and how they should be interpreted. The chi square (χ^2) statistic is a well-established measure, calculated from the formula: $(N-1)F_{ML}$, where N is the sample size and F_{ML} is the minimum fit function under maximum likelihood estimation. If the sample size is large, it follows a central chi-square distribution with a number of degrees of freedom equal to that of the model under evaluation. A small value of χ^2 indicates superior fit of the model. From the central chi-square distribution, the χ^2 statistic, together with the number of degrees of freedom (df) of the model, can be used to obtain the probability, p, that the specified model is appropriate *and* could be applied to another sample of the same population and achieve a χ^2 statistic that is the same, or greater. Thus, a higher value of p indicates superior model fit (Byrne, 2010). A significance level of p>0.05 is often chosen. Although the χ^2 value is frequently used to assess model fit, there are some difficulties associated with its use, as discussed by Kline (2011): the value of χ^2 can be elevated by sample size and therefore, for very large samples (Kline suggests N≈5000), a significant p value can be obtained, despite good fit. Further problems discussed by Kline include inflated or reduced values of this statistic when the assumption of multivariate normality is not met and higher values if correlations between variables are high. Furthermore, if a study is under powered, the risk of accepting a poorly fitting model is high.

In contrast to the chi square statistic, which compares the covariance matrix implied by the model to that of the sample population and identifies discrepancies in excess of what would be expected by chance, or due to sampling error, the root mean square error of association (RMSEA) does not distinguish between model fit and discrepancy due to sampling error and is considered to be an approximate fit index. The RMSEA is derived from the formula:

$$RMSEA = \sqrt{\frac{\chi_M^2 - df_M}{df_M(N-1)}}$$

Where χ_M^2 is the chi-square value for the model; df_M is the number of degrees of freedom of the model and N is the sample size. Values of RMSEA that are closer to 0 indicate superior fit. Byrne (2010) has summarised popular interpretation of the RMSEA value as follows: <0.05 indicates good model fit; 0.05 to 0.08 is 'reasonable'; 0.08 to 0.1 'mediocre' and >0.1 is poor. However, cautious interpretation of all fit indices is advocated, as it may not be appropriate to apply rules such as these to all models or all studies (Kline, 2011). RMSEA and other indices of fit should be interpreted alongside measures of overall model fit and consideration of whether the results of the model are in keeping with researcher's expectations and contemporary evidence.

The comparative fit index (CFI) is a measure of how well a model performs, relative to a baseline (or independence) model, in which covariances between variables from the sample population are assumed to be zero. It is derived from the formula:

$$CFI = \frac{\chi_M^2 - df_M}{\chi_B^2 - df_B}$$

Where χ_M^2 is the chi-square value for the model under scrutiny; df_M is the number of degrees of freedom of this model; χ_B^2 is the chi-square value for the baseline model; and df_B is the respective number of degrees of freedom. The three measures discussed here (chi square, RMSEA and CFI) were chosen to describe model fit of the latent growth curve analyses of DAS28 and HAQ-DI. In addition, the standardised residuals covariances, which are a measure of the residual difference between the model implied covariances and those derived from the sample population, were also reported. The assumption of multivariate normality was checked for the models.

2.5.4.3 Latent class growth analysis.

Latent growth curve models describe change in outcome over time, but the sample population is treated as one large group and the results represent

mean change for the whole cohort. Clinical experience demonstrates that inter-individual variation in RA outcome is likely to be significant. For example, some patients may have more aggressive forms of RA and experience greater disease activity than others. Similarly, patients respond differently to treatment with the same medication. Latent class growth analysis (LCGA) can be applied to test the hypothesis that there are distinct groups of cases within a population, whereby each group follows a defined growth curve, or trajectory. LCGA is a specific form of growth mixture modelling (GMM), in which groups of patients following a specific trajectory are identified, but the variation within groups is assumed to be zero. That is, the values of the mean intercept, linear and quadratic slopes are estimated for each group, but the variances of these parameters are constrained to zero (Dalhy, 2012). There is some debate surrounding the most suitable indicator of the optimal number of growth trajectories, but the Bayesian Information Criterion (BIC) is popular as it has been shown to perform well (Jung and Wickrama, 2008). Furthermore, the number of trajectories should be chosen with consideration of additional factors, including parsimony and interpretability of the model.

The present analyses were performed to test the hypotheses that there are distinct groups of patients with early RA, with each group following a defined growth curve, or trajectory for DAS28 and HAQ-DI. The values of Akaike information criterion (AIC) and BIC were compared for models with successive numbers of trajectories and smaller values of BIC and AIC indicated improved fit. In addition entropy, Lo, Mendell and Rubin likelihood ratio test (LMR-LRT) and the bootstrap likelihood ratio test (BLRT) were also considered. For the latter 2 tests, a significance level of $p<0.05$ was selected to indicate that the model fit was superior to a model with one less trajectory. Entropy is not exactly an indicator of model fit, but indicates how well subjects from the sample are classified into the trajectories described. It ranges from 0 to 1, with values approaching 1 indicating superior classification (Celeux and Soromenho, 1996).

The results of the LCGA were reported in terms of:

- The number of trajectory classes identified
- The number of cases allocated to each class

- Average latent class probabilities for most likely latent class membership
- A description of each trajectory
- A graphical representation of each trajectory, compared to the mean values observed for cases grouped into each class

Once the number of trajectories was identified and each trajectory class described as above, variables predictive of class membership were tested using multinomial logistic regression. Predictor variables applied to this analysis were: YEAR cohort, gender, RF positivity, ACPA positivity, *HLA-DRB1*-shared epitope positivity, and IMD quartile. A sub-analysis of YEAR C data was also carried out to test the hypothesis that DAS28 and HAQ-DI are influenced by the three additional variables: smoking (pack years), obesity (BMI), and comorbidities (present or absent).

Using the numbers of trajectories for DAS28 and HAQ-DI identified by the latent class growth analyses, a dual trajectory analysis (Nagin and Tremblay, 2001) was conducted. That is, the trajectories of DAS28 and HAQ-DI were estimated simultaneously by a model that combined the parallel process model described in Section 2.5.4.2 and LCGA. The trajectories estimated by the model were described and compared to previous trajectories of DAS28 and HAQ-DI identified by the LCGA. It was then possible to determine the probability of a patient being assigned to one HAQ-DI trajectory group, based upon their DAS28 trajectory group. Predictors of DAS28 / HAQ-DI dual trajectory class were obtained using multinomial logistic regression.

2.5.4.3.1 Post-hoc analysis: non-inflammatory causes of patient reported disease activity and disability

Once the trajectory groups were identified, consideration was given to potential factors contributing to HAQ-DI, other than inflammation due to RA. These included increased age, comorbidity and non-inflammatory causes of pain and disability such as psychological distress and passive coping. Whilst age in years was readily available in this cohort, data were not collected on indices of psychological distress and data on comorbidity were limited. As an indicator of non-inflammatory components of disease, a ‘DAS28-P’ index was calculated, which was similar to the index described by McWilliams and

colleagues (reviewed in Chapter 1, Section 1.8.1). In YEAR, baseline ESR was missing in 36% of cases, compared to 8% missing for CRP, so a DAS28-P index was calculated using the CRP instead of ESR, by modifying the formula described by McWilliams *et al.* Thus, the DAS28-P(CRP) index was calculated as follows:

$$\frac{(0.56 \times \sqrt{TJC28}) + (0.014 \times VAS)}{(0.28 \times \sqrt{SJC28}) + (0.56 \times \sqrt{TJC28}) + 0.36 \times \ln(CRP+1) + (0.014 \times VAS) + 0.96}$$

The DAS28-P(CRP) index was included as a covariate in the multinomial logistic regression model of predictors of DAS28/HAQ-DI dual trajectory.

Due to the limited information collected on co-morbidities (described in Table 2-2), and the large quantity of missing data on this variable (described in Chapter 3, Section 3.4), it was not possible to add this covariate into the regression models. Instead, numbers of co morbidities were compared across DAS28 / HAQ-DI dual trajectory groups.

The LCGA, multinomial logistic regression analyses and dual trajectory analysis were carried out using Mplus version 6.1 [Muthén, L. K., & Muthén, B. O. (1998-2011). Mplus User's Guide. Sixth Edition. Los Angeles, CA: Muthén & Muthén.].

2.5.5 Handling of missing data

All subjects who gave consent to participate in YEAR B or C, with recorded symptom durations of 24 months or less, were included in the linear regression analyses, regardless of the quantity of missing data. For the latent growth curves and LCGA, a small number of cases could not be included as there were no recorded DAS28 or HAQ-DI values available (detailed in Chapter 3, Section 3.4).

The data were inspected in order to determine whether variables were normally distributed and the pattern of missingness and any causes for missing values were determined. Data were assumed to be MAR. To account for missing data in the linear regression analysis, MI was carried out using Stata for windows version 21.1 (Statacorp LP, Texas, USA), whilst maximum likelihood estimation was used for the latent growth curve models

and LCGA. Maximum likelihood was chosen for this analysis as evidence from simulation studies indicate that it is as robust as multiple imputation (Chapter 1 paragraph.1.7.2.2.) and in addition, it is the default method for handling missing data used by the Mplus program.

2.5.5.1 Auxiliary variables

Auxiliary variables are collected from the sample population and are not covariates in the final statistical model; they are either correlated with the value of the variable(s) with missing data, or are correlated with the fact that it is missing. Including auxiliary variables in the imputation model reduces bias in the estimates obtained from the analysis model and ideally, collection of auxiliary variables should be considered during the design of a study. For example, ESR can be a used as an auxiliary variable in an imputation model for CRP. Auxiliary variables were investigated in a simulation study by Collins et al. (2001), who concluded that an 'inclusive approach', in which all auxiliary variables were incorporated into the imputation model, produced less bias than more conservative methods.

In the YEAR dataset, variables had not been collected specifically to include as auxiliary components to imputation models. Pearson correlations between variables in the analysis models and others in the dataset were used to judge which would be suitable for application as auxiliary variables and are presented in Chapter 3, 3.5. Initially, the suggested correlation of r ≥0.5 proposed by Graham (2009) was considered as a cut- off for inclusion of an auxiliary variable. However, as this approach would have resulted in the inclusion of 12 auxiliary variables in the MI model in addition to the 11 variables already included in the linear regression analysis, a more conservative cut-off of a Pearson correlation of ≥0.7 was used instead. This approach was adopted in order to avoid bias which can occur if too many auxiliary variables are included in an MI model, especially where the correlation between variables is low (less than 0.7) and the ratio of complete cases to variables in the model is also low, resulting in too many parameters in the regression model (Hardt *et al.*, 2012). As the auxiliary variables selected also contained missing data, there was an additional potential for bias if too many auxiliary variables were included. In addition to correlation

with imputed variables, auxiliary variables were also considered if they were predictive of missingness, which was determined using logistic regression. Auxiliary variables were selected if odds ratios for predicting missingness were statistically significant and either less than 0.9 or greater than 1.2.

2.5.5.2 Multiple imputation

The MI model included all variables in the analysis model (including outcome variables) and auxiliary variables from the YEAR dataset, as discussed in paragraph 2.5.5.1. Imputed variables were baseline RF, ACPA, pain and fatigue VAS, DAS28, EMS, and HAQ-DI, 6 month DAS28 and HAQ-DI, and 12 month DAS28 and HAQ-DI. Ten imputed datasets were generated, via an iterative Marcov-chain Monte Carlo method using chained equations with predictive mean matching (pmm) for continuous variables (DAS28, HAQ-DI, EMS baseline fatigue VAS and baseline pain VAS) and logistic regression for baseline RF and ACPA status. To account for differences between the 2 cohorts, the imputation model included a 'by' specification, so that data from YEAR B was used to impute missing YEAR B variables and the same rule applied for YEAR C data. EMS was imputed as a continuous variable and then collapsed into categories. Changes in DAS28 after 6 and 12 months were calculated as separate variables in the imputed dataset, to be applied as the outcome variable in the linear regression analyses that followed. The Stata syntax for the MI procedure for the YEAR dataset is shown in Box 1. Here, the initial command '`mi impute chained`' instructed the program to impute missing values using chained equations. This was followed by the type of model used for imputation, predictive mean matching: '`(pmm)`' and then the variables to be imputed. Where '`(Logit)`' was specified, logistic regression was used to impute RF and ACPA. As mentioned above, the '`by(YEAR_cohort)`'command was added so that missing data from YEAR B or C were only imputed using data from the same cohort. Finally, the '`add (10)`'component of the syntax was included to indicate that 10 imputations were to be added. Auxiliary variables were included in the imputation models, as described in Paragraph 2.5.5.1, but these variables also contained missing data and were therefore imputed alongside the variables for the analysis

model. If the auxiliary variables were not imputed, the resulting datasets contained missing values.

```
mi impute chained (pmm) DASCRP3v_1 PAIN_RANGE1
FATIGUE_RANGE1 RaschHAQ_1 EMS1 DAS28CRP3_6 RaschHAQ_6
DAS28CRP3_12 RaschHAQ_12 (logit) RF1 ACPA(pmm) DAS28CRP3_3
TJC28_1 TJC28_6 SJC28_6 TJC28_12 SJC28_12 = Gender AgeBL S_D,
by (YEAR_cohort) add (10)
```

Box 1 Stata syntax for multiple imputation of Yorkshire Early Arthritis Register data

See text (Section 2.5.5.2) for explanation of syntax.
Variables were coded as follows: ACPA,anti-citrullinated peptide antibodies (positive or negative); AgeBL, patient age (in years) at baseline; EMS1, early morning stiffness at baseline (minutes); FATIGUE_RANGE1, Fatigue visual analogue score at baseline; DAS28CRP3v_1, DAS28CRP3_3, DAS28CRP3_6, DAS28CRP3_12, disease activity score based upon count of 28 joints and C-reactive protein at baseline, 3, 6 and 12 months, respectively; PAIN_RANGE1, pain visual analogue score at baseline; RaschHAQ_1, RaschHAQ_6, RaschHAQ_12, Rasch transformed health assessment questionnaire score at baseline, 6 and 12 months, respectively; RF1, rheumatoid factor positive or negative at baseline; S_D, symptom duration at baseline; SJC28_6, SJC28_12, swollen joint count (from a total of 28 joints) at 6 and 12 months, respectively; TJC28_1, TJC28_6, TJC28_12, tender joint count (from a total of 28 joints) at baseline, 6 and 12 months, respectively; YEAR_cohort, Yorkshire Early Arthritis Register cohort (B or C).

Variables with fewest missing values were imputed first, which is the default order of the Stata program. For YEAR B, the order of imputation was: baseline TJC, baseline EMS, pain VAS, HAQ-DI (baseline), RF, fatigue VAS, DAS28 (baseline), TJC (6 months), SJC (6 months), HAQ-DI (6 months), TJC (12 months), SJC (12 months), HAQ-DI (12 months), DAS28 (3 months), DAS28 (6 months), DAS28 (12 months) and then ACPA. For YEAR C, the imputation order was: EMS, HAQ-DI (baseline), baseline TJC, pain VAS, RF, fatigue VAS, DAS28 (baseline), DAS28 (3 months), TJC (12 months), HAQ-DI (6 months), SJC (12 months), HAQ-DI (12 months), SJC (6 months), TJC (6 months), DAS28 (12 months), DAS28 (6 months), then ACPA. Following imputation of missing values and generation of 10 complete datasets, the data were summarised using means of continuous variables and percentages of categorical variables. These statistics were then compared to those of the original dataset to demonstrate that imputed values were reasonable.

Linear regression models of predictors of baseline DAS28, HAQ-DI and change in these outcomes at 6 and 12 months were applied to the dataset and the estimates were merged, as described by Rubin (1987). The MI results were compared to those of a complete case analysis and explanations sought for any differences in results between the 2 analyses, as suggested in published guidelines on the reporting of MI analyses (Sterne *et al.*, 2009). The reasons for conducting this comparison were twofold: firstly, to see how missing data may have affected the analysis and second, to check for discrepancies that may highlight flaws in the imputation model, such as those identified by Hippisley-cox and colleagues (2007), which resulted in revision of their cardiovascular risk model.

2.5.5.3 Maximum likelihood estimation for incomplete data.

This default method for handling missing data employed by statistical packages with structural equation modelling capacity was utilised when the latent growth curve models and LCGA models were estimated.

2.6 Summary of analytical approach

The statistical techniques used to analyse the YEAR data in this Thesis are both cross section and longitudinal. An initial exploration of baseline predictors of change in DAS28 and HAQ-DI after 6 and 12 months, which is cross sectional, used linear regression. To avoid bias caused by missing data, MI was employed for these analyses. The longitudinal analyses of change in DAS28 and HAQ-DI over 24 months included latent growth models, which described change over time, and LCGA, which identified trajectory classes of change in outcome within the sample population. These models used maximum likelihood estimation to avoid bias due to missing data. Multinomial logistic regression was used to identify baseline predictors of trajectory class. The following chapters contain the results of the analysis of YEAR data, starting with a description of the cohort and an explanation of how auxiliary variables (for missing data management) were selected, in Chapter 3. Chapter 4 addresses change in disease activity, whilst change in disability is described in Chapter 5. The final results Chapter 6 addresses how change in disease activity influenced change in disability, using a parallel process growth curve model and dual trajectory analysis to describe this relationship.

Chapter 3 Methods 2: summary statistics and missing data

3.1 Introduction

The objectives of the present Chapter are to summarise the baseline demographic and clinical characteristics of cases recruited to YEAR, account for missing values and explain how auxiliary variables were sought from all available data so that missing values could be handled in subsequent statistical models. Methods applied to manage missing data for analyses within this Thesis were detailed in 2.5.5, including the use of auxiliary variables to reduce bias. The quantity of missing data are presented and reasons for missingness are given, where possible. Patterns of missing data are described and also correlations between auxiliary variables and variables used as covariates in the analyses. Furthermore, results of logistic regression analyses that were completed in order to identify predictors of missing values are also presented here.

3.2 Description and comparison of Yorkshire Early Arthritis Register B and C cohorts

Between 1997 and 2002, 783 RA patients were recruited to YEAR B, and 831 were recruited to YEAR C between 2002 and 2009. Of these cases, 18 withdrew consent and were therefore excluded from YEAR B and 9 withdrew consent from YEAR C. During the course of follow up of some patients, an alternative diagnosis became apparent and the previous diagnosis of RA was considered to be no longer valid: such patients were removed from the database. In YEAR B, there were 16 cases of alternative diagnosis, which included; osteoarthritis (6), psoriatic arthritis (2), gout (1), fibromyalgia (1), ankylosing spondylitis (1) and in 5 cases, the alternative diagnosis was unrecorded. In YEAR C, alternative diagnoses included; osteoarthritis (2), psoriatic arthritis (2), reactive arthritis (1) and one unrecorded alternative diagnosis. Cases excluded because symptom duration exceeded 24 months totalled 26 from YEAR B and 25 from YEAR C. Although the selection criteria for entry into the YEAR cohort included patients with a symptom duration of less than 12 months, this part of the criteria was occasionally overlooked in practice, and patients were included despite

documented symptom durations of up to 15 years in YEAR B (median symptom duration 6.5 months, range 1 to 180 months) and 13 years in YEAR C (median symptom duration 7.2 months, range 1 to 156 months). In such cases, YEAR clinical record forms (and hospital records, where available) confirmed that individuals had a longstanding consultant- made diagnosis of RA and / or had received treatment with DMARDs for several years. Although such deviations from the protocol occurred infrequently, they highlighted the importance of regular training for data collectors, especially as new study nurses and doctors became involved as the study progressed. Patients with symptom durations exceeding that specified by the protocol were more likely to be included in YEAR if they were recruited from Airedale hospital (where the mean symptom duration of the 18 patients included was 16.0 months), St James's hospital, (mean from 22 cases was 10.7 months), or Barnsley hospital (mean symptom duration of 51 cases was 10.0) Forty one (YEAR B) and 57 (YEAR C) cases excluded because symptom duration was not recorded. A total of 691 cases from YEAR B and 725 cases from YEAR C were therefore included in the analyses. This information is illustrated in Figure 3-1.

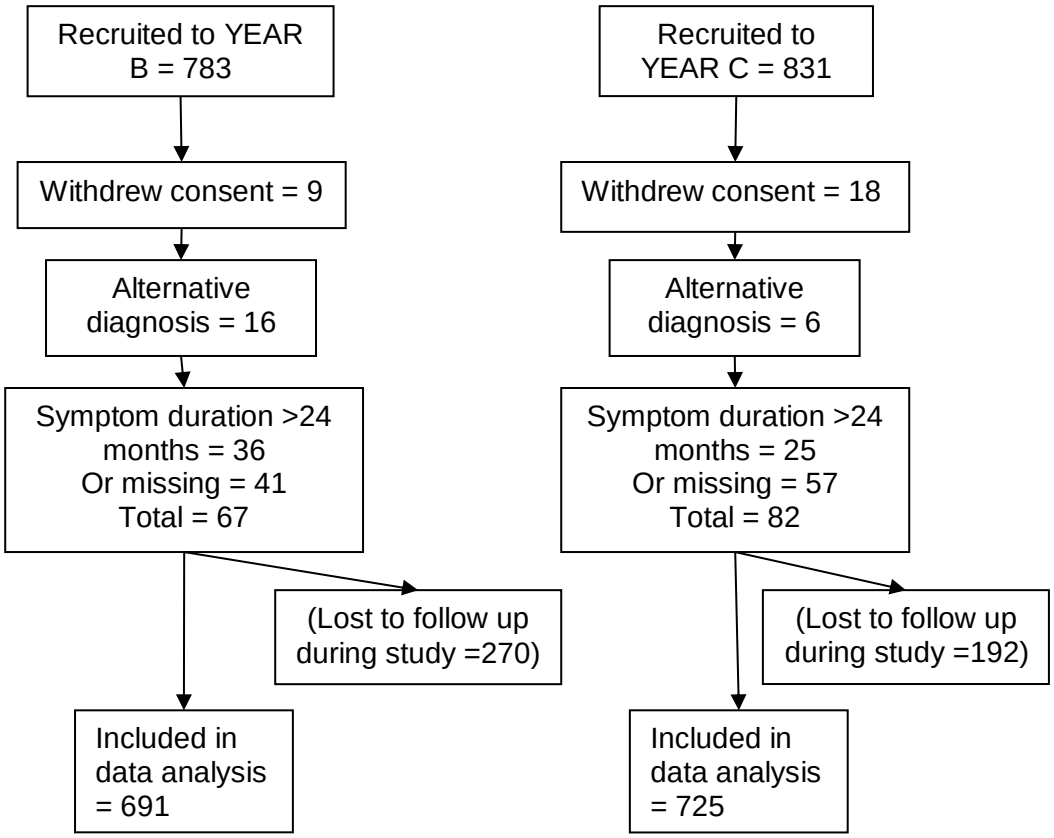

Figure 3-1 Diagram to illustrate the numbers of cases included in the analyses of data from Yorkshire Early Arthritis Register
YEAR, Yorkshire Early Arthritis Register

YEAR B and C can be considered consistent with other early RA cohorts, (reviewed in 1.7.1 and Table 1-2) with 65-67% females, 70-71% RF positive and 64-65% of those tested ACPA positive; however, there were some differences between the 2 YEAR cohorts. As detailed in Table 3-1, which gives summary statistics for YEAR B and YEAR C, participants of YEAR C had lower DAS28 and HAQ-DI at baseline, 6 and 12 months. This difference is most likely due to the fact that some patients, who could have been recruited to YEAR C, were instead enrolled into the randomised controlled trials described in Chapter 2, Paragraph 2.1.1, and that for 2 of these studies, baseline disease activity was higher than that of patients from the YEAR C cohort. The mean baseline DAS28 of 145 cases in the PROWD study (Bejarano *et al.*, 2008) was 6.0 and the mean baseline DAS28 of 112 cases included in the IDEA study (Nam *et al.*, 2014a) was 5.0 in cases who received MTX and 5.5 in those who received Infliximab. However, in the EMPIRE study, mean baseline DAS28 was lower than that

of the YEAR C cohort: the study recruited 110 cases and the mean baseline DAS28 was 4.17 in the placebo group and 4.10 in the treatment group (Nam JL 2013). The mean symptom duration at baseline was longer for YEAR C participants (7.5 months, compared to 6.5 months), which was unexpected: prompt referral from primary care should facilitate early treatment and therefore, with improved treatment strategies and communication with primary care, reduced baseline symptom duration with time was anticipated.

3.2.1 Biological therapies

During follow up, 7 YEAR C patients started treatment with TNF inhibitors. In 1 case, infliximab was started 9 months after the baseline visit and in 2 cases it was started after 12 months. Etanercept was started after 18 months in 3 cases and one further case started adalimumab after 12 months. All were included in subsequent analyses No subjects in YEAR B started treatment with biological therapies during the 24 month follow up period.

Table 3-1 Description of Yorkshire Early Arthritis Register B and C cohorts

		YEAR B N=691		YEAR C N=725	
Categorical data: N (%)					
Female gender		448	(65)	485	(67)
Ethnicity:	Caucasian	641	(97)	672	(95)
	Non Caucasian	22	(3)	35	(5)
Comorbidities:	None	241	(35)	363	(50)
	Any	104	(15)	250	(34)
	Hypertension	86	(12)	163	(23)
	Ischaemic heart disease	31	(5)	77	(10)
	Diabetes	23	(3)	43	(6)
	Chronic airways disease	50	(7)	84	(12)
	Renal disease	5	(1)	17	(2)
	Cerebrovascular disease	5	(1)	29	(4)
	Peripheral vascular disease	4	(1)	25	(3)
	Chronic liver disease	1	(0)	6	(1)
RF positive		448	(71)	465	(70)
ACPA positive		244	(65)	309	(64)
HLA-DRB1 'Shared Epitope' positive		266	(72)	421	(66)
Current or ex-smoker		Not available		433	(61)
Baseline EMS	0-35 minutes	158	(23)	255	(35)
	40-75 minutes	170	(25)	159	(22)
	90-210 minutes	231	(33)	140	(19)
	≥220 minutes	132	(19)	171	(24)

Table 3-1, continued.

		YEAR B		YEAR C	
Continuous data: mean (SD)					
Age (years)		57.7	(14.3)	57.6	(14.1)
Symptom duration (months)		6.5	(4.3)	7.5	(4.3)
Baseline VAS pain (cm)		6.3	(2.7)	5.8	(2.6)
Baseline VAS fatigue (cm)		4.8	(3.2)	4.5	(3.3)
Body mass index (Kg/m^2)		Not available		27.3	(6.0)
DAS28	Baseline	5.3	(1.3)	4.7	(1.5)
	6 months	3.8	(1.6)	3.5	(1.5)
	12 months	3.4	(1.5)	3.0	(1.4)
HAQ-DI	Baseline	10.2	(4.5)	9.4	(4.6)
	6 months	8.1	(5.1)	7.4	(5.1)
	12 months	7.6	(5.0)	6.7	(5.1)

Missing values were excluded from total number of cases when percentages were calculated. Percentages given are rounded to nearest per cent and standard deviations to one decimal place.
ACPA, anti-citrullinated peptide antibodies, cm, centimetres; DAS28, disease activity score based upon count of 28 joints; EMS, early morning stiffness; HAQ-DI, disability index of health assessment questionnaire; *HLA-DRB1, human leucocyte antigen DRB1* gene; Kg/m^2, kilograms per metre squared; N, number of participants; RF, rheumatoid factor; SD, standard deviation; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register.

3.3 Variable distributions.

Histograms of continuous variables revealed that age, DAS28 and HAQ-DI at baseline were approximately normally distributed for both YEAR cohorts (Appendix 6, Figures 6A to 6G). The histograms of symptom duration at baseline (Figure 6B) showed positively skewed distributions, with more patients having shorter symptom duration at baseline (cases with symptom duration of over 24 months were excluded as described in 3.2 and Chapter 2, 2.5). The distributions of pain and fatigue VAS (Figure 6C and 6D, respectively) were affected by the modal values for these variables: for fatigue, the most commonly recorded VAS was 0 cm (148 cases in YEAR B and 159 in YEAR C), whilst for pain, this value was 10 cm, reported by 62 patients in YEAR B and 46 in YEAR C. The histograms of change in HAQ-DI after 6 and 12 months (Figures 6F and 6G) revealed that the most

common value was 0, or no change from baseline. For YEAR B, there was no change in HAQ-DI in 54 and 45 cases after 6 and 12 months, respectively, whilst in YEAR C there was no change in HAQ-DI for 79 cases after 6 months and 57 cases after 12 months. As expected HAQ-DI improved for most cases (so that there was negative change), and therefore these distributions were all negatively skewed. Although some variables were not normally distributed, they were not transformed prior to inclusion in the regression models so that results were more readily interpreted. Instead, multivariate normality was assessed after the linear regression models were applied to the data of the complete cases.

3.4 Missing data

Missing values for the analyses in this Thesis are listed in Table 3-2. From a possible 41,789 observations (20,039 from YEAR B and 21,750 from YEAR C), there were 9,105 (22%) missing. It is difficult to compare the quantity of missing data to that of other cohorts as it is not often reported, or if it is, the rate of missingness usually refers to a single variable. For example, in ERAS, drug start and stop dates were the most frequently missing at around 10% and the main clinical and laboratory measures were non-missing in 94% of cases (Young *et al.*, 2011). These data suggest that YEAR contained more missing values than ERAS and it is likely that the methods of data management, including reminding patients to attend appointments, were more effective in ERAS.

As illustrated in Table 3-2, more data were missing from YEAR B than YEAR C (29% vs. 15%, respectively). The most frequently missing data were presence or absence of comorbidities in YEAR B, with up to 51% of values not recorded (Table 3-2). Data on the presence of the *HLA-DRB1* shared epitope and ACPA were more frequently missing from YEAR B than YEAR C (46% vs. 14% and 46% vs. 33%, respectively). As mentioned in 2.2.4.3, some of this information was obtained from analysis of stored blood samples, but if no stored sample was available, patients were contacted and asked to provide them retrospectively. This was more successful for the

patients from YEAR C, who had been involved with the YEAR project more recently. Therefore, this discrepancy was expected.

In some cases, either DAS28 or HAQ-DI was not captured at any point during follow up and in 1 case, neither DAS28 nor HAQ-DI were captured. In YEAR B, there were 6 cases where DAS28 was never captured and 5 cases where HAQ-DI was missing at all visits. In YEAR C, there were 12 cases where no DAS28 was recorded and 1 case with no HAQ-DI values. Such cases were excluded from the latent growth curve and LCGA analyses because, although missing data were accounted for using maximum likelihood estimation in the growth curve analyses, (outlined in Section 2.5.5.3), this was not possible for cases where all values of the outcome variable were missing.

Table 3-2 Missing values in Yorkshire Early Arthritis Register

Variables			Missing observations: N (%) YEAR B (Total N=691)		YEAR C (Total N=725)	
Female gender			0	(0)	0	(0)
Ethnicity			28	(4)	18	(3)
Age in years			0	(0)	0	(0)
Symptom duration in months			0	(0)	0	(0)
Current or ex-smoker			Not available		17	(2)
Index of multiple deprivation			55	(8)	35	(5)
Comorbidities	Hypertension		319	(46)	72	(10)
	Ischaemic heart disease		332	(48)	58	(8)
	Diabetes		332	(48)	65	(9)
	Chronic airways disease		354	(45)	60	(8)
	Renal disease		356	(49)	59	(8)
	Cerebrovascular disease		356	(49)	59	(8)
	Peripheral vascular disease		339	(49)	6	(8)
	Chronic liver disease		338	(51)	57	(8)
Baseline EMS			12	(2)	33	(5)
RF			25	(4)	57	(8)
ACPA			315	(46)	239	(33)
HLA-DRB1 Shared Epitope			320	(46)	105	(14)
Baseline VAS pain			13	(3)	54	(7)
Baseline VAS fatigue			38	(5)	94	(13)
DAS28		Baseline	55	(8)	102	(14)
		3 months	219	(32)	104	(14)
		6 months	229	(33)	221	(31)
		12 months	229	(33)	182	(25)
		18 months	337	(49)	242	(33)
		24 months	323	(47)	244	(30)
HAQ-DI		Baseline	25	(4)	47	(6)
		6 months	160	(23)	143	(20)
		12 months	199	(29)	146	(20)
		18 months	279	(40)	199	(27)
		24 months	288	(42)	512	(30)

Table 3-2, continued

Total observations expected: N	20039	21750
Total observations missing: N (%)	5875 (29)	3230 (15)

ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score based upon count of 28 joints; EMS, early morning stiffness; HAQ-DI, disability index of health assessment questionnaire; *HLA-DRB1*, human leucocyte antigen DRB1; N, number of observations; RF, rheumatoid factor; SD, standard deviation; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register.

3.4.1 Reasons for missing values

The most common reason for missing data was failure to attend scheduled appointments. The numbers of cases from YEAR B and C who attended at each data collection time point are listed in Table 3-3. For YEAR B, the number of cases with data recorded for each visit declined from baseline, until the final, 24 month visit. Data collection for YEAR C declined until 12 and 18 months, with numbers of cases captured at these time points exceeding that of the previous, 9 month visit. These fluctuations in numbers of patients attending appointments likely reflect the efforts of the study team to contact non- attenders and encourage attendance at subsequent visits.

Table 3-3 Numbers of cases attending data collection visits in the Yorkshire Early Arthritis Register

Time	YEAR B	YEAR C	Total YEAR (B+C)
Baseline	691	725	1416
3 months	606	621	1227
6 months	564	597	1161
9 months	No visit	556	556
12 months	514	617	1131
18 months	430	558	988
24 months	421	532	1016

YEAR, Yorkshire Early Arthritis Register.

3.4.1.1 Loss to follow up

In some cases, patients recruited to the YEAR cohorts were lost to follow up altogether, which was also frequently due to non-attendance. The numbers of cases lost to follow up increased with time, as shown in Table 3-4, and were greater in YEAR B than C. This is likely due to improved data

management in YEAR C, where patients were more often contacted in the event of failure to meet a scheduled appointment. A total of 270 (40%) patients were lost to follow up from YEAR B and as mentioned above, the most common reason for this was non-attendance at scheduled appointments. Attrition occurred when patients moved away (10), died (9), withdrew from the study when they no longer wished to participate in data collection (9), required biological therapy (3), or if co-morbid conditions such as cancer (2) or dementia (1) made attendance and data collection difficult. For all other cases lost to follow up from YEAR B (236), no reasons other than non-attendance at scheduled appointments were recorded. From YEAR C, 193 (26%) cases were lost to follow up. This occurred if subjects died (15), moved away (9), required biological therapy (9), or decided not to continue with data collection (8). The remaining 151 cases lost to follow up were unexplained despite attempts to uncover reasons behind such attrition through hospital records.

Table 3-4 Cumulative numbers of cases lost to follow up

	YEAR B N=691 Lost to follow up (%)	YEAR C N=725 Lost to follow up (%)
Baseline	0 (0)	0 (0)
3 months	33 (5)	23 (3)
6 months	71 (10)	35 (5)
9 months	No visit	55 (8)
12 months	135 (20)	69 (10)
18 months	206 (30)	113 (16)
24 months	270 (40)	192 (26)

N, total number of cases; YEAR, Yorkshire Early Arthritis Register

Cases lost to follow up were slightly younger than those who were not (mean age of 56.9, versus 58.1 years). They also had a slightly higher baseline HAQ-DI (10.2, compared to 9.6), baseline pain VAS (6.2, versus 6.0cm) and duration of EMS (154 minutes, compared to 142). However, baseline DAS28 and fatigue VAS were the same (5.0 and 5.3cm, respectively), irrespective of whether cases completed 24 months' of follow up.

3.4.1.2 Incomplete data collection and missing data patterns

Another cause of missing data, other than non- attendance at appointments, was omission by the data collector. When this occurred some, but not all, of

the data for a specific visit were recorded. This is evident from the patterns of missing data, which are shown in Figure 3-2 (A and B). In this Figure, missing values are indicated by a red bar and observed values are white. Missing data patterns, which represent groups of cases with identical combinations of missing observations, are numbered for descriptive purposes. The overall missing data patterns were non- monotone. In YEAR B over 80% of cases had no missing data at baseline (corresponding to pattern 1, shown in Figure 3-2 (A), YEAR B), but the most common pattern of missingness, which represented 6% of cases at baseline, was missing CRP and DAS28 (corresponding to pattern 15 in Figure 3-2 (A) YEAR B), despite efforts to look up CRP values on hospital databases during the data validation and cleaning process. A likely explanation for this is that, at the time of data collection, some of the hospital laboratories had a cost-saving policy of measuring only one inflammatory marker and therefore only ESR was available in some cases. At the baseline visit, CRP was missing for 22%, 20% and 15% of cases from Dewsbury, York and Halifax hospitals, respectively, which represented a total of 38 (5%) cases. In all except one of these cases, ESR was available at the baseline visit, indicating that a blood sample had been taken at the time, yet CRP was unavailable. The next most common pattern of missingness of YEAR B baseline data was absence of the fatigue variable only (pattern 8), which occurred in 4% and was likely due to omission by the patient. In YEAR B, comorbidity data were frequently missing (Table 3-2) because the yes / no tick boxes on the clinical record forms were unfilled. In 282 cases from YEAR B, there were no available data on comorbidities, possibly indicating that this question was overlooked altogether. This is likely as there were fewer co- existent medical problems recorded for the whole of YEAR B compared to YEAR C (Table 3-1): for example, only 12% of YEAR B cases had hypertension, compared to 23% in YEAR C. However, in another 60 cases, one or two comorbidities were present and no information was provided for the remainder, suggesting that this section of the clinical record form was incomplete in some instances where a negative response was intended.

For 78% of cases in YEAR C, baseline data were complete, and this corresponds to pattern 1 in the YEAR C section of Figure 3-2 (A). The most common missing data patterns here were for EMS and RF to be missing concurrently (4%, represented by pattern 7), or for CRP, TJC, SJC, DAS28, RF and EMS to be missing (4%, represented by pattern 26).

Missing data patterns for the longitudinal data, including measurement of DAS28 and HAQ at 6 and 12 months, are illustrated in Figure 3-2 (B). Again, the most commonly occurring pattern from both cohorts was for no data to be missing, and this is represented by pattern 1 for YEAR B and C in Figure 3-2 (B). In YEAR B, the next most common pattern of missingness occurred in 14% of cases, when DAS28 and HAQ-DI at 6 and 12 months were all missing (pattern 64). Given that, at 6 months, 10% of cases in YEAR B were lost to follow up, this common missing data pattern was anticipated. The next most common pattern of missing data (9%) included missing DAS28 and HAQ-DI at 6 months (pattern 26). In YEAR C, the most common pattern was missing HAQ-DI and DAS28 at 6 months (8% of cases, pattern 45), followed by missing HAQ-DI and DAS28 at 12 months (7% of cases, pattern 29).

3.4.1.3 Item non-response

In some cases, participants did not answer the entire HAQ and only part of the questionnaire was completed. Of the 7215 questionnaires, 1% were partially complete and therefore treated as missing.

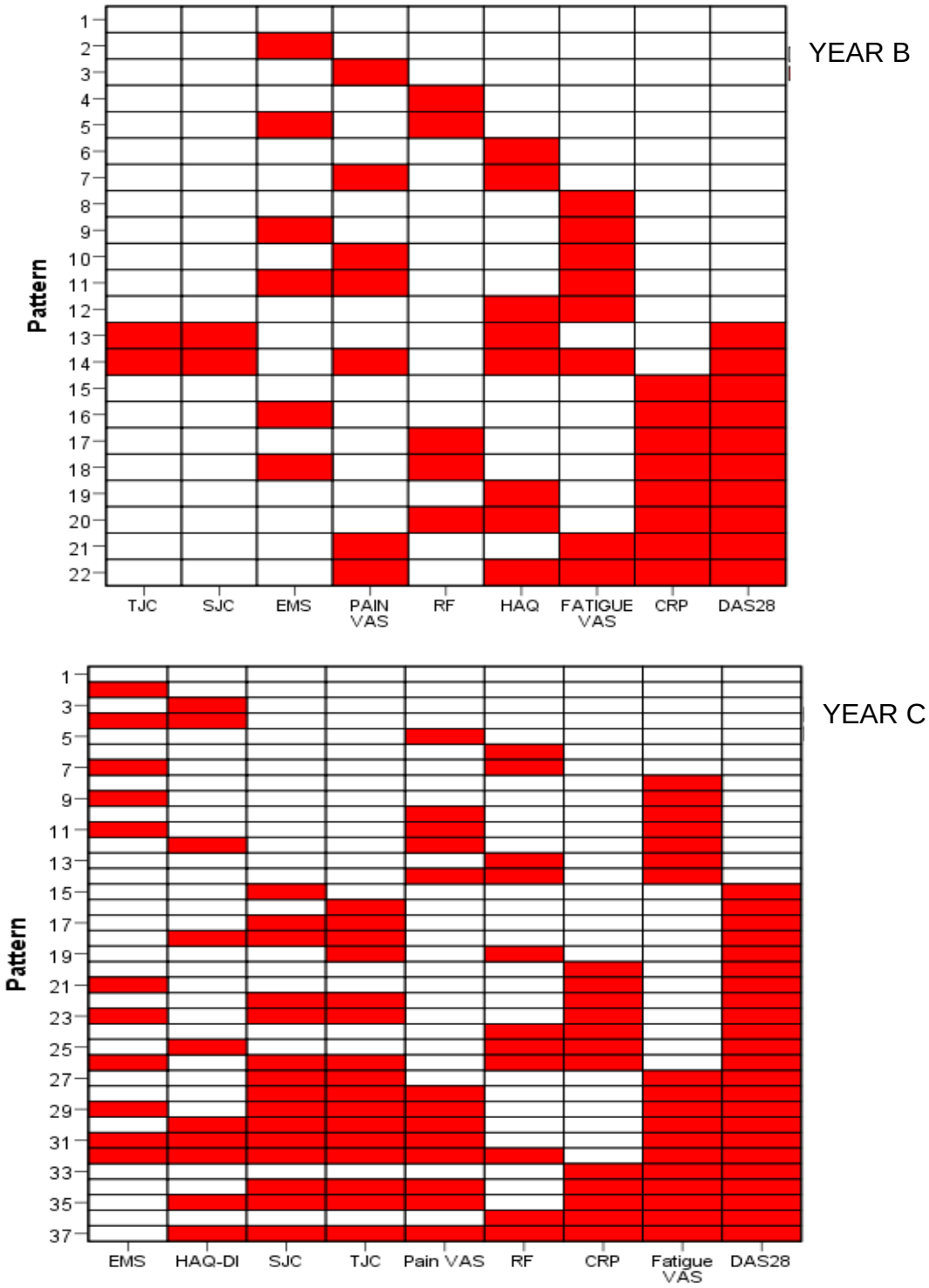

Figure 3-2 (A) Missing data patterns from Yorkshire Early Arthritis Register B and C at baseline

Red bars indicate values missing from the baseline data collection visit, whilst white bars indicate observed values. Variables are ordered such that the frequency of missingness increases from left to right: In YEAR C, EMS is the least frequently missing variable, whilst DAS28 at is the most frequently missing. The missing data patterns are labelled with numbers and are arranged from top to bottom, starting with groups of cases with least missing data for the far right variable, and then the next most frequently missing variable, and then the next and so on. All variables are at baseline.

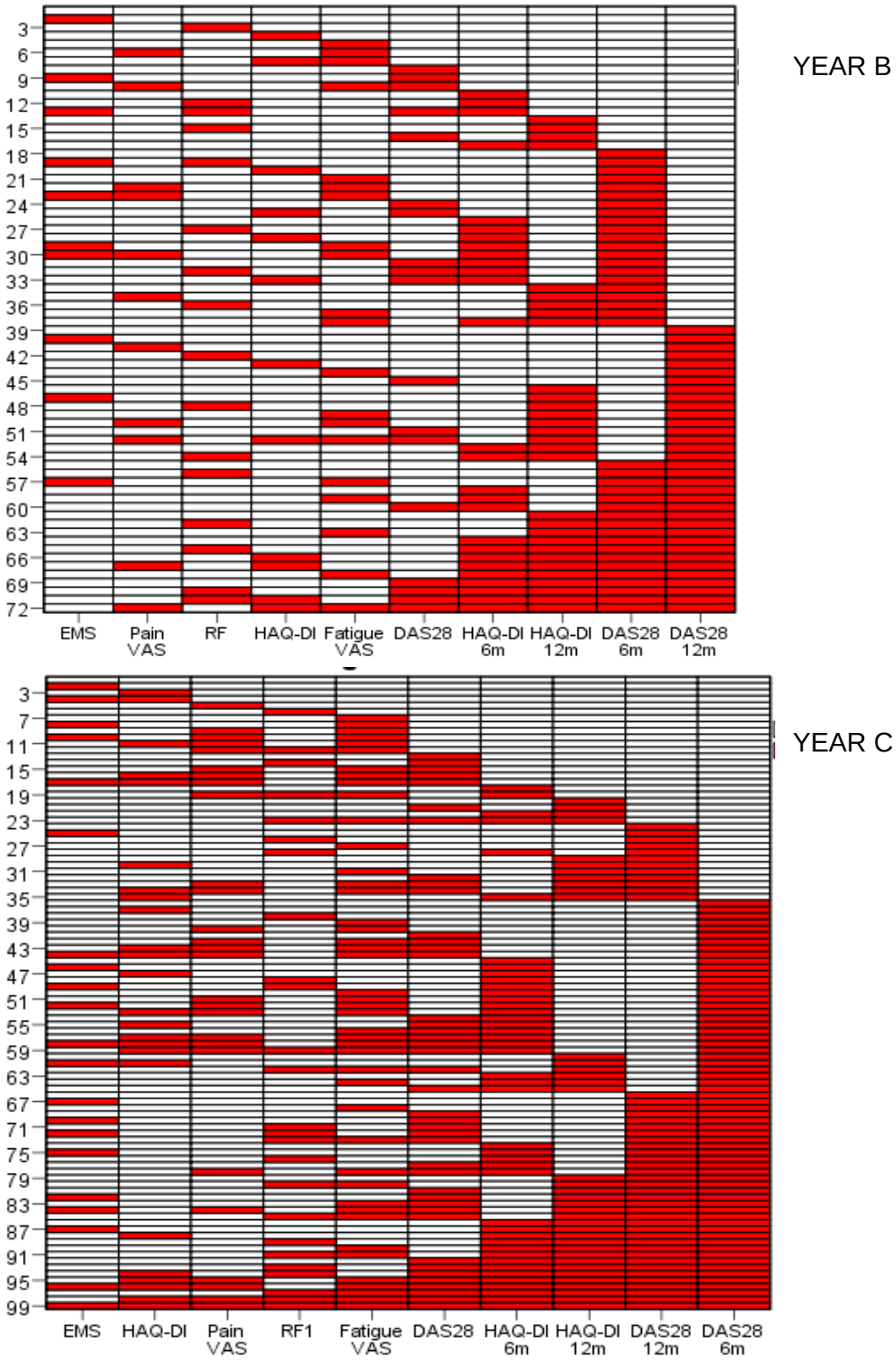

Figure 3-2 (B) Missing data patterns from Yorkshire Early Arthritis Register B and C including 6 and 12 month disease activity and Health Assessment Questionnaire

Red bars indicate values missing from the baseline data collection visit, whilst white bars indicate observed values. Variables are ordered such that the frequency of missingness increases from left to right: EMS is the least frequently missing variable,

whilst DAS28 at 12m is the most frequently missing. The missing data patterns are labelled with numbers and are arranged from top to bottom, starting with groups of cases with least missing data for the far right variable, and then the next most frequently missing variable, and then the next and so on.
Variables are at baseline, unless otherwise stated.
CRP, C-reactive protein; DAS28, disease activity score based upon count of 28 joints and using CRP measurement; EMS, early morning stiffness; HAQ-DI, disability index component of the health assessment questionnaire; m, months; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue score.

3.5 Auxiliary variables

3.5.1 Auxiliary variables for multiply imputed data

The methods for selection of auxiliary variables were described in Chapter 2, 2.5.5.1. Auxiliary variables were similar for YEAR B and YEAR C. Baseline disease activity VAS was correlated with baseline pain VAS, but the 2 variables were always missing together and therefore the former was not a suitable auxiliary variable for pain VAS. With the exception of baseline DAS28, where correlation with SJC was 0.69 (YEAR B) and 0.64 (YEAR C), tender and swollen joint counts at a given time point were highly correlated (Pearson correlation, r ≥0.7) with DAS28 calculated at the same time. ESR and CRP were not strongly correlated with corresponding DAS28. This likely reflects the method of calculation of DAS28, which uses the natural logarithm of CRP or ESR. Disease activity VAS was not applied for calculation of 3 variable DAS28 used here, but is used for calculation of the 4 variable DAS28, and did not show strong correlation with DAS28 measured at the same time point. Pearson correlation between HAQ-DI at any given time point and HAQ-DI at all previous visits was ≥0.5 in both cohorts and ≥0.7 in most cases in YEAR C. Although 3 month HAQ-DI was strongly correlated with HAQ-DI at 6 (r = 0.78), 12 (r = 0.79), 18 (r = 0.78) and 24 months (r = 0.72) in YEAR C, it was not collected in YEAR B, and because of this, it was not a suitable auxiliary variable for the multiple imputation model. Similar correlations were not observed for DAS28, where the strongest correlation, of 0.67, was between 18 and 24 months DAS28 in YEAR C. Pearson correlations between potential auxiliary variables and variables included in the analyses are given in Tables 3-5 (YEAR B) and 3-6 (YEAR C).

Table 3-5 Pearson correlations between imputed variables and potential auxiliary variables collected in Yorkshire Early Arthritis Register B

Auxiliary variable		Baseline imputed variable (IV)					3m IV	6m IV		12m IV		18m IV		24m IV	
Time	Variable	Pain (1)	Fatigue (1)	EMS (1)	DAS28 (1,2)	HAQ (1,2)	DAS28 (2)	DAS28 (1,2)	HAQ (1,2)	DAS28 (1,2)	HAQ (1,2)	DAS28 (2)	HAQ (2)	DAS28 (2)	HAQ (2)
BL	ESR	0.09	0.11	0.06	0.29	0.27	0.20	0.18	0.21	0.17	0.18	0.20	0.19	0.05	0.17
	CRP	0.15	0.13	0.08	0.36	0.28	0.24	0.18	0.21	0.12	0.18	0.06	0.12	0.02	0.16
	DAVAS	0.72	0.42	0.23	0.51	0.45	0.24	0.24	0.26	0.24	0.29	0.23	0.27	0.17	0.30
	TJC	0.31	0.27	0.18	0.82	0.40	0.28	0.24	0.27	0.15	0.24	0.15	0.26	0.17	0.30
	SJC	0.16	0.15	0.15	0.69	0.26	0.23	0.18	0.12	0.06	0.06	0.02	0.15	0.08	0.24
	DAS28	0.42	0.30	0.21	1.00	0.41	0.33	0.25	0.24	0.17	0.20	0.11	0.21	0.14	0.27
	HAQ	0.41	0.36	0.20	0.41	1.00	0.33	0.30	0.56	0.22	0.51	0.24	0.52	0.14	0.52
3m*	ESR	x	x	x	x	x	0.13	0.06	0.06	0.05	0.06	0.03	0.05	0.03	0.02
	CRP	x	x	x	x	x	0.46	0.15	0.04	0.04	0.01	0.04	0.04	0.00	0.00
	TJC	x	x	x	x	x	0.84	0.12	0.02	0.04	0.04	0.04	0.08	0.01	0.07
	SJC	x	x	x	x	x	0.75	0.09	0.01	0.01	0.01	0.02	0.02	0.03	0.05
	DAS28	x	x	x	x	x	1.00	0.58	0.41	0.45	0.40	0.41	0.43	0.24	0.37
6m	ESR	x	x	x	x	x	x	0.10	0.09	0.09	0.09	0.07	0.04	0.07	0.05
	CRP	x	x	x	x	x	x	0.49	0.09	0.10	0.03	0.05	0.00	0.01	0.02
	DAVAS	x	x	x	x	x	x	0.66	0.54	0.44	0.46	0.42	0.41	0.29	0.34
	TJC	x	x	x	x	x	x	0.85	0.41	0.03	0.06	0.06	0.02	0.05	0.03
	SJC	x	x	x	x	x	x	0.77	0.27	0.02	0.10	0.03	0.01	0.00	0.01
	DAS28	x	x	x	x	x	x	1.00	0.62	0.55	0.48	0.48	0.47	0.31	0.42
	HAQ	x	x	x	x	x	x	0.62	1.00	0.43	0.76	0.41	0.69	0.23	0.65
12m	ESR	x	x	x	x	x	x	x	x	0.15	0.17	0.13	0.00	0.04	0.07
	CRP	x	x	x	x	x	x	x	x	0.44	0.05	0.11	0.10	0.01	0.06
	DAVAS	x	x	x	x	x	x	x	x	0.65	0.52	0.46	0.46	0.42	0.49

Table 3-5, continued

Auxiliary variable		Baseline imputed variable (IV)					3m IV	6m IV		12m IV		18m IV		24m IV	
Time	Variable	Pain	Fatigue	EMS	DAS28	HAQ	DAS28	DAS28	HAQ	DAS28	HAQ	DAS28	HAQ	DAS28	HAQ
12m	TJC	x	x	x	x	x	x	x	x	0.83	0.34	0.15	0.04	0.11	0.05
	SJC	x	x	x	x	x	x	x	x	0.74	0.21	0.10	0.01	0.05	0.00
	DAS28	x	x	x	x	x	x	x	x	(1.00)	0.50	0.57	0.51	0.50	0.47
	HAQ	x	x	x	x	x	x	x	x	0.50	(1.00)	0.49	0.80	0.32	0.73
18m	ESR	x	x	x	x	x	x	x	x	x	x	0.12	0.11	0.01	0.07
	CRP	x	x	x	x	x	x	x	x	x	x	0.52	0.07	0.03	0.02
	DAVAS	x	x	x	x	x	x	x	x	x	x	0.47	0.40	0.10	0.15
	TJC	x	x	x	x	x	x	x	x	x	x	0.82	0.24	0.01	0.08
	SJC	x	x	x	x	x	x	x	x	x	x	0.73	0.13	0.05	0.04
	DAS28	x	x	x	x	x	x	x	x	x	x	1.00	0.56	0.56	0.49
	HAQ	x	x	x	x	x	x	x	x	x	x	0.56	1.00	0.33	0.80
24m	ESR	x	x	x	x	x	x	x	x	x	x	x	x	0.10	0.07
	CRP	x	x	x	x	x	x	x	x	x	x	x	x	0.26	0.05
	DAVAS	x	x	x	x	x	x	x	x	x	x	x	x	0.46	0.28
	TJC	x	x	x	x	x	x	x	x	x	x	x	x	0.84	0.14
	SJC	x	x	x	x	x	x	x	x	x	x	x	x	0.74	0.04
	DAS28	x	x	x	x	x	x	x	x	x	x	x	x	1.00	0.50
	HAQ	x	x	x	x	x	x	x	x	x	x	x	x	0.50	1.00

Correlations between imputed variables and potential auxiliary variable that are greater than 0.7 are highlighted in grey.
*At the 3 month visit, disease activity VAS and HAQ-DI were not collected.
Numbers in parentheses (1,2) indicate which method was used to manage missing data, where 1 indicates that missingness of the variable was accounted for using multiple imputation (for the subsequent linear regression analysis detailed in Chapter 3) and 2 indicates that the missing data were handled using maximum likelihood estimation (in the growth curve and latent class growth analyses).
BL, baseline; CRP, C-reactive protein; DAS28, disease activity score based upon a count of 28 swollen and tender joints and CRP; DA VAS, diseaseactivity visual analogue score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; HAQ, of health assessment questionnaire (Rasch transformed variable of disease activity component used); IV, imputed variable; m, months; X, not applicable: variables collected at a later date were not used to predict earlier variables.

Table 3-6 Pearson correlations between imputed variables and potential auxiliary variables collected in Yorkshire Early Arthritis Register C

Auxiliary variable		Baseline imputed variable (IV)					3m IV		6m IV		9m IV		12m IV		18m IV		24m IV	
Time	Variable	Pain (1)	Fatigue (1)	EMS (1)	DAS28 (1,2)	HAQ (1,2)	DAS28 (2)	HAQ (2)	DAS28 (1,2)	HAQ (1,2)	DAS28 (1,2)	HAQ (1,2)	DAS28 (1,2)	HAQ (1,2)	DAS28 (2)	HAQ (2)	DAS28 (2)	HAQ (2)
BL	ESR	0.21	0.05	0.01	0.38	0.25	0.12	0.17	0.10	0.08	0.15	0.12	0.10	0.06	0.06	0.02	0.11	0.06
	CRP	0.21	0.10	0.09	0.45	0.26	0.17	0.19	0.25	0.17	0.24	0.17	0.19	0.13	0.17	0.17	0.15	0.11
	DAVAS	0.78	0.48	0.31	0.46	0.51	0.15	0.27	0.21	0.29	0.21	0.28	0.18	0.23	0.22	0.26	0.17	0.25
	TJC	0.40	0.27	0.20	0.75	0.42	0.34	0.32	0.36	0.28	0.33	0.12	0.35	0.12	0.33	0.13	0.25	0.30
	SJC	0.32	0.13	0.18	0.64	0.28	0.23	0.16	0.22	0.10	0.21	0.30	0.19	0.33	0.12	0.31	0.07	0.12
	DAS28	0.45	0.25	0.18	1.00	0.45	0.36	0.32	0.38	0.26	0.33	0.27	0.32	0.26	0.32	0.28	0.26	0.27
	HAQ	0.48	0.37	0.27	0.45	1.00	0.26	0.66	0.30	0.63	0.31	0.63	0.30	0.56	0.30	0.58	0.25	0.56
3m	ESR	x	x	x	x	x	0.17	0.15	0.11	0.12	0.12	0.16	0.08	0.12	0.10	0.14	0.07	0.10
	CRP	x	x	x	x	x	0.46	0.19	0.26	0.18	0.24	0.15	0.17	0.18	0.11	0.14	0.19	0.14
	DAVAS	x	x	x	x	x	0.54	0.58	0.38	0.49	0.35	0.49	0.30	0.47	0.20	0.41	0.22	0.41
	TJC	x	x	x	x	x	0.81	0.15	0.38	0.12	0.27	0.10	0.21	0.07	0.11	0.10	0.19	0.05
	SJC	x	x	x	x	x	0.72	0.06	0.26	0.15	0.16	0.16	0.13	0.13	0.04	0.04	0.12	0.12
	DAS28	x	x	x	x	x	1.00	0.57	0.52	0.40	0.47	0.41	0.39	0.37	0.27	0.35	0.31	0.34
	HAQ	x	x	x	x	x	0.57	1.00	0.41	0.78	0.44	0.79	0.45	0.78	0.38	0.72	0.33	0.69
6m	ESR	x	x	x	x	x	x	x	0.12	0.13	0.11	0.14	0.11	0.10	0.14	0.17	0.09	0.12
	CRP	x	x	x	x	x	x	x	0.49	0.20	0.18	0.12	0.14	0.13	0.17	0.15	0.19	0.12
	DAVAS	x	x	x	x	x	x	x	0.60	0.65	0.43	0.55	0.32	0.51	0.32	0.48	0.33	0.47
	TJC	x	x	x	x	x	x	x	0.83	0.20	0.31	0.13	0.26	0.10	0.15	0.13	0.16	0.07
	SJC	x	x	x	x	x	x	x	0.71	0.08	0.19	0.04	0.13	0.00	0.04	0.03	0.07	0.01
	DAS28	x	x	x	x	x	x	x	1.00	0.62	0.66	0.50	0.57	0.48	0.49	0.44	0.46	0.41
	HAQ	x	x	x	x	x	x	x	0.62	1.00	0.53	0.81	0.48	0.79	0.42	0.75	0.40	0.73
9m	ESR	x	x	x	x	x	x	x	x	x	0.08	0.15	0.12	0.15	0.13	0.14	0.08	0.15
	CRP	x	x	x	x	x	x	x	x	x	0.49	0.12	0.20	0.12	0.10	0.09	0.17	0.15
	DAVAS	x	x	x	x	x	x	x	x	x	0.63	0.63	0.44	0.55	0.39	0.50	0.38	0.49
	TJC	x	x	x	x	x	x	x	x	x	0.83	0.15	0.27	0.14	0.14	0.13	0.20	0.18
	SJC	x	x	x	x	x	x	x	x	x	0.70	0.07	0.17	0.09	0.07	0.06	0.13	0.08

Table 3-6, continued

Auxiliary variable		Baseline imputed variable (IV)					3m IV		6m IV		9m IV		12m IV		18m IV		24m IV	
Time	Variable	Pain	Fatigue	EMS	DAS28	HAQ	DAS28	HAQ	DAS28	HAQ	DAS28	HAQ	DAS28	HAQ	DAS28	HAQ	DAS28	HAQ
9m	DAS28	x	x	x	x	x	x	x	x	x	1.00	0.61	0.63	0.51	0.56	0.51	0.52	0.49
	HAQ	x	x	x	x	x	x	x	x	x	0.61	1.00	0.55	0.85	0.48	0.83	0.41	0.78
12m	ESR	x	x	x	x	x	x	x	x	x	x	x	0.17	0.16	0.18	0.16	0.16	0.16
	CRP	x	x	x	x	x	x	x	x	x	x	x	0.42	0.20	0.20	0.15	0.17	0.16
	DAVAS	x	x	x	x	x	x	x	x	x	x	x	0.59	0.64	0.39	0.53	0.40	0.53
	TJC	x	x	x	x	x	x	x	x	x	x	x	0.82	0.14	0.24	0.11	0.24	0.06
	SJC	x	x	x	x	x	x	x	x	x	x	x	0.72	0.06	0.12	0.02	0.11	0.02
	DAS28	x	x	x	x	x	x	x	x	x	x	x	1.00	0.63	0.65	0.57	0.57	0.53
	HAQ	x	x	x	x	x	x	x	x	x	x	x	0.63	1.00	0.49	0.86	0.48	0.83
18m	ESR	x	x	x	x	x	x	x	x	x	x	x	x	x	0.24	0.19	0.16	0.15
	CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	0.38	0.17	0.11	0.09
	DAVAS	x	x	x	x	x	x	x	x	x	x	x	x	x	0.52	0.53	0.29	0.30
	TJC	x	x	x	x	x	x	x	x	x	x	x	x	x	0.84	0.11	0.24	0.12
	SJC	x	x	x	x	x	x	x	x	x	x	x	x	x	0.71	-0.02	0.10	0.01
	DAS28	x	x	x	x	x	x	x	x	x	x	x	x	x	1.00	0.61	0.67	0.55
	HAQ	x	x	x	x	x	x	x	x	x	x	x	x	x	0.61	1.00	0.53	0.86
24m	ESR	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.12	0.12
	CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.43	0.16
	DAVAS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.48	0.49
	TJC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.80	0.08
	SJC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.70	0.00
	DAS28	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1.00	0.56
	HAQ	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	0.56	1.00

Correlations between imputed variables and potential auxiliary variable that are greater than 0.7 are highlighted in grey.
Numbers in parantheses (1,2) indicate which method was used to manage missing data, where 1 indicates that missingness of the variable was accounted for using multiple imputation and 2 indicates that the missing data was handled using maximum likelihood estimation.
BL, baseline; CRP, C-reactive protein; DAS28, disease activity score based upon a count of 28 swollen and tender joints and CRP; DAVAS, disease activity visual analogue score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; HAQ, of health assessment questionnaire (Rasch

transformed variable of disease activity component used); IV, imputed variable; m, months; X, not applicable: variables collected at a later date were not used to predict earlier variables.

As well as using variables that correlated with those to be included in analyses, auxiliary variables were selected if they predicted missingness of a variable in the dataset. Table 3-7 gives details of logistic regression analyses used determine which variables were associated with missingness in YEAR B and Table 3-8 gives the corresponding data for YEAR C. Odds ratios that were less than 0.9 or greater than 1.2 were considered significant, as described in 2.5.5.1. In YEAR C, higher 3 month DAS28 was associated with lower likelihood of missing DAS28 at 6 months (OR 0.74, 95% CI 0.66-0.84), 12 months (OR 0.83, 95% CI 0.75-0.92) and 24 months (OR 0.86, 95% CI 0.78-0.96) and lower likelihood of missing HAQ-DI at 6 months (OR 0.79, 95% CI 0.71-0.88), 12 months (OR 0.84, 95% CI 0.76-0.93), 18 months (OR 0.87, 95% CI 0.78-0.96) and 24 months (OR 0.89, 95% CI 0.80-0.99).

Table 3-7 Predictors of missingness in imputed baseline to twelve month variables from the Yorkshire Early Arthritis Register B dataset

Odds ratios of missingness in imputed YEAR B variables (95% CI)

	PVAS BL	FVAS BL	DAS28 BL	EMS BL	RF BL	HAQ BL	DAS28 6m	HAQ 6m	DAS28 12m	HAQ 12m
Baseline predictor variables										
TJC	0.93	0.97	0.99	1.00	1.02	1.01	1.00	1.00	0.99	0.99
	(0.86, 1.01)	(0.93, 1.01)	(0.95, 1.02)	(0.94, 1.07)	(0.97, 1.07)	(0.96, 1.07)	(0.99, 1.02)	(0.98, 1.03)	(0.22, 1.10)	(0.97, 1.01)
SJC	1.00	0.97	0.96	0.98	1.05	0.98	0.99	0.97	0.98	0.98
	(0.92, 1.10)	(0.92, 1.02)	(0.91, 1.00)	(0.89, 1.07)	(0.99, 1.11)	(0.91, 1.05)	(0.97, 1.02)	(0.94, 0.99)	(0.95, 1.00)	(0.95, 1.00)
DA	x	1.00	1.00	1.00	1.01	1.02	1.00	1.00	1.00	1.00
VAS		(0.98, 1.01)	(0.99, 1.01)	(0.98, 1.02)	(1.00, 1.03)	(1.00, 1.04)	(1.00, 1.01)	(0.99, 1.00)	(0.99, 1.01)	(0.99, 1.00)
CRP	1.01	1.00	1.00	0.99	1.00	1.00	1.00	1.00	1.00	1.00
	(0.99, 1.02)	(1.00, 1.01)	(0.97, 1.03)	(0.96, 1.01)	(0.98, 1.01)	(0.99, 1.01)	(0.99, 1.00)	(1.00, 1.00)	(1.00, 1.01)	(1.00, 1.01)
ESR	1.00	1.00	1.00	1.01	1.00	1.00	1.00	1.00	1.01	1.00
	(0.97, 1.02)	(0.98, 1.02)	(0.99, 1.02)	(0.99, 1.04)	(0.98, 1.02)	(0.98, 1.02)	(0.99, 1.01)	(0.99, 1.01)	(1.00, 1.01)	(0.99, 1.01)

Table 3-7, continued

Odds ratios of missingness in imputed YEAR B variables (95% CI)

	PVAS BL	FVAS BL	DAS28 BL	EMS BL	RF BL	HAQ BL	DAS28 6m	HAQ 6m	DAS28 12m	HAQ 12m
3 month predictor variables										
PVAS	0.99 (0.96, 1.02)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	1.02 (0.99, 1.05)	1.02 (0.99, 1.03)	1.00 (0.98, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
FVAS	1.01 (0.98, 1.04)	1.01 (1.00, 1.02)	1.00 (0.98, 1.01)	1.04 (1.00, 1.08)	1.01 (1.00, 1.03)	1.00 (0.99, 1.02)	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)
EMS	1.00 (0.99, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
DAS28	0.89 (0.54, 1.45)	0.96 (0.74, 1.24)	0.86 (0.66, 1.13)	1.18 (0.63, 2.23)	1.46 (0.96, 2.22)	0.86 (0.62, 1.20)	1.03 (0.89, 1.18)	1.01 (0.92, 1.28)	1.04 (0.91, 1.18)	1.03 (0.90, 1.18)
6 month predictor variables										
PVAS	x	x	x	x	x	x	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
FVAS	x	x	x	x	x	x	1.00 (1.00, 1.01)	1.00 (0.98, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)
DAVAS	x	x	x	x	x	x	1.00 (1.00, 1.01)	1.00 (0.99, 1.02)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)

Table 3-7, continued

Odds ratios of missingness in imputed YEAR B variables (95% CI)

	PVAS BL	FVAS BL	DAS28 BL	EMS BL	RF BL	HAQ BL	DAS28 6m	HAQ 6m	DAS28 12m	HAQ 12m
EMS	x	x	x	x	x	x	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
DAS28	x	x	x	x	x	x	x	0.87 (0.63, 1.22)	1.11 (0.96, 1.27)	1.10 (0.95, 1.28)
HAQ	x	x	x	x	x	x	1.03 (0.99, 1.07)	x	1.05 (1.01, 1.09)	1.05 (1.00, 1.09)
12 month predictor variables										
PVAS	x	x	x	x	x	x	x	X	1.01 (1.00, 1.02)	1.01 (1.00, 1.03)
FVAS	X	x	x	x	x	X	x	x	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)
DAVAS	X	X	x	x	x	x	x	x	1.01 (1.00, 1.02)	1.02 (1.00, 1.03)
EMS	X	x	x	x	x	x	x	X	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
DAS28	X	x	x	x	x	x	x	x	x	1.04 (0.76, 1.42)
HAQ	x	x	x	x	x	x	x	x	1.04 (0.98, 1.01)	x

Odds ratios were obtained using logistic regression analyses controlled for age, gender and symptom duration. Significant (OR < 0.9 or >1.2) predictors of missing imputed variables are highlighted in grey.
Where pain VAS was missing for the baseline visit, disease activity VAS was also missing.

BL, baseline; CI, confidence interval; DAS28, disease activity score from 28 joints; DAVAS, disease activity visual analogue score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; FVAS, fatigue visual analogue score; HAQ, disability index of the health assessment questionnaire (Rasch transformed); m, months; PVAS, pain visual analogue score; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; x, not applicable: data were collected at a later appointment and were therefore not used to predict missingness in earlier variables.

Table 3-8 Predictors of missingness in imputed baseline to twelve month variables from the Yorkshire Early Arthritis Register C dataset

	Odds ratios of missingness in imputed YEAR C variables (95% CI)									
	PVAS BL	FVAS BL	DAS28 BL	EMS BL	RF BL	HAQ BL	DAS28 6m	HAQ 6m	DAS28 12m	HAQ 12m
Baseline predictor variables										
Smoker	1.40 (0.75, 2.59)	1.47 (0.91, 2.38)	1.36 (0.92, 2.02)	1.21 (0.83, 1.76)	0.99 (0.69, 1.41)	0.96 (0.68, 1.34)	1.04 (0.76, 1.41)	1.08 (0.80, 1.47)	1.10 (0.81, 1.49)	1.18 (0.87, 1.61)
TJC	0.97 (0.92, 1.03)	0.99 (0.96, 1.02)	1.00 (0.97, 1.03)	1.01 (0.98, 1.03)	1.00 (0.97, 1.02)	1.00 (0.97, 1.02)	1.01 (0.99, 1.03)	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)
SJC	0.95 (0.94, 1.06)	1.00 (0.96, 1.04)	1.02 (0.98, 1.05)	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)
DAVAS	X	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)
CRP	1.00 (0.99, 1.00	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
ESR	0.99 (0.98, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)

Table 3-8, continued

3 month predictor variables										
PVAS	x	x	x	x	x	x	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
FVAS	x	x	x	x	x	x	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)
DAVAS	x	x	x	x	x	x	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
EMS	x	x	x	x	x	x	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
DAS28	x	x	x	x	x	x	0.74 (0.66, 0.84)	0.79 (0.71, 0.88)	0.83 (0.75, 0.92)	0.84 (0.76, 0.93)
HAQ	x	x	x	x	x	x	1.00 (0.96, 1.04)	0.98 (0.95, 1.02)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)
6 month predictor variables										
PVAS	x	x	x	x	x		0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)
FVAS	x	x	x	x	x		1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
DAVAS	x	x	x	x	x		0.99 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
EMS	x	x	x	x	x		1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
DAS28	x	x	x	x	x		X	0.87 (0.76, 1.01)	0.89 (0.79, 1.01)	0.92(0.82, 1.04)

Table 3-8, continued

HAQ	x	x	x	x	x	x	0.98 (0.94, 1.03)	x	0.98 (0.94, 1.01)	0.98 (0.95, 1.01)
12 month predictor variables										
PVAS	x	x	x	x	x	x	x	x	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)
FVAS	X	x	x	x	x	x	x	x	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
DAVAS	X	X	x	x	x	x	x	x	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
EMS	X	x	x	x	x	x	x	x	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
DAS28	X	x	x	x	x	x	x	x	x	0.96 (0.85, 1.08)
HAQ	x	x	x	x	x	x	x	x	0.99 (0.95, 1.02)	x

Odds ratios were obtained using logistic regression analyses controlled for age, gender and symptom duration. Significant (OR < 0.9 or >1.2) predictors of missing imputed variables are highlighted in grey.
Where pain VAS was missing for the baseline visit, disease activity VAS was also missing.
BL, baseline; CI, confidence interval; DAS28, disease activity score from 28 joints; DAVAS, disease activity visual analogue score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; FVAS, fatigue visual analogue score; HAQ, disability index of the health assessment questionnaire (Rasch transformed); m, months; PVAS, pain visual analogue score; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; x, not applicable: data were collected at a later appointment and were therefore not used to predict missingness in earlier variables.

3.5.2 Auxiliary variables for missing data handled by maximum likelihood estimation

Missing data were handled by maximum likelihood estimation in the latent growth curve and LCGA and included DAS28 values at baseline, 3,6 12, 18 and 24 months and HAQ-DI values at baseline, 6, 12, 18 and 24 months. Correlations between DAS28 and HAQ-DI at these time points and other variables in the dataset have already been described in Tables 3-5 and 3-6. Variables predictive of missingness in these outcomes up to 12 months were given in Tables 3-7 and 3-8. Indicators of missingness in DAS28 and HAQ-DI at 18 and 24 months are presented in Table 3-9. Only 3 month DAS28 predicted missingness in YEAR C (but not YEAR B), whereby odds of missingness in DAS28 and HAQ-DI were lower with increased value of 3 month DAS28. Covariates in the multinomial logistic regression analysis of predictors of trajectory class also contained missing data and predictors of missingness in these variables are displayed in Table 3-10. In YEAR B there were no significant predictors of missingness in covariates, however, in YEAR C higher baseline TJC and DAS28 were associated with less likelihood of missingness in IMD and higher baseline HAQ-DI was associated with a lower likelihood of missing smoking status.

Table 3-9 Predictors of missingness in imputed eighteen and twenty-four month variables from Yorkshire Early Arthritis Register

	Odds ratios of missingness in imputed YEAR B variables (95% CI)				Odds ratios of missingness in imputed YEAR C variables (95% CI)			
	DAS28 18m	HAQ 18m	DAS28 24m	HAQ 24m	DAS28 18m	HAQ 18m	DAS28 24m	HAQ 24m
Baseline predictor variables:								
TJC	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)	1.00 (0.99, 1.03)	1.01 (0.98, 1.03)	1.00 (0.98, 1.02)	1.01 (1.00, 1.02)
SJC	0.97 (0.95, 0.99)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	1.00 (0.98, 1.03)	1.01 (0.98, 1.03)	0.99 (0.96, 1.01)	1.00 (1.00, 1.01)
DAVAS	1.00 (0.55, 1.20)	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)	0.99 (0.99, 1.01)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)
CRP	1.00 (0.71, 1.09)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
ESR	0.89 (0.62, 1.27)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.01 (0.99, 1.01)	1.01 (1.00, 1.01)	1.01 (0.99, 1.02)	1.01 (0.99, 1.01
3 month predictor variables:								
PVAS	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.01 (0.99, 1.01)
FVAS	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.01 (0.99, 1.01)	1.01 (0.99, 1.01)	1.01 (1.00, 1.01)
EMS	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)	0.99 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)
DAS28	1.05 (0.93, 1.18)	1.06 (0.94, 1.21)	1.05 (0.93, 1.19)	1.06 (0.93, 1.20)	0.91 (0.82, 1.01)	0.87 (0.78, 0.98)	0.86 (0.78, 0.96)	0.89 (0.80, 0.99)
HAQ	x	x	x	x	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)	1.02 (0.98, 1.06)	1.03 (0.99, 1.07)
6 month predictor variables:								
PVAS	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)
FVAS	0.99 (0.99, 1.00)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)
EMS	0.99 (0.99, 1.0)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

Table 3-9, continued

	DAS28 18m	HAQ 18m	DAS28 24m	HAQ 24m	DAS28 18m	HAQ 18m	DAS28 24m	HAQ 24m
DAS28	1.06 (0.95, 1.19)	1.11 (0.98, 1.25)	1.12 (0.99, 1.26)	1.09 (0.97, 1.23)	1.09 (0.96, 1.23)	1.02 (0.89, 1.17)	0.97 (0.86, 1.10)	1.00 (0.88, 1.14)
HAQ	1.02 (0.98, 1.05)	1.03 (1.00, 1.07)	1.04 (1.01, 1.17)	1.04 (1.00, 1.08)	1.04 (1.00, 1.07)	1.05 (1.01, 1.10)	1.02 (0.98, 1.05)	1.03 (0.99, 1.07)
9 month predictor variables								
PVAS	x	x	x	X	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (0.99, 1.01)	1.01 (1.00, 1.01)
FVAS	x	x	x	x	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
EMS	x	x	x	x	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.00)
DAS28	x	x	x	x	1.20 (1.03, 1.38)	1.08 (0.93, 1.27)	1.01 (0.92, 1.21)	1.19 (1.03, 1.37)
HAQ					1.04 (1.00, 1.08)	1.04 (1.00, 1.09)	1.03 (0.99, 1.07)	1.04 (1.00, 1.09)
12 month predictor variables								
PVAS	1.01 (1.00, 1.01)	1.03 (0.89, 1.19)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)	1.01 (1.00, 1.01)	1.01 (1.01, 1.02)
FVAS	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.01 (1.000, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)
EMS	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
DAS28	1.00 (0.89, 1.15)	1.03 (0.89, 1.19)	0.99 (0.87, 1.13)	1.06 (0.93, 1.22)	1.03 (1.19, 0.47)	1.06 (0.91, 1.23	1.03 (0.90, 1.18)	1.13 (0.98, 1.30)
HAQ	1.01 (0.97, 1.04)	1.01 (0.97, 1.06)	1.02 (0.99, 1.07)	1.03 (0.99, 1.07)	1.04 (1.01, 1.08)	1.05 (1.01, 1.10)	1.04 (1.01, 1.08)	1.07 (1.02, 1.11)
18 month predictor variables								
PVAS	1.00 (0.98, 1.01)	1.01 (0.99, 1.03)	1.00 (0.99, 1.01)	0.99 (0.99, 1.01)	1.00 (0.99, 1.00)	0.97 (0.96, 0.98)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
FVAS	1.00 (1.00, 1.00)	1.00 (0.98, 1.00)	0.99 (0.98, 1.1)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	0.97 (0.96, 0.98)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
EMS	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)

Table 3-9, continued

	DAS28 18m	HAQ 18m	DAS28 24m	HAQ 24m	DAS28 18m	HAQ 18m	DAS28 24m	HAQ 24m
DAS28	x	1.11 (0.79, 1.57)	0.95 (0.79, 1.14)	0.94 (0.76, 1.15)	X	0.82 (0.60, 1.12)	0.97 (0.83, 1.13)	1.07 (0.91, 1.25)
HAQ	1.01 (0.97, 1.04)	x	1.01 (0.97, 1.06)	1.03 (0.98, 1.08)	0.99 (0.95, 1.05)	X	1.02 (0.98, 1.06)	1.04 (0.99, 1.09)
24 month predictor variables								
PVAS	X	X	0.99 (0.98, 1.00)	1.01 (0.99, 1.02)			1.01 (0.99, 1.02)	1.01 (0.99, 1.04)
FVAS	X	X	1.00 (0.99, 1.01)	1.00 (0.99, 1.12)			1.01 (0.99, 1.02)	1.01 (0.99, 1.03)
EMS	X	X	0.99 (0.99, 1.01)	1.00 (0.99, 1.00)			0.99 (0.99, 1.00)	1.00 (1.00, 1.00)
DAS28	X	X	x	1.12 (0.85, 1.47)			X	1.12 (0.77, 1.63)
HAQ	x	x	1.02 (0.97, 1.08)	x			1.01 (0.94, 1.07)	X

Odds ratios were obtained using logistic regression analyses controlled for age, gender and symptom duration. Significant (OR < 0.9 or >1.2) predictors of missing imputed variables are highlighted in grey.

CI, confidence interval; CRP, C-reactive protein; DAS28, disease activity score from 28 joints; DAVAS, disease activity visual analogue score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; FVAS, fatigue visual analogue score; HAQ, disability index of the health assessment questionnaire (Rasch transformed); m, months; PVAS, pain visual analogue score; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; x, not applicable: data were collected at a later appointment and were therefore not used to predict missingness in earlier variables.

Table 3-10 Predictors of missingness in Yorkshire Early Arthritis Register B and C covariates included in the multinomial logistic regression models

	Odds ratios of missingness in imputed YEAR B variables (95% CI)			
	RF	ACPA	Shared epitope	IMD
Baseline predictor variables				
TJC	0.85 (0.68, 1.07)	1.01 (0.98, 1.07)	1.01 (1.03, 1.17)	0.94 (0.93, 1.16)
SJC	1.04 (0.89, 1.21)	1.08 (1.03, 1.14)	1.06 (1.00, 1.11)	1.07 (0.98, 1.18)
CRP	0.99 (0.95, 1.02)	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)	0.99 (0.97, 1.01)
ESR	0.99 (0.97, 1.02)	1.01 (0.99, 1.02)	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)
DAS28	4.53 (0.42, 48.9)	0.65 (0.41, 1.03)	1.46 (0.53, 4.02)	1.46 (0.53, 4.02)
HAQ	1.02 (0.88, 1.18)	1.05 (0.98, 1.11)	0.99 (0.93, 1.05)	0.90 (0.78, 1.02)

	Odds ratios of missingness in imputed YEAR C variables (95% CI)						
	RF	ACPA	Shared epitope	IMD	Smoking	BMI	Co-morbidities
Baseline predictor variables							
TJC	1.00 (0.91, 1.11)	1.00 (0.96, 1.05)	1.00 (0.96, 1.05)	0.84 (0.72, 0.97)	1.20 (1.01, 1.40)	0.99 (0.92, 1.06)	1.02 (0.11, 1.05)
SJC	0.99 (0.89, 1.10)	1.00 (0.96, 1.04)	1.00 (0.96, 1.04)	0.93 (0.82, 1.06)	0.90 (0.76, 1.08)	0.99 (0.92, 1.05)	1.02 (0.98, 1.05)
CRP	1.01 (1.00, 1.02)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.97, 1.01)	1.01 (1.00, 1.03)	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)
ESR	1.01 (1.00, 1.03)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)	1.01 (0.98, 1.04)	1.00 (0.99, 1.01)	1.01 (0.98, 1.01)
DAS28	0.86 (0.51, 1.44)	1.03 (0.80, 1.34)	1.08 (0.83, 1.39)	3.06 (1.02, 9.19)	0.55 (0.23, 1.07)	1.06 (0.69, 1.62)	1.13 (0.97, 1.32)
HAQ	0.90 (0.79, 1.02)	1.03 (0.98, 1.08)	1.02 (0.97, 1.08)	0.91 (0.80, 1.04)	0.77 (0.61, 0.96)	0.99 (0.92, 1.07)	1.04 (0.99, 1.09)

ACPA, anti-citrullinated peptide antibodies; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DAS28, disease activity score from 28 joints; ESR, erythrocyte sedimentation rate; HAQ, disability index of the health assessment questionnaire (Rasch transformed); IMD, index of multiple deprivation; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

3.5.3 Auxiliary variables summary

There were 6 auxiliary variables selected for the linear regression analyses of change in DAS28 and HAQ-DI at 6 and 12 months, including TJC at baseline and TJC and SJC at 6 and 12 months, together with DAS28 at 3 months. There were 10 auxiliary variables suitable for the latent growth curve of change in DAS28, which were TJC at baseline and TJC and SJC at all other time points. For the growth curve analysis of change in HAQ-DI, the only auxiliary variable was DAS28 at 3 months. Although HAQ-DI measured at any given point correlated with HAQ-DI at a later time, all HAQ-DI measurements were already included in the model and would therefore be taken into account when missing data were accounted for using maximum likelihood estimation. Table 3-11 summarises which auxiliary variables were used in the multiple imputation and maximum likelihood estimation models. There are some imputed variables, such as HAQ-DI at baseline and covariates in the linear regression models, for which there were no suitable auxiliary variables. Auxiliary variables used for missing covariates in the multinomial logistic regression models included baseline TJC and DAS28, which predicted missing IMD, and baseline HAQ-DI, which predicted missing smoking status.

Table 3-11 Summary of auxiliary variables

Analysis	Imputed variable	Auxiliary variables
Linear regression of change in DAS28	DAS28 at baseline	Baseline TJC
	DAS28 at 6 months	3m DAS28 6m TJC 6m SJC
	DAS28 at 12 months	3m DAS28 12m TJC 12m SJC
Linear regression of change in HAQ-DI	HAQ-DI at 6 months	3m DAS28 3m HAQ-DI
	HAQ-DI at 12 months	3m DAS28 3m HAQ-DI 6m HAQ-DI
Latent growth curve model of change in DAS28 and LCGA	DAS28 at baseline	Baseline TJC
	DAS28 at 3 months	3m TJC 3m SJC
	DAS28 at 6 months	3m DAS28 6m TJC 6m SJC
	DAS28 at 12 months	3m DAS28 12m TJC 12m SJC
	DAS28 at 18 months	18m TJC 18m SJC
	DAS28 at 24 months	3m DAS28 24m TJC 24m SJC
Latent growth curve model of change in HAQ-DI and LGCA.	HAQ-DI at 6 months	3m DAS28 3m HAQ-DI
	HAQ-DI at 12 months	3m DAS28 3m HAQ-DI 6m HAQ-DI
	HAQ-DI at 18 months	3m DAS28 3m HAQ-DI 6m HAQ-DI 12m HAQ-DI
	HAQ-DI at 24 months	3m DAS28 6m HAQ-DI 12m HAQ-DI 18m HAQ-DI
Multinomial logistic regression models of predictors of trajectory class	IMD	Baseline TJC Baseline DAS28
	Smoking status	Baseline HAQ-DI

BL, baseline; DAVAS, disease activity visual analogue score; DAS28, disease activity score based upon a count of 28 joints; HAQ-DI, disability index component of health assessment questionnaire; IMD, index of multiple deprivation; IV, imputed variable;

LCGA, latent class growth analysis; m, months; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue score.

3.6 Summary of Yorkshire Early Arthritis Register characteristics

In total, 1416 YEAR cases were included in the analyses presented here. Of these, 691 cases were from YEAR B and 725 cases were from YEAR C. The cohort was similar to other early RA cohorts in terms of the proportion of females and number of patients with positive antibodies (RF and ACPA, detailed in Section 3.2). There were differences between YEAR B and C, with higher mean baseline DAS28 and HAQ-DI in the former cohort, which were likely due to differences in recruitment, where some patients were recruited to randomised controlled trials instead of YEAR C (discussed in 3.2). A significant amount of data were missing from YEAR, which was more marked in YEAR B than YEAR C (29% vs. 15%, respectively). In order to minimise the impact of missing data, MI and maximum likelihood estimation were applied and auxiliary variables (summarised in Section 3.5 and Table 3-11) were included to reduce the risk of bias in estimates obtained from the analyses.

Chapter 4 Change in disease activity over time

4.1 Introduction

Recent decades have seen much interest in predicting drug responses and prognosis in early RA, owing to the availability and cost of biologic agents. There is strong evidence that preferable outcomes are achieved through early and aggressive suppression of inflammation due to RA (as stated in Chapter 1, 1.6); however, identification of patients most likely to benefit from this approach remains a challenge, despite the wealth of research that has been conducted to define predictors of RA outcome in terms of disease activity (reviewed in Chapter 1, 1.8.2). The aims of the analyses in this Chapter were to explore potential baseline clinical predictors of change in disease activity measured by DAS28, which is the parameter upon which current NICE recommendations for use of biologic agents in RA is based (Section 1.6 and Figure 1-2). The first analysis used cross-sectional statistical methods (as described in Section 1.7.1.2), in keeping with most of the published data on predictors of change in RA outcomes, and examined change after 6 and 12 months' therapy with standard DMARDs, to see whether information from the YEAR cohort can add to previously published work. An additional aspect to this analysis was that missing data were handled using MI. Of the evidence reviewed in 1.8.2 and summarised in Table 1-5, some analyses were limited to cases with complete data, (ERAS Study Group, 2000, Jacobi *et al.*, 2003, Hyrich *et al.*, 2006, Saevarsdottir *et al.*, 2011, Rojas-Serrano *et al.*, 2011, Ma *et al.*, 2012) and 2 analyses used a 'last observation carried forward' approach to missing data (van der Woude *et al.*, 2012, Lu *et al.*, 2014). However in most cases, the methods for handling missing data were not reported (Gonzalez-Gay *et al.*, 2002, Hider *et al.*, 2009, Mattey *et al.*, 2009, Mori *et al.*, 2010, Soderlin *et al.*, 2011, Jayakumar *et al.*, 2012, Andersson *et al.*, 2013, Arnold *et al.*, 2014), but were likely to have been complete case analyses. The reason for this surmise is that other missing data management techniques are usually described, although it is acknowledged that this assumption may not be accurate. Only two studies used modern methods of managing missing data: one used MI (van der Woude *et al.*, 2009) and another used a method that was probably

maximum likelihood estimation (the method was described but not explicitly identified) (Harrison *et al.*, 2005). Although analysis of complete cases is associated with bias (reviewed in 1.7.2.2), it is not possible to say whether these published results are likely to have been affected in this way, as patterns of missing data were not reported and in all papers except one (Jayakumar *et al.*, 2012), quantities of missing data were not given. However, differences between the present analysis and those previously published could be attributed to the different missing data management techniques.

The data were also analysed using a longitudinal approaches to describe change in DAS28: growth curve analysis and LCGA. The latter identifies trajectories, or classes, of change in DAS28 within the sample population and once these are identified, baseline predictors of class membership can be determined using multinomial logistic regression. The missing data were handled using maximum likelihood estimation to reduce bias in the estimates and to retain statistical power.

4.2 Comparison of original and imputed data

Summary statistics for the YEAR cohorts were described in Chapter 3, Table 3-1. Mean values of continuous imputed variables and percentages of categorical variables are presented in Table 4-1, which compares these values to those of the original dataset. The means of the imputed values were similar to those of the original data, which is reassuring that imputed variables were reasonable. Furthermore, proportions of patients who were RF positive and who reported EMS duration within each of the 4 categories were similar between original and imputed data.

Table 4-1 Comparison of summary statistics of imputed and original Yorkshire Early Arthritis Register variables

Categorical variables: (%)		Original dataset	Imputed dataset
Female gender		66	66
RF positive		71	72
ACPA positive		64	64
Baseline EMS	0-35 minutes	29	29
	40-75 minutes	23	24
	90-210 minutes	27	27
	≥220 minutes	21	20
Continuous variables: mean (SE)			
Age (years)		57.7 (0.38)	57.7 (0.38)
Symptom duration (months)		7.1 (0.11)	7.1 (0.11)
Baseline VAS pain (cm)		6.0 (0.11)	5.9 (0.08)
Baseline VAS fatigue (cm)		4.6 (0.13)	4.7 (0.08)
DAS28	Baseline	5.0 (0.04)	5.0 (0.04)
	6 months	3.6 (0.05)	3.6 (0.05)
	12 months	3.2 (0.05)	3.2 (0.05)
HAQ-DI	Baseline	9.8 (0.12)	9.8 (0.12)
	6 months	7.7 (0.15)	7.8 (0.14)
	12 months	7.1 (0.15)	7.2 (0.15)

Percentages rounded to nearest percent, mean values to one decimal place and standard errors to two decimal places. All variables are at baseline, unless otherwise stated.

ACPA, anti-citrullinated peptide antibodies; cm, centimetres; DAS28, disease activity score based upon count of 28 joints; EMS, early morning stiffness; HAQ-DI, disability index of health assessment questionnaire; N, number of participants; RF, rheumatoid factor; SE, standard error of the estimate; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register.

4.3 Baseline predictors of change in disease activity after six months

The mean change in DAS28 from baseline to 6 months, estimated from the MI dataset, was -1.36 units (SE 0.05, negative change indicated reduction in score). The linear regression model explained approximately 27% of the variance in change in DAS28 (equivalent to the R-square value of the complete case model) and the coefficient corresponding to the constant in this model indicated that the mean change in DAS28 after 6 months, for YEAR B, female, RF and ACPA negative patients with 0 to 35 minutes baseline EMS and mean values of symptom duration, baseline DAS28, pain and fatigue VAS (hereafter referred to as the 'baseline patient') was close to this value, at -1.37 (SE 0.13, $p<0.0001$). The results of the linear regression analysis are shown in Table 4-2. The model suggested that YEAR C patients saw a 0.21 unit greater drop in DAS28 after 6 months than those in YEAR B (SE 0.09, p0.026). Male gender was also a significant predictor of greater reduction in disease activity: on average, DAS28 reduced by 0.19 units more in males than females after 6 months (SE 0.09, $p=0.032$). Baseline fatigue VAS was an independently statistically significant predictor, not only of change in DAS28 after 6 months, but in all models of change in DAS28 and HAQ-DI: there was less reduction in disease activity and disability with greater baseline fatigue. Each cm of baseline fatigue VAS predicted a 0.05 unit less reduction in DAS28 at 6 months (SE 0.02, $p=0.007$, Table 4-2). As expected, higher baseline DAS28 was associated with greater subsequent fall in DAS28 (probably because the higher the initial recorded DAS28, the greater the possible decline after 6 and 12 months). There were no significant interactions between YEAR cohort and the other independent variables, indicating that the effects of the variables in the model were valid for both YEAR B and YEAR C patients. The Wald tests for significance of the overall effect of the interaction between EMS categories and YEAR cohort confirmed that these were non-significant (F statistic 0.53, degrees of freedom, df 252, p 0.6606) and therefore, the interactions between YEAR cohort and EMS categories were not retained in the final model.

Table 4-2 Predictors of change in disease activity from baseline to six months in Yorkshire Early Arthritis Register

	Multiple imputation analysis N=1416			Complete case analysis N=530		
Predictor	Coefficient (β)	SE	p	Coefficient (β)	SE	p
YEAR C	**-0.21**	**0.09**	**0.026**	-0.02	0.13	0.903
Male gender	**-0.19**	**0.09**	**0.032**	-0.23	0.13	0.082
Age*	-0.02	0.03	0.457	-0.06	0.05	0.199
SD (months)	0.00	0.01	0.924	0.01	0.01	0.640
RF positive	0.13	0.13	0.299	0.17	0.16	0.295
ACPA positive	0.22	0.15	0.139	0.27	0.15	0.079
Pain VAS	0.02	0.02	0.471	0.00	0.03	0.954
Fatigue VAS	**0.05**	**0.02**	**0.001**	**0.06**	**0.02**	**0.007**
EMS 40-75 minutes	0.03	0.12	0.824	0.03	0.17	0.840
90-210 minutes	0.00	0.12	0.974	0.08	0.18	0.673
≥220 minutes	-0.21	0.12	0.107	-0.28	0.21	0.172
DAS28	**-0.67**	**0.04**	**<0.0001**	**-0.64**	**0.06**	**<0.0001**
Constant	**-1.37**	**0.13**	**<0.0001**	**-1.52**	**0.19**	**<0.0001**

Results of linear regression analysis using centred continuous independent variables (value of independent variable -mean of that variable). Outcome variable was change in DAS28 after 6 months (DAS28 at 6 months – baseline DAS28).
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
*Age was entered into the model (as age in years)/10.
For EMS, the referent category was 0-35 minutes.
Independent variables were measured at baseline.
ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score from counts of 28 joints; EMS, early morning stiffness duration; N, number (of cases); p, probability (statistical significance); RF, rheumatoid factor; SD, symptom duration; SE, standard error; VAS, visual analogue score (measured in centimetres); YEAR, Yorkshire Early Arthritis Register.

The results of the MI model were compared to those of a complete case model, as unexplained inconsistencies may indicate errors in the imputation process (as described in Chapter 2, 2.5.5.2). This revealed that regression coefficients and SE were similar between the 2 analyses, with slightly smaller SE in the MI model. As in the MI analysis, the Wald test indicated that the interaction effect between cohort and categories of EMS duration was non-significant in this model (F statistic 1.32, 506 df, p = 0.2647). Smaller SEs may have been obtained owing to the greater number of cases included in the MI model. The greatest difference between coefficients was found corresponding to the effects of YEAR C cohort, which was greater in the MI analysis (-0.21), compared to the complete case analysis (-0.02, Table 4-2). However, this difference of 0.19 units of DAS28 was small.

Fit of the linear regression model was checked as described in Chapter 2, 2.5.4.1, by assessing the distribution of the standardised residual values (where residuals were the difference between the value of the actual outcome variable and that predicted by the model and the standardised residual is the value of the actual residual, divided by its SE) and examining the residual versus fitted values plot, which is shown in Figure 4-1. This revealed that the variance of residual values was not dependent on the outcome variable (that is, the assumption of homoscedasticity was met). The histogram in Figure 4-2 shows normally distributed residuals, with a mean of approximately zero. The values of the standardised residuals were all within the range -3.3 to 3.3, suggesting that there were no outliers.

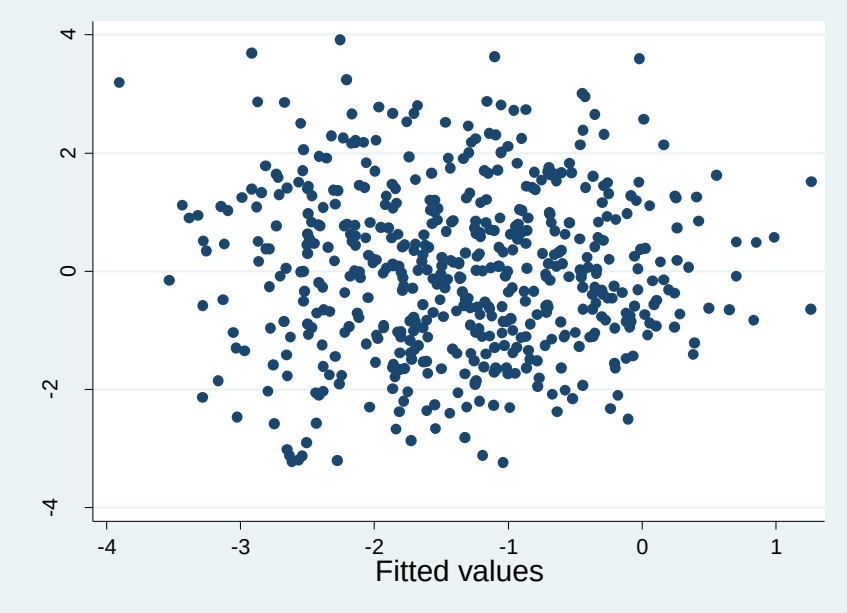

Figure 4-1 Residual versus fittted scatterplot for the linear regression model of change in Disease Activity Score using counts of 28 joints (DAS28) after 6 months for participants of Yorkshire Early Arthritis Register

Residual values represented the difference between observed change in DAS28 and change in DAS28 predicted by the model, whilst fitted values are those predicted by the model.

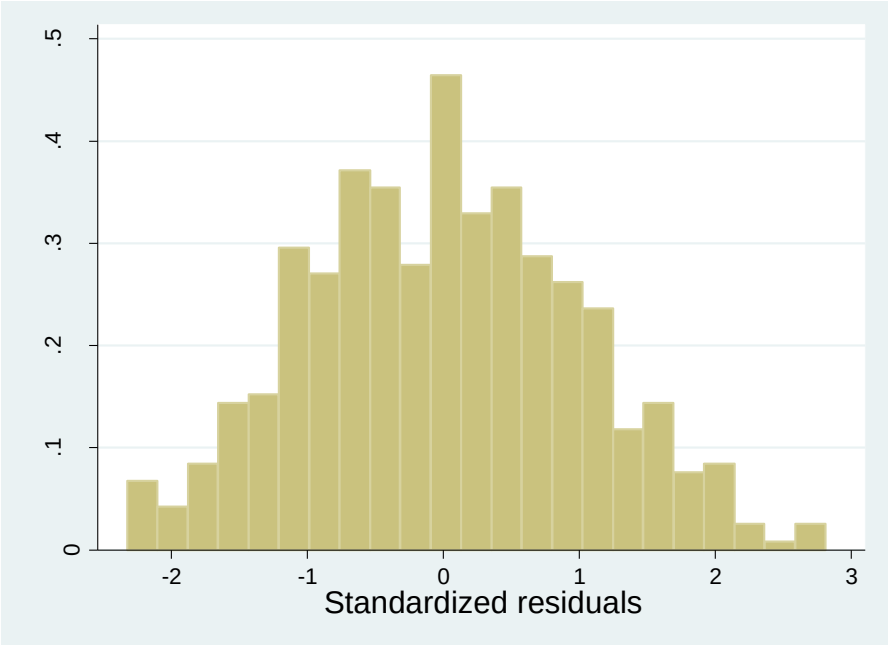

Figure 4-2 Histogram to show distribution of residuals from the linear regression analysis of change in Disease Activity Score using counts of 28 joints (DAS28) after 6 months in Yorkshire Early Arthritis Register

Residual values represent the difference between actual change in DAS28 and change in DAS28 predicted by the model.

Range of standardised residual values (equal to actual residual divided by its standard error): -2.33 to 2.81.

4.4 Baseline predictors of change in disease activity after twelve months

After 12 months, the mean reduction in DAS28, estimated from the MI data, was 1.75 units (SE 0.05) and overall, 33% of the variance of change in DAS28 after 12 months was explained by the complete case linear regression analysis (indicated by the adjusted R square value). Table 4-3 shows the results of the linear regression analysis of change in DAS28 after 12 months in which the change in DAS28 for the 'baseline patient' (defined in 4.3) was -1.78, consistent with the estimated mean. The effect of gender on change in DAS28 after 12 months almost reached statistical significance: males' DAS28 reduced by 0.16 units more after 12 months compared to females' (SE 0.09, p 0.079). One of the independently statistically significant variables in the model was fatigue VAS, also significant in the model of change in DAS28 after 6 months (4.3): each cm of baseline fatigue predicted a 0.03 unit less reduction in DAS28 at 12 months (SE 0.01, 0.023). Pain VAS was also a significant predictor of change in DAS28 after 12 months but its effect depended upon cohort. On average, reduction in DAS28 after 12 months was 0.06 units less per cm of baseline pain VAS for patients in YEAR B (SE 0.03, p 0.039), but for patients in YEAR C, the effect of baseline pain VAS on change in DAS28 was in the opposite direction: each cm of baseline pain VAS was associated with a 0.01 unit fall in DAS28. Thus, the effect of pain VAS was negligible in YEAR C, but it was associated with a slightly lesser reduction in DAS28 for patients in YEAR B. Another significant difference between YEAR B and C patients was found in relation to the effect of EMS category in this model. Although the group of YEAR B patients reporting baseline EMS ≥220 minutes did not have a significantly different change in DAS28 after 12 months compared to those reporting EMS 0-35 minutes, the effect was different for YEAR C patients, for whom the average fall in DAS28 after 12 months was 0.55 units greater if baseline EMS was ≥220 minutes than if it was 0-35 minutes. The effect of baseline DAS28 on change in DAS28 was also different between the two cohorts. For YEAR B cases, fall in DAS28 was 0.87 units per unit of baseline DAS28, whereas for YEAR C cases, this value was 0.71 per unit of baseline DAS28. As indicated in Table 4-1, mean baseline DAS28 was lower in YEAR C, so this difference may indicate a variable rate of change in DAS28, that is, the change in DAS28 per unit of time

may differ depending on baseline DAS28, or cohort, or the rate may slow down or speed up with time. This will be explored further in 4.5, where growth curves of change in DAS28 with time are described.

As for the linear regression model of change in DAS28 after 6 months (Section 4.3), a Wald test was carried out to determine whether the interactions between cohort and different categories of EMS were significant in the MI and complete case models. The results indicated that the interactions were significant in the MI model (F statistic 2.82, df=369, p=0.0389), but not in the model using complete cases, (F statistic 0.93, df= 515, p=0.4278). Thus, these interactions were retained in the MI model, but not in the analysis of the complete cases and therefore, differences in the coefficients for EMS categories between the 2 types of analysis were expected. Further comparison of the complete case and MI analyses revealed similar coefficients and SE. One of the more marked differences between the 2 analyses is found relating to the coefficients for ACPA, which was a significant predictor in the complete case model (DAS28 reduction 0.32 units less in ACPA positive cases, SE 0.15, p 0.037), but not the MI model (DAS28 reduction 0.17 units less in ACPA positive cases, SE 0.13, p 0.227). ACPA status was the most frequently missing variable in the dataset (46% missing, Chapter 3, Table 3-2) and this may contribute to bias in estimates obtained through analysis of the complete cases. The presence of auto antibodies has been linked to worse outcome, especially lower likelihood of remission in RA (reviewed in 1.8.2.3), but the present analysis did not support this finding. The difference between results from the complete case and MI analyses highlights the potential for bias in complete case analysis caused by missing data.

Table 4-3 Predictors of change in disease activity from baseline to twelve months in Yorkshire Early Arthritis Register

	Multiple imputation analysis N=1416			Complete case analysis N=539		
	Coefficient (β)	SE	p	Coefficient (β)	SE	p
Main model effects:						
YEAR C	-0.19	0.17	0.268	-0.17	0.13	0.172
Male gender	-0.16	0.09	0.079	**-0.40**	**0.13**	**0.002**
Age†	-0.02	0.03	0.618	-0.40	0.05	0.392
SD	-0.00	0.01	0.757	0.01	0.01	0.676
RF positive	0.11	0.12	0.347	0.07	0.16	0.667
ACPA positive	0.17	0.13	0.227	**0.32**	**0.15**	**0.037**
Pain VAS	**0.06**	**0.03**	**0.041**	0.06	0.04	0.098
Fatigue VAS	**0.03**	**0.01**	**0.023**	**0.05**	**0.03**	**0.023**
EMS 40-75 min	-0.11	0.17	0.502	0.07	0.16	0.683
90-210 min	0.16	0.16	0.328	0.22	0.17	0.201
≥220 min	0.27	0.22	0.226	-0.26	0.20	0.180
DAS28	**-0.87**	**0.06**	**<0.0001**	**-0.90**	**0.09**	**<0.0001**
Interaction effects:						
Cohort*Pain VAS	-0.07	0.04	0.096	**-0.10**	**0.05**	**0.032**
Cohort*EMS:						
40-75 min	0.18	0.81	0.417	Not included in model		
90-210 min	-0.01	0.23	0.950			
≥220 min	-0.55	0.28	0.058			
Cohort*DAS28	0.16	0.08	0.052	**0.31**	**0.11**	**0.004**
Constant	**-1.78**	**0.15**	**<0.0001**	**-1.80**	**0.17**	**<0.0001**

Results of linear regression analysis. Outcome variable was change in DAS28 after 12 months (DAS28 at 12 months – baseline DAS28).
Statistically significant (p<0.05) coefficients are highlighted in **bold.**
†Age was entered into the model (as age in years)/10.
*Indicates an interaction effect between 2 variables.
For EMS, the referent category was 0-35 minutes.
Independent variables were measured at baseline.
ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score from counts of 28 joints; EMS, early morning stiffness duration; min, minutes; N, number (of cases); NS, non significant model interaction, where p ≥0.10, therefore not included in the final model; p, probability (statistical significance); RF, rheumatoid factor; SD, symptom duration; SE, standard error; VAS, visual analogue score (measured in centimetres); YEAR, Yorkshire Early Arthritis Register.

To assess the fit the linear regression model, a scatterplot of the residuals versus fitted values (Figure 4-3) was inspected and as there was no discernible pattern to the scatterplot, the assumption of homoscedasticity was met. A histogram of the distribution of the residuals (Figure 4-4) showed that they were approximately normally distributed with a mean close to zero and that their range fell within -3.3 to 3.3, which confirmed that there were no outliers.

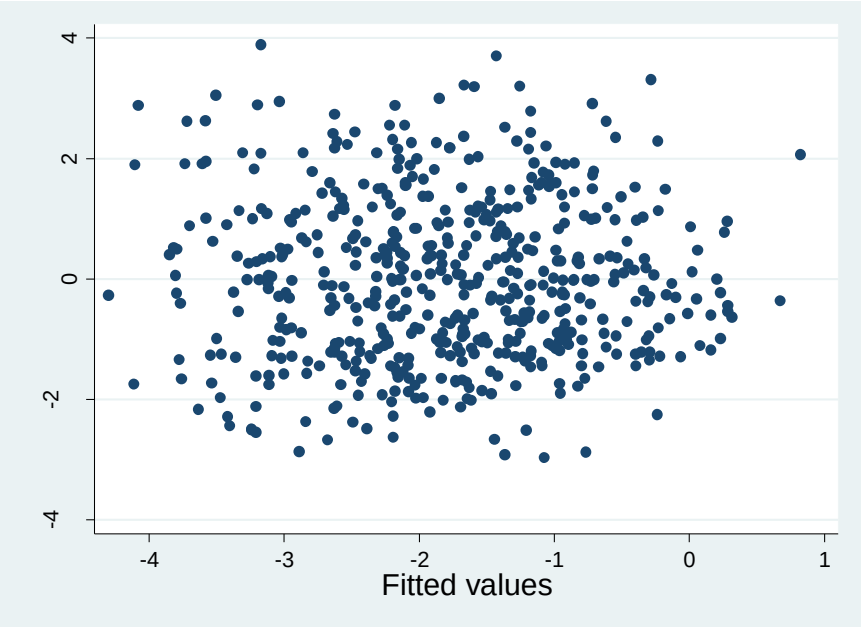

Figure 4-3 Residual versus fittted plot for the linear regression model of change in Disease Activity Score using counts of 28 joints (DAS28) after 12 months for participants of Yorkshire Early Arthritis Register
Residual values represented the difference between observed change in DAS28 and change in DAS28 predicted by the model, whilst fitted values are those predicted by the model.

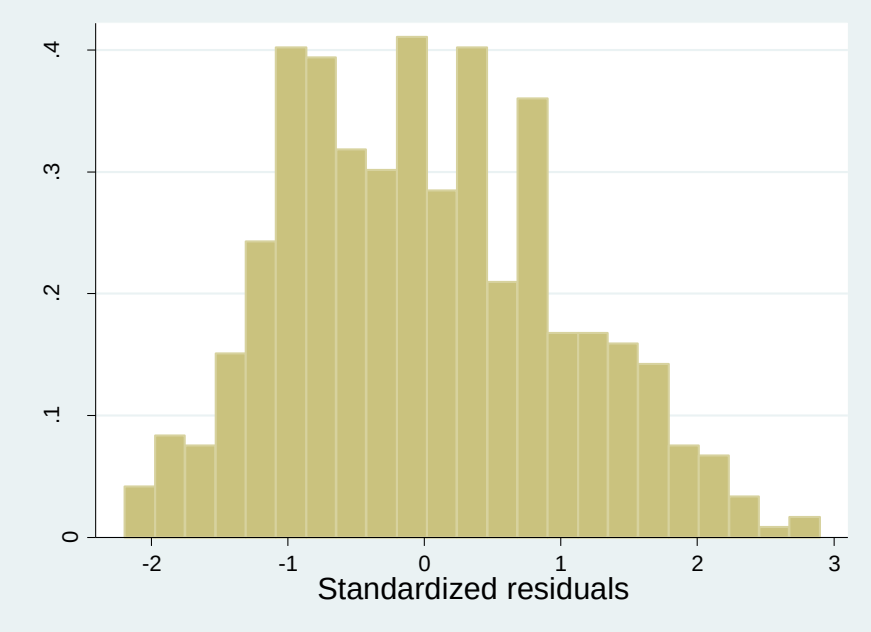

Figure 4-4 Histogram to show distribution of residuals from the linear regression analysis of change in Disease Activity using counts of 28 joints (DAS28) after 12 months in Yorkshire Early Arthritis Register
Residual values represent the difference between actual change in DAS28 and change in DAS28 predicted by the model.
Range of standardised residual values (equal to actual residual divided by its standard error): -2.19 to 2.90

4.5 Latent growth curve model of change in disease activity

4.5.1 Mean disease activity over time

Table 4-4 gives mean values of DAS28 at each data collection visit for the YEAR cohort as a whole, and then for YEAR B and C separately. As expected, DAS28 decreased with time, which was likely due to treatment for RA. However, the mean values did not reduce steadily with time, and the greatest reduction in DAS28 occurred initially, from baseline to 3 months. After the initial fall, mean DAS28 continued to decline, but at a slower rate. In YEAR B, mean DAS28 actually increased slightly towards the end of data collection, from 18 to 24 months.

Table 4-4 Means and standard errors of Disease Activity Score from a count of twenty-eight swollen and tender joints (DAS28) in Yorkshire Early Arthritis Register

	Mean DAS28 (SE)		
Time	YEAR (whole cohort)	YEAR B	YEAR C
Baseline	5.01 (0.07)	5.32 (0.05)	4.70 (0.06)
3 months	3.61 (0.05)	3.91 (0.07)	3.38 (0.06)
6 months	3.62 (0.05)	3.81 (0.07)	3.45 (0.07)
12 months	3.21 (0.07)	3.42 (0.07)	3.04 (0.06)
18 months	3.10 (0.05)	3.26 (0.08)	2.98 (0.07)
24 months	3.02 (0.05)	3.32 (0.08)	2.79 (0.06)

DAS28, disease activity score based upon count of 28 tender and swollen joints and C-reactive protein; SE, standard error; YEAR, Yorkshire Early Arthritis Register.

4.5.2 Linear growth curve model of change in disease activity

Data from 1397 participants of YEAR were included in the current analysis. In 18 cases, DAS28 was missing from all visits and these were excluded. The linear model did not fit the data well, which was expected, as the mean values of DAS28 did not decrease by the same amount at each visit (as shown in Table 4-4), and therefore were not expected to follow a linear trend with time. The poor fit of the model was confirmed by the χ^2 value: 939.03, degrees of freedom (df)= 20, statistical probability of obtaining a χ^2 value as high, or higher, if the model was a perfect fit to the data, $p < 0.0001$. Furthermore, the CFI value was small (0.537) and RMSEA too high for good model fit (0.181; 90% CI 0.172 to 0.191).

Although the model was a poor fit to the data and was rejected, it is described here for the purpose of comparison with subsequent models. Parameters estimated by the model are displayed in Table 4-5. The estimated mean intercept from the model, which represented the mean DAS28 at baseline, was 4.43 (SE 0.06, $p<0.001$), which was lower than the mean value of 5.01 calculated directly from the data (Table 4-5). This discrepancy between the model-estimated value and the sample mean DAS28 at baseline was reflected by the relatively high value of the intercept variance (0.92). The mean slope of the model, which represented the mean change in DAS28 per unit time, where

one unit of time was 3 months, was -0.17 (SE 0.01, p<0.001). In other words, according to the model, DAS28 decreased by 0.17 units on average, every 3 months. The negative value of the covariance (-0.02) indicated that a higher baseline DAS28 (or intercept) was associated with greater reduction in DAS28 per unit time (or slope), and although its value was small, it was statistically significant (p=0.033). Thus, the model implied that rate of change in DAS28 was greater with higher baseline DAS28. The model included YEAR cohort as a time- invariant covariate and therefore, the effects of cohort on intercept and slope were estimated. The model implied that for YEAR C cases, mean baseline DAS28 (intercept) was 0.57 units lower than for cases from YEAR B (SE 0.07, p <0.001). This was close to the difference of 0.62 units, obtained by simply subtracting mean baseline DAS28 in YEAR C from that of YEAR B. The difference in the rate of change in DAS28 was not statistically significant (estimate 0.02, SE 0.01 and p = 0.193), which implied that DAS28 declined by the same amount every 3 months in YEAR B and C. The differences in the sample means and means estimated in the model are illustrated in Figure 4-5, which compares the linear growth curve estimated by the model and the actual mean values of DAS28 against time.

Table 4-5 Parameters estimated by the linear growth curve model of change in disease activity over time in Yorkshire Early Arthritis Register

Parameter	Estimate	(SE)	p
Mean intercept	4.43	0.06	<0.001
Intercept variance	0.92	0.07	<0.001
Mean linear slope	-0.17	0.01	<0.001
Linear slope variance	0.02	0.00	<0.001
Intercept/ linear slope covariance	-0.02	0.01	0.033
Regression of parameters on YEAR C cohort			
Mean intercept on YEAR cohort	-0.57	0.07	<0.001
Mean slope on YEAR cohort	0.02	0.01	0.193

P, statistical probability; SE, standard error, YEAR, Yorkshire Early Arthritis Register

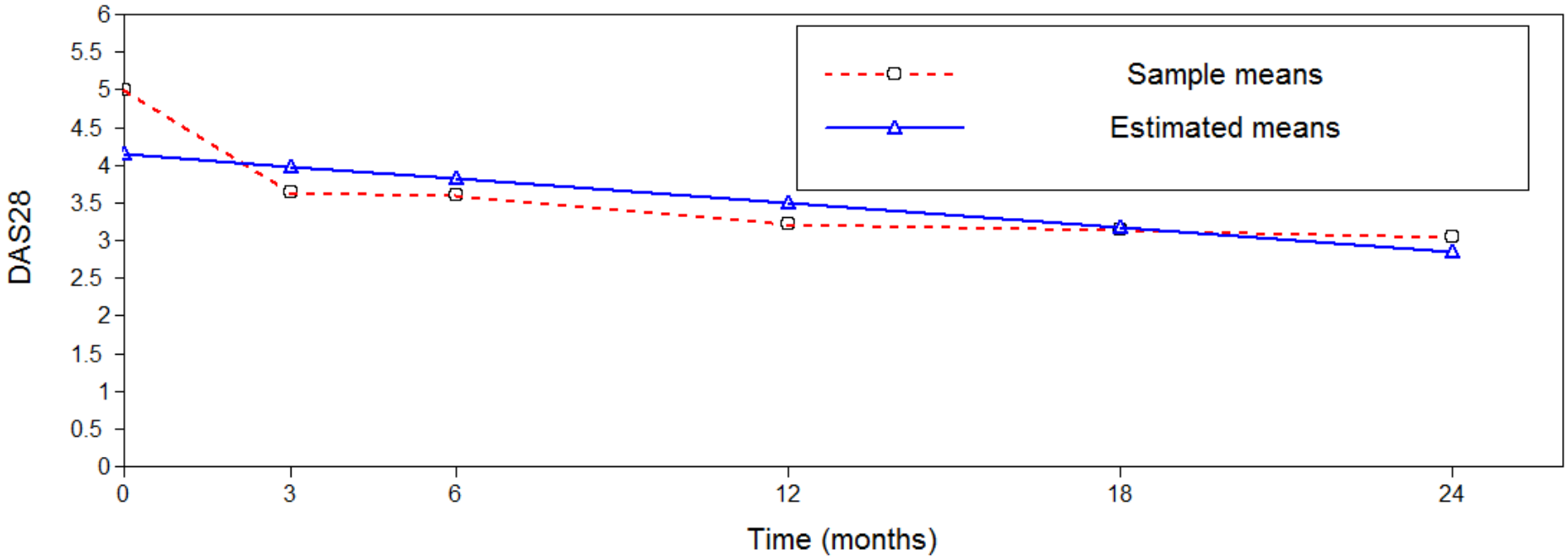

Figure 4-5 Graph to show how the sample mean Disease Activity Score from a count of 28 joints (DAS28) changed with time, compared to the means estimated by the linear growth curve model of change in DAS28 in Yorkshire Early Arthritis Register
Estimated means refers the means estimated by the linear growth curve, which are shown compared to the sample means.
DAS28, disease activity score based upon count of 28 swollen and tender joints and C-reactive protein.

4.5.3 Quadratic growth curve model of change in disease activity

As the linear model was not a good fit to the data and the sample means appeared to follow a curved rather than linear change over time, a quadratic component was added to the model. The estimates produced by the model are shown in Table 4-6. Again, there was poor fit of the model suggested by the χ^2 value of 403.321, df 15, p=<0.0001, CFI of 0.805 and RMSEA of 0.136 (90% CI 0.125- 0.148). The mean intercept estimated by the quadratic model, which represented the mean DAS28 at baseline, was 5.02 (SE 0.05, p<0.001). The mean linear slope was -0.64 (SE0.03, p<0.001), which implied that DAS28 initially reduced by 0.64 units every 3 months, and the mean quadratic slope was 0.05 (SE 0.00, p<0.001) which implied that the rate of reduction in DAS28 reduced slightly with time.

In this model, the variances of the intercept, linear and quadratic slope values, which represented variation in baseline DAS28 and change in DAS28 over time were 0.73 (SE 0.07, P<0.001), 0.16 (SE 0.02, p<0.001) and 0.00 (SE 0.00, p<0.001), respectively. The covariance between intercept (baseline DAS28) and linear slope (initial rate of change in DAS28) was -0.003, suggesting that initial rate of reduction in DAS28 was slightly more marked with increasing baseline DAS28, however, this result was not statistically significant (SE 0.03, p=0.924). The covariance between the intercept and quadratic slope (-0.004, SE 0.003, p=0.239) was also non-significant, but its slight negative value indicated that fall in DAS28 may have become more marked with time in cases with higher baseline DAS28. The covariance between linear and quadratic slopes was -0.0017 (SE 0.003, p<0.001), so in cases with higher initial rate of change in DAS28 (that is, a positive change in DAS28 score, so it may have increased initially), the rate of fall in DAS28 should have increased with time. This is a plausible finding, especially as a delay in drop in DAS28 could be attributed to a delay in treatment for RA. However, the magnitude of the covariance was small, indicating that although this relationship between initial rate of change in DAS28 and subsequent change in this rate was detected, the size of the effect was not large.

The model implied that there were significant differences for the two cohorts and that the mean intercept, or baseline DAS28 was 0.67 units lower in YEAR C (SE 0.07, $p<0.001$). Furthermore, the mean initial rate of change (linear slope) was more positive in YEAR C. That is, DAS28 did not fall as quickly for participants of YEAR C, where the model estimated initial fall in DAS28 was 0.51, compared to a fall in DAS28 of 0.64 units per 3 months in YEAR B. There was also a statistically significant difference in quadratic slope between cohorts: the overall quadratic slope was positive, which implied that the rate of reduction in DAS28 slowed with time. The estimate for the quadratic slope component of the model was 0.05 for YEAR C, compared to 0.06 in YEAR B. This very small difference of 0.01 units of DAS28 is unlikely to have clinical significance.

Inspection of the growth curve (shown in Figure 4-6) suggested an improvement over the linear model illustrated in Figure 4-5 in terms of the shape of the curve, but there were significant differences between the fitted curve and the sample means, especially at 3, 12 and 18 months. Therefore, to improve the fit of the curve, the next model allowed free estimation of factor loadings related to the effect of time on DAS28 at certain time points.

Table 4-6 Parameters estimated by the quadratic growth curve model of change in disease activity over time in Yorkshire Early Arthritis Register

Parameter	Estimate	(SE)	p
Mean intercept	5.07	(0.05)	<0.001
Intercept variance	0.58	0.12	<0.001
Mean linear slope	-0.64	(0.03)	<0.001
Linear slope variance	0.18	0.04	<0.001
Mean quadratic slope	0.06	(0.00)	<0.001
Quadratic slope variance	0.00	0.00	<0.001
Intercept/ linear slope covariance	0.03	0.06	0.656
Intercept/ quadratic slope covariance	-0.01	0.01	0.242
Linear slope/ quadratic slope covariance	-0.02	0.01	<0.001
Regression of parameters on YEAR C cohort			
Mean intercept on YEAR cohort	-0.67	0.07	<0.001
Mean linear slope on YEAR cohort	0.13	0.04	0.002
Mean quadratic slope on YEAR cohort	-0.014	0.005	0.003

P, (statistical) probability; SE, standard error; YEAR, Yorkshire Early Arthritis Register.

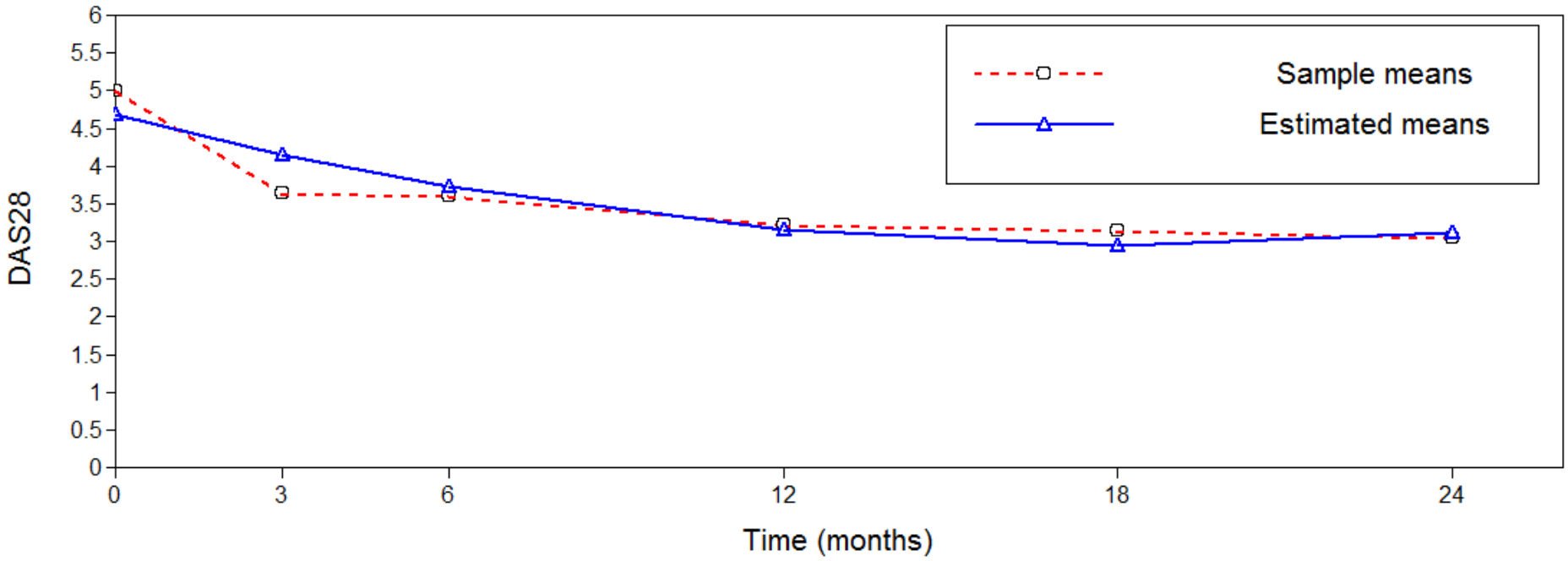

Figure 4-6 Graph to show how the sample mean Disease Activity Score from a count of 28 joints (DAS28) changed with time, compared to the means estimated by the quadratic growth curve model of change in disease activity in Yorkshire Early Arthritis Register

Estimated means refers the means estimated by the quadratic growth curve, which are shown compared to the sample means.
DAS28, disease activity score based upon count of 28 swollen and tender joints and C-reactive protein.

4.5.4 Freed loading growth curve model of change in disease activity

The third growth curve model applied to investigate change in DAS28 was a freed loading model, in which the factor loadings of linear slope onto DAS28 at baseline and 24 months were specified as 0 and 1, respectively, whilst the remaining factor loadings from linear slope to DAS28 at 3,6,12 and 18 months were freely estimated by the model (freed loading models were explained in Chapter 2, 2.5.4.2). The model fit was an improvement on previous models, as implied by the lower χ^2 value of 155.657, df 16, $p<0.0001$. The CFI value was also improved (0.930) and RMSEA was acceptable: 0.079 (90% CI 0.68, 0.091). The parameters estimated by the model are displayed in Table 4-7. The model-estimated intercept, or mean baseline DAS28, was 5.31 (SE 0.06), and was closer to the sample mean baseline DAS28 of 5.32 than the intercepts of the linear or quadratic models. The mean linear slope estimated by the model (or mean change in DAS28) was -2.00, which implied that DAS28 reduced by 2.00 units per 24 months. However, the variance of this estimate (1.75) suggested that there was considerable inter-individual variation in this rate of change in DAS28. The linear slopes at 3,6,12, and 18 months were freely estimated by the model and the estimates of linear slope at these time points represented change in DAS28 as a proportion of overall change in DAS28 at 24 months (which was fixed at 1). At 3 months, most of the change in DAS28 had occurred, with an estimated factor loading from linear slope to DAS28 at 3 months of 0.67. The corresponding factor loadings to DAS28 at 6, 12, and 18 months were 0.74, 0.94 and 0.97, respectively. Thus, the model implied that mean DAS28 followed a downward trend from baseline to 24 months with maximal reduction at 24 months. When these model-implied results are compared to the sample means (Table 4-4), the growth curve described by this model seems appropriate. The model-estimated covariance between intercept and linear slope was -0.91 (SE 0.12, $p<0.001$), which implied that higher baseline DAS28 (or intercept) was associated with a greater rate of reduction of DAS28 (or linear slope). As higher initial DAS28 has a greater potential for

negative change, this was anticipated and was closer to what was expected than the results of the previous models: the value of this covariance was -0.02 (SE 0.01, p=0.033) according to the linear model and 0.03 (SE 0.06, p=0.656) according to the quadratic model.

Table 4-7 also lists values of the variances of the random error, or measurement error, for the value of DAS28 at each time point. R square values were calculated, using the sample means and variances of DAS28 at each time point, and indicated that variation in DAS28 explained by the model was between 80% and 99%, except for DAS28 measured at 12 months, which was only 45%. It is also noteworthy that the estimates of variance in measurement error were all statistically significant.

Therefore, the model explained most of the variability in DAS28 over time and fit indices indicated a reasonable fit of the model to the data, which was confirmed by graphical representation of the model, shown in Figure 4-7. Here, model predicted means are compared to the sample means and there appears to be better fit than the previous two models. However, there was considerable inter-individual variation, as indicated by the estimates of variance and shown in Figure 4-8, where recorded DAS28 scores from a random sample of 140 cases (approximately 10%) were plotted to show that trend in DAS28 varied considerably between individuals. Further investigation into the variation in DAS28 growth curves between participants was therefore warranted and is provided by exploration of growth class analysis in the following analysis (Section 4.6).

Table 4-7 Parameters estimated by the freed loading growth curve model of change in disease activity over time in Yorkshire Early Arthritis Register

Parameter	Estimate	SE	p
Mean intercept	5.31	0.06	<0.001
Intercept variance	1.37	0.15	<0.001
Mean linear slope	-2.00	0.07	<0.001
Linear slope variance	1.75	0.20	<0.001
Linear slope at baseline	0.00		
Linear slope at 3m	0.67	0.02	<0.001
Linear slope at 6m	0.74	0.02	<0.001
Linear slope at 12m	0.94	0.02	<0.001
Linear slope at 18m	0.97	0.02	<0.001
Linear slope at 24m	1.00		
Intercept/ linear slope covariance	-0.91	0.12	<0.001
Regression of parameters on YEAR C cohort			
Mean intercept on YEAR cohort	-0.62	0.08	<0.001
Mean linear slope on YEAR cohort	0.18	0.10	0.064
Variances of error associated with measurement of:		SE	R^2
DAS28 at baseline	0.64	0.15	0.80
DAS28 at 3 months	1.63	0.08	0.99
DAS28 at 6 months	1.29	0.07	0.94
DAS28 at 12 months	0.85	0.05	0.45
DAS28 at 18 months	0.91	0.06	0.81
DAS28 at 24 months	0.93	0.06	0.80

DAS28, disease activity based upon count of 28 joints; P, statistical probability; R^2, R-Square value, or variance in parameter explained by the model; SE, standard error.

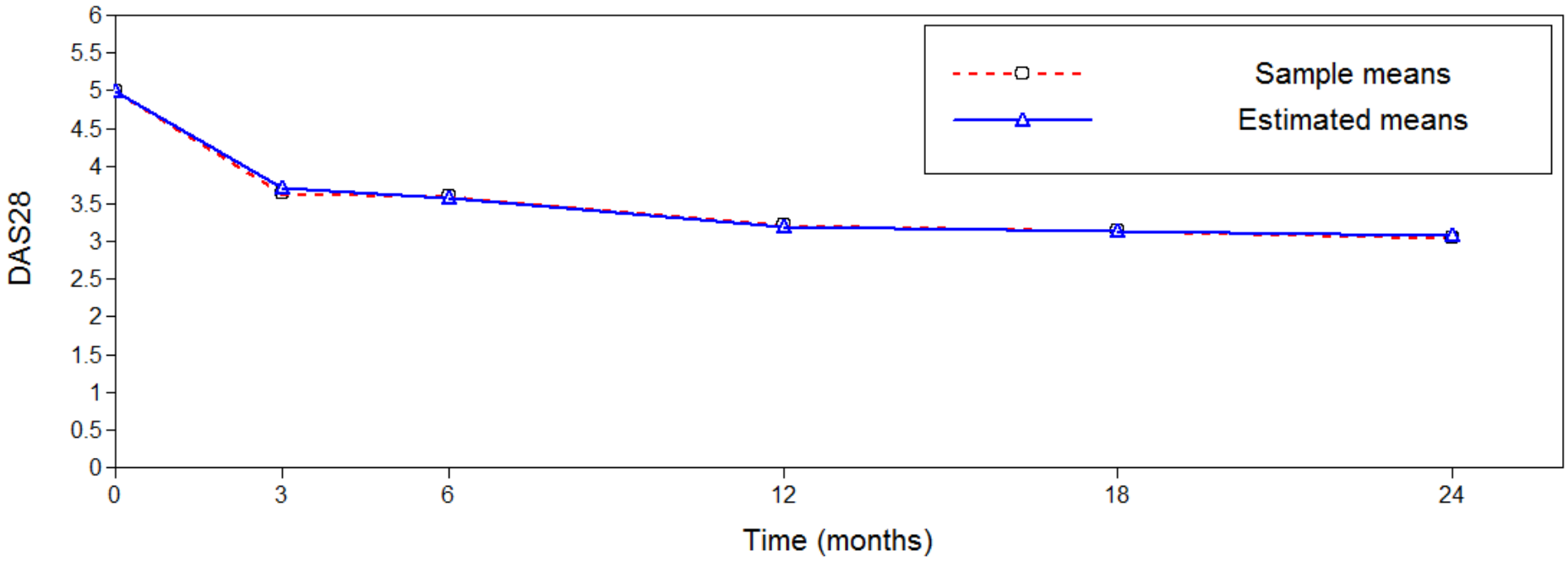

Figure 4-7 Graph to show how the sample mean Disease Activity Score from a count of 28 joints (DAS28) changed with time, compared to the means estimated by the freed loading growth curve model of change in disease activity in Yorkshire Early Arthritis Register

Estimated means refers the means estimated by the freed loading growth curve, which is shown compared to the sample means.
DAS28, disease activity score based upon count of 28 swollen and tender joints and C-reactive protein.

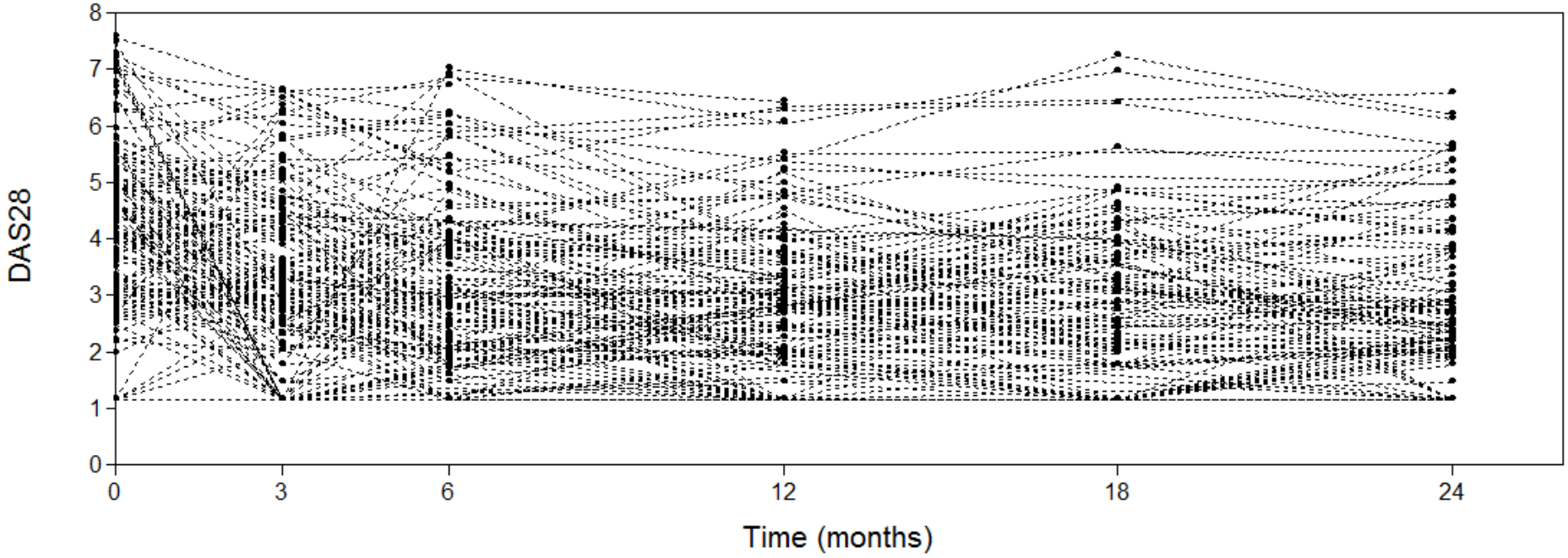

Figure 4-8 Graph to show actual values of Disease Activity Score from a count of 28 joints (DAS28) from a random sample of 140 cases from Yorkshire Early Arthritis Register

DAS28, disease activity score based upon count of 28 swollen and tender joints and C-reactive protein

4.6 Identification of latent trajectories of change in disease activity

Using the freed loading growth curve described in 4.5.4, increasing numbers of trajectories were applied to the model and indices of fit (including AIC, BIC, LMR-LRT and BLRT, as described in 2.5.4.3) were compared in order to determine the optimal number of trajectories. Also presented here are the numbers of cases within each class, average probability of class membership, and descriptions and graphical representations of each trajectory. Table 4-6 displays the fit indices for successive numbers of trajectories, together with the numbers of cases assigned to each class. Based upon this information, the 2 class model (trajectories are shown in Figure 4-9) was accepted as the best fit. This is because the BIC does not improve significantly when a third class is added to the 2 class model. Furthermore, entropy reduced from 0.605 to 0.516 with the addition of a third class, suggesting the three class model did not fit the data as well. Inspection of the 3 trajectories, which are graphically displayed in Figure 4-10, reveals that class 1 cases had DAS28 scores that were highest at baseline, and remained high (>4.75) throughout follow up, class 2 cases had the lowest DAS28 scores at baseline and throughout, whilst class 3 cases had high DAS28 at the start, which then fell dramatically and by 18 months, the trajectory was similar to that of class 2.

In the 2 class model, a quarter of cases were assigned to class 1 and the remainder to class 2. Class 1 may be described as ‘high DAS28’, because for this trajectory mean DAS28 remained high, over 4.7, throughout the study. The mean probability of a patient assigned to trajectory 1 actually belonging to this class was 0.81 and therefore, there was a probability of 0.19 of actually belonging to trajectory 2. For the 75% of cases assigned to class 2, ‘low DAS28’, mean DAS28 fell sharply from 0 to 3 months and then continued to reduce throughout follow up, to approximately 2.7 at 24 months. There was a probability of 0.90 that a patient assigned to trajectory 2 belonged to this class and 0.10 that they should have been classified in the other.

Out of interest, a 4 class model also was tested, but was rejected for several reasons. The first reason was that the solution produced non equal highest log-likelihood values, indicating that it was a local maximum. Finding local maxima is a recognised problem associated with LCGA, especially with higher numbers of trajectory classes, and indicates that the solution provided by the software was the best for the given start values, but may not be the best overall solution (Berlin *et al.*, 2014). The number of random starts were increased from 500 to 600 to give the final 4 class model, but the decrease in BIC was modest compared to that of the 3 class model and entropy was only 0.594, which was lower than that of the model with 2 classes.

Table 4-8 Fit indices and numbers of cases in each trajectory for models of change in disease activity with increasing numbers of trajectory classes

Number of trajectory classes in model	Number of cases assigned to each class, based on the estimated model (%)			AIC	BIC	Adjusted BIC	LMR-LRT p-value	BLRT p-value	Entropy
1	Trajectory 1	1398	(100)	86563	87469	86920			
2	Trajectory 1	359	(25)	20244	20349	20285	<0.0001	<0.0001	0.605
	Trajectory 2	1038	(75)						
3	Trajectory 1	312	(25)	20236	20356	20283	0.0014	<0.0001	0.516
	Trajectory 2	257	(18)						
	Trajectory 3	797	(57)						
4	Trajectory 1	11	(1)	20215	20351	20269	0.0184	<0.0001	0.594
	Trajectory 2	374	(27)						
	Trajectory 3	365	(26)						
	Trajectory 4	647	(46)						

*For the 4 class model, log-likelihood values were not equal, indicating that the solution was probably a local maximum.

AIC, Akaike information criteria; BIC, Bayesian information criteria; BLRT, Bootstrap likelihood ratio test; LMR-LRT, Lo, Mendell and Rubin likelihood ratio test; p, statistical probability

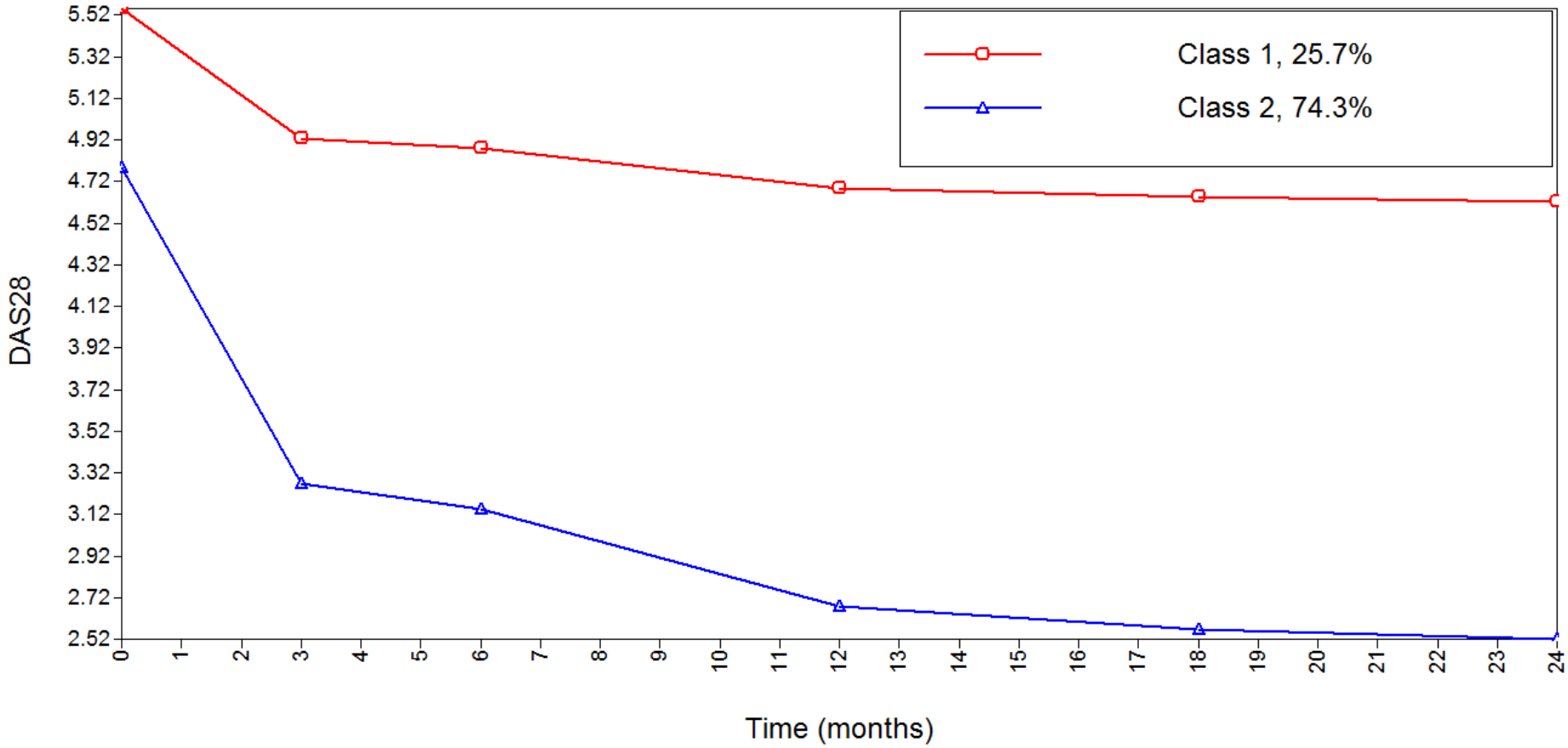

Figure 4-9 Illustration of the two latent trajectory classes of change in Disease Activity Score based upon counts of 28 joints (DAS28)

The proportion of cases assigned to each trajectory class is given as a percentage of the whole cohort.
DAS28, disease activity score based upon count of 28 swollen and tender joints and C-reactive protein.

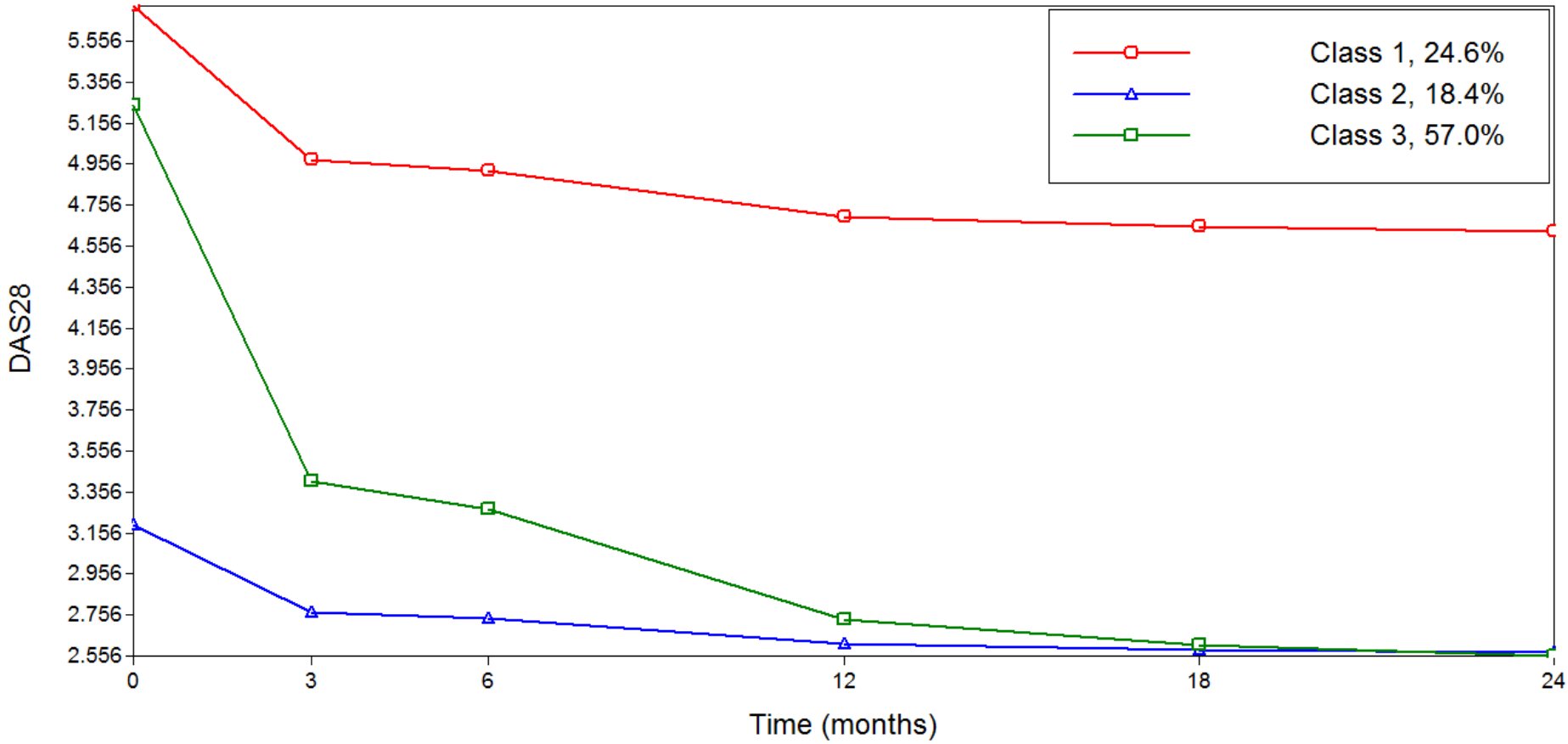

Figure 4-10 Illustration of the three latent trajectory classes of change in Disease Activity Score based upon counts of 28 joints (DAS28)

The proportion of cases assigned to each trajectory class is given as a percentage of the whole cohort.
DAS28, disease activity score based upon count of 28 swollen and tender joints and C-reactive protein.

4.7 Predictors of disease activity trajectory class membership

For trajectory class 2, the 'low DAS28' group, membership was more likely in male patients (OR 1.49; 95% CI 1.12, 1.90; p=0.007) and less likely in cases who were ACPA positive (OR 0.58; 95% CI 0.37, 0.92; p=0.020), or those reporting higher baseline fatigue. There was a 10% reduction in the odds of falling into the low disease activity trajectory per cm of baseline fatigue VAS: OR=0.90; 95% CI 0.86, 0.94; p<0.001. Membership of either YEAR cohort did not significantly affect the trajectory class membership and neither did IMD quartile, RF, or possession of one or more shared epitope alleles. In a prior model that did not include fatigue VAS (results are shown in Appendix 7), IMD significantly predicted DAS28 trajectory. IMD quartile 1, which represented the most deprived, compared to the least deprived areas was associated with membership of the less favourable trajectory: OR 1.50; 95% CI 1.10, 2.04, p=0.030. As this suggested that there may be an association between baseline variables and IMD, mean values were compared across the 4 quartiles of IMD, shown in Appendix 8. Mean fatigue VAS was highest for those represented by IMD 2 and lowest for the least deprived, IMD 4. A one-way between groups analysis of variance indicated that there was a small but statistically significant difference of 0.71cm of fatigue VAS between IMD groups 2 and 4 (p=0.030).

To see whether there was a difference if 2 copies of the shared epitope were present, a further model was tested, comparing the effect of one and two copies to no shared epitope alleles, but the effects were not statistically significant: regression coefficient for one copy was -0.118 (p=0.545) and for two copies -0.357 (p=0.110). The results of the multinomial logistic regression analysis of class 2 membership are displayed in Table 4-9.

Table 4-9 Results of multinomial logistic regression analysis of predictors of class 2 trajectory ('low disease activity') membership

Predictor	Coefficient	Odds ratio	(95% CI)		p
YEAR C cohort	0.06	1.06	(0.78,	1.41)	0.690
Male gender	**0.40**	**1.49**	**(1.12,**	**1.90)**	**0.007**
Age (years)	-0.00	1.00	(0.99,	1.01)	0.661
RF positive	-0.10	0.90	(0.60,	1.37)	0.631
ACPA positive	**-0.55**	**0.58**	**(0.37,**	**0.92)**	**0.020**
Shared epitope positive	-0.24	0.79	(0.54,	1.16)	0.223
IMD quartile 1	-0.34	0.71	(0.49,	1.04)	0.082
2	-0.24	0.79	(0.54,	1.15)	0.217
3	0.03	1.03	(0.70,	1.52)	0.890
Fatigue VAS (cm)	**-0.10**	**0.90**	**(0.86,**	**0.94)**	**<0.001**

Results of multinomial logistic regression analysis.
Outcome variable was membership of class 2 trajectory, described in 4.6.
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
For IMD, the referent category was the 4th quartile, which was the least deprived group: higher levels of deprivation were represented by reducing quartile number .
Independent variables were measured at baseline.
ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; cm, centimetres; p, probability (statistical significance); RF, rheumatoid factor; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register.

4.7.1 Sub analysis of Yorkshire Early Arthritis Register C

In order to test whether trajectory class was influenced by factors such as BMI, smoking and the presence of comorbidities, a sub analysis of all 713 cases from YEAR C with at least one DAS28 measurement was undertaken. Although this analysis was likely to have less power than the analysis of the whole cohort, the covariates of interest were not collected as part of YEAR B (or were largely missing, in the case of comorbidities) and therefore YEAR B could not be included in the present analysis. The growth curve model and its latent classes were identified again, for this smaller sample, and then the predictors of trajectory class membership were identified.

4.7.1.1 Latent growth curve model of change in disease activity in Yorkshire Early Arthritis Register C

As anticipated, the growth curve that best fit the data from YEAR C was a freed loading model, which is the same model type that was the best fit for the whole cohort. Table 4-10 gives fit indices for the linear, quadratic and freed loading

growth curve models applied to YEAR C and shows that the freed loading model had the lowest Chi-square and RMSEA values and the highest CFI.

Table 4-10 Fit statistics for successive models of change in disease activity in Yorkshire Early Arthritis Register C

Model	χ^2	df	p	CFI	RMSEA
Linear	403.9	16	<0.0001	0.649	0.184
Quadratic	206.6	12	<0.0001	0.824	0.151
Freed loading	87.1	12	<0.0001	0.932	0.094

CFI, comparative fit index; df, degrees of freedom; p, (statistical) probability; RMSEA, root mean square error of approximation; χ^2 Chi Square.

Table 4-11 gives the estimates derived from the freed loading model of change in DAS28 in YEAR C, which were similar to those for the whole cohort (Table 4-7), but with a lower value of the intercept, which represents the lower baseline mean DAS28 in YEAR C.

Table 4-11 Parameters estimated by the freed loading growth curve model of change in disease activity over time in Yorkshire Early Arthritis Register C

Parameter	Estimate	SE	p
Mean intercept	4.68	0.06	<0.001
Intercept variance	1.48	0.20	<0.001
Mean linear slope	-1.89	0.07	<0.001
Linear slope variance	1.70	0.26	<0.001
Linear slope at baseline	0.00		
Linear slope at 3m	0.65	0.03	<0.001
Linear slope at 6m	0.68	0.03	<0.001
Linear slope at 12m	0.89	0.03	<0.001
Linear slope at 18m	0.93	0.03	<0.001
Linear slope at 24m	1.00		
Intercept/ linear slope covariance	-0.93	0.22	<0.001

m, months; SE, standard error; p, (statistical) probability.

4.7.1.2 Identification of latent trajectories of change in disease activity in Yorkshire Early Arthritis Register C

Two trajectory classes were also selected for the YEAR C sub analysis, based upon the fit indices shown in Table 4-12 and the fact that in the 3 class model, the solution was likely to have been a local maximum because log- likelihood ratios were not equal for multiple starting values. The 2 trajectories are illustrated in Figure 4-11. Class 1, which included 77% of the cases from YEAR C, was more favourable, with a mean DAS28 that dropped steeply from baseline to 3 months and then continued to fall down to approximately 2.27 at 24 months. On the other hand, the less favourable class 2 included 23% of cases with higher mean DAS28 at baseline that remained persistently moderate throughout follow up (>4.47), with a slight overall reduction from 3 to 24 months.

Table 4-12 Fit indices and numbers of cases in each trajectory for models with increasing numbers of trajectory classes of disease activity in Yorkshire Early Arthritis Register C

Number of trajectory classes in model	Number of cases assigned to each class, based on the estimated model (%)			AIC	BIC	Adjusted BIC	LMR-LRT p-value	BLRT p-value	Entropy
1	Trajectory 1	713	(100)	43794	44516	44014			
2	Trajectory 1	549	(77)	10915	10997	10940	0.0007	<0.0001	0.663
	Trajectory 2	164	(23)						
3*	Trajectory 1	257	(36)	10903	10999	10932	0.2368	<0.0001	0.645
	Trajectory 2	82	(11)						
	Trajectory 3	374	(52)						

*For the 3 class model, log-likelihood values were not equal, indicating that the solution was probably a local maximum.
AIC, Akaike information criteria; BIC, Bayesian information criteria; BLRT, Bootstrap likelihood ratio test; LMR-LRT, Lo, Mendell and Rubin likelihood ratio test; p, (statistical) probability.

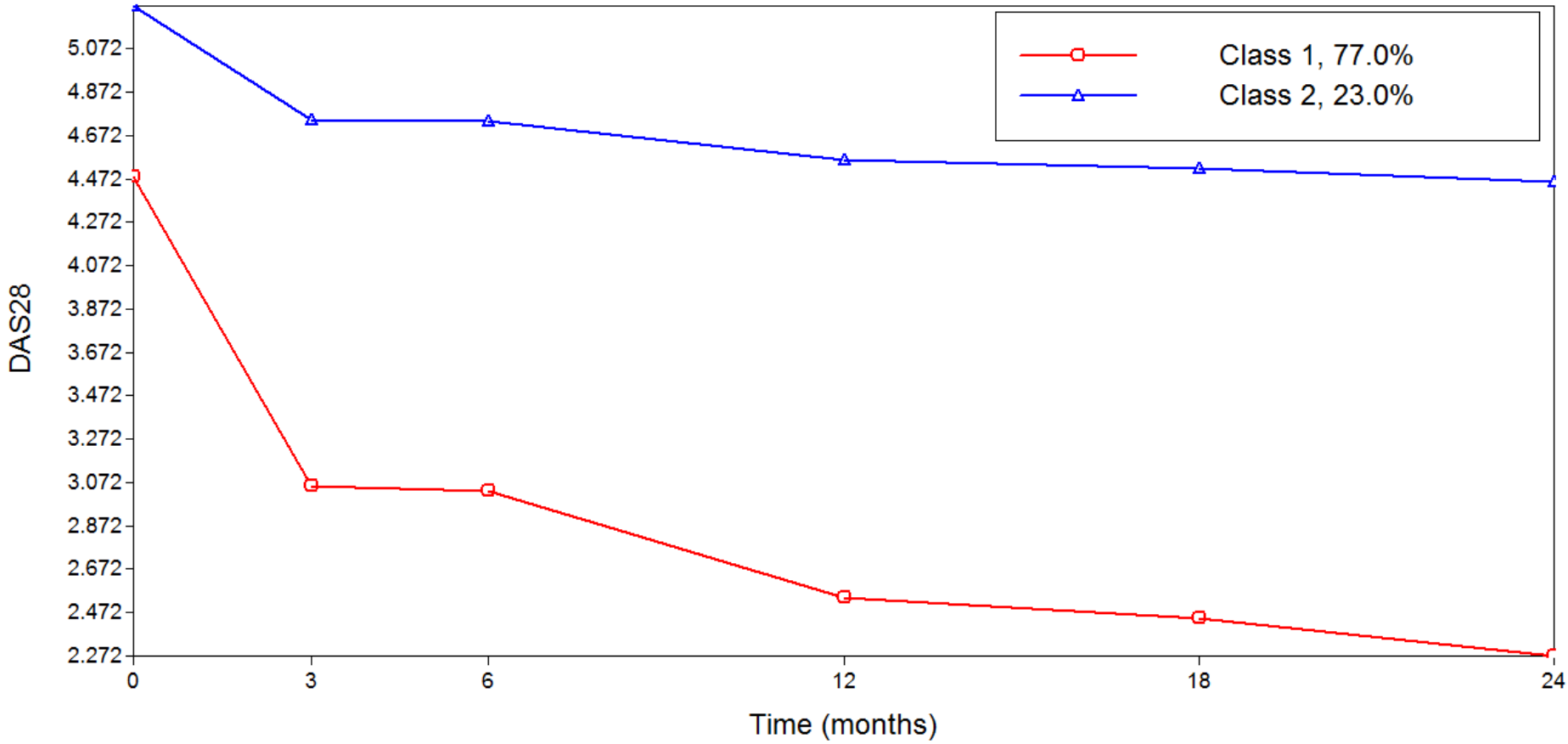

Figure 4-11 Illustration of the two latent trajectory classes of change in Disease Activity Score based upon counts of 28 joints (DAS28) for Yorkshire Early Arthritis Register C

The proportion of cases assigned to each trajectory class is given as a percentage of the whole cohort.
DAS28, disease activity score based upon counts of 28 joints and C-reactive protein.

4.7.1.3 Predictors of disease activity trajectory class membership in Yorkshire Early Arthritis Register C

Table 4-13 summarises the results of the multinomial logistic regression analysis of predictors of trajectory class 2 (least favourable) membership. Predictors of trajectory class membership 2 were: ACPA positivity (OR 1.99; 95% CI 1.05, 3.77; p=0.034), higher BMI, and greater baseline fatigue. A single unit increase in baseline BMI was associated with a 4% increase in the odds of membership of trajectory class 2 and a 1cm increase in baseline VAS was associated with a 10% increase in the odds of trajectory class 2 membership. Contrary to the analysis of the whole cohort, gender did not have a significant effect on trajectory class in YEAR C. Lower SES was almost significant (at the 5% level of statistical significance) as a predictor of membership of the poorer outcome trajectory. Compared to those in the 4th quartile of IMD (that is, the high SES quartile), those in the 1st quartile were more likely to belong to the less favourable class 2 trajectory: OR 1.83; 95%CI 0.99, 3.40; p=0.054. In a prior model that did not include fatigue VAS (shown in Appendix 7, Table 7B), the lower 2 quartiles of IMD predicted worse DAS28 trajectory: OR of membership of more favourable trajectory was 0.54; 95% CI 0.32, 0.88; p=0.039 and 0.55; 95% CI 0.34, 0.90; p=0.045 for the lowest and second-lowest quartiles of IMD, respectively. Similarly, in the model without fatigue, male gender predicted the more favourable DAS28 cohort: OR 2.13; 95% CI 1.46, 3.10; p=0.001. A relationship between fatigue VAS and IMD quartile has already been observed (Section 4.7 and Appendix 8), and furthermore, mean baseline fatigue VAS was greater in women than men: 5.01cm, compared to 3.99cm. Age, RF positivity, baseline number of pack years of cigarette smoking and the presence of comorbidities were not significant predictors of trajectory class membership.

Table 4-13 Results of multinomial logistic regression analysis of predictors of disease activity class 2 trajectory (less favourable) membership for Yorkshire Early Arthritis Register C

Predictor	Coefficient	Odds ratio	(95% CI)		p
Male gender	-0.11	0.90	(0.58,	1.38)	0.618
Age (years)	-0.00	1.00	(0.98,	1.01)	0.839
RF positive	-0.14	0.87	(0.49,	1.55)	0.640
ACPA positive	**0.69**	**1.99**	**(1.05,**	**3.77)**	**0.034**
Shared epitope positive	0.13	1.14	(0.85,	1.51)	0.384
IMD quartile 1	0.61	1.83	(0.99,	3.40)	0.054
2	0.43	1.53	(0.83,	2.82)	0.171
3	0.34	1.40	(0.74	2.67)	0.304
BMI (Kg/m^2)	**0.04**	**1.04**	**(1.00,**	**1.07)**	**0.033**
Smoking (pack years)	0.01	1.01	(0.99,	1.02)	0.185
Comorbidities	0.22	1.24	(0.76,	2.02)	0.386
Fatigue VAS (cm)	**0.09**	**1.10**	**(1.03,**	**1.17)**	**0.006**

Results of multinomial logistic regression analysis.
Outcome variable was membership of class 2 trajectory, described in 4.7.1.3.
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
For IMD, the referent category was the 4th quartile, which was the least deprived group: higher levels of deprivation were represented by reducing quartile number .
Independent variables were measured at baseline.
One pack year was the equivalent of smoking 20 cigarettes per day for one year.
Comorbidities were classified as present /absent.
ACPA, anti-citrullinated peptide antibodies; BMI, body mass index; CI, confidence interval; cm, centimetres; IMD, index of multiple deprivation; Kg/m^2, kilograms per metre square; p, (statistical) probability; RF, rheumatoid factor; VAS, visual analogue score.

4.8 Summary of predictors of change in disease activity

The present chapter has explored potential predictors of change in disease activity, measured by DAS28, over 24 months in early RA using both cross-sectional and longitudinal methods. In the cross-sectional approach, linear regression with MI to account for missing data was used to investigate change in DAS28 from baseline to 6 and 12 months. The results are summarised in Table 4-14. As expected, higher baseline DAS28 was associated with greater subsequent fall, which is likely because there is greater scope for reduction, the greater the initial value. Another expected finding was that DAS28 continued to fall after the 6 month assessment, as optimisation of RA treatment continued, and therefore, decrease in DAS28 from baseline was greater after 12 months than 6 months. Reduction in DAS28 was more marked for male patients and greater baseline fatigue VAS was predictive of lesser reduction in DAS28. Male gender as a predictor of superior outcome in RA is well described (1.8.2.1), so this result was in keeping with previous findings; however, fatigue as a predictor of outcome has not been previously reported. Contrary to previous reports (reviewed in 1.8.2.3) autoantibodies and symptom duration were not statistically significant predictors of change in DAS28 in the cross sectional analyses, but it is noteworthy that ACPA status was the most frequently missing variable and this could possibly have distorted the results.

Data from YEAR B and C were analysed together in the regression models, but differences between the 2 cohorts were considered and ‘cohort’ was included as a predictor variable, together with interactions between ‘cohort’ and each of the other predictor variables. Higher baseline DAS28 was associated with a greater fall in DAS28 after 12 months, as described above, however this effect was less marked for YEAR C cases. In addition, YEAR C patients had a slightly greater (0.21 unit) fall in DAS28 after 6 months, which could be due to different treatment approaches, where YEAR C patients were offered MTX as first line treatment and YEAR B were offered SSA. Another difference between the two cohorts related to the effect of baseline pain VAS on change in DAS28 after 12 months: for YEAR B cases, there

was a very small (0.06 unit) lesser reduction in DAS28 per cm of baseline pain VAS, whilst the effect in YEAR C was even smaller (0.01 unit), but in the opposite direction, that is, associated with a greater decline in DAS28. Although the effects of pain VAS are in opposing directions for YEARs B and C, the sizes of these effects are probably small enough to be considered negligible.

Table 4-14 Summary of results from linear regression analyses of change in disease activity after six and twelve months

	Predictors of change in DAS28 from baseline	
	6 months	12 months
Mean change from baseline	-1.36	-1.75
Significant baseline predictors of greater reduction:		
	Male gender	
	YEAR C cohort	
		Pain VAS (YEAR C, small/ negligible effect)
	DAS28	DAS28
Significant baseline predictors of lesser reduction:		
	Fatigue VAS	Fatigue VAS
		Pain VAS (YEAR B)
Variation in outcome explained by model:		
	27%	33%

DAS28, disease activity score based upon counts of 28 joints; EMS, early morning stiffness; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register.

The longitudinal analyses used a latent growth curve to describe change in DAS28 over time, and then LCGA to determine an optimal number of growth curve trajectories, of which 2 were identified. Multinomial logistic regression was applied to identify baseline predictors of trajectory class membership. The same analyses were repeated using only YEAR C data in order to test the influence of additional covariates that were not available in YEAR B. Table 4-15 summarises the results of these analyses. Male gender was predictive of more favourable outcome in the analysis that included the whole YEAR cohort, whilst ACPA positivity and greater fatigue VAS predicted

worse outcome. Additionally, the sub analysis of YEAR C data revealed that greater BMI was also associated with membership of the less favourable trajectory class. Covariates that were not significant predictors of trajectory class were RF status, shared epitope status, pack years of smoking and comorbidities. However, limitations of the sub analysis included loss of power due to the smaller number of cases.

Table 4-15 Summary of results from multinomial logistic regression analyses of predictors of disease activity trajectory class

	Whole cohort N=1398	YEAR C sub-analysis N=713
Cases in less favourable class	359 (25%)	164 (23%)
Cases in more favourable class	1038 (75%)	549 (77%)
Significant baseline predictors of more favourable trajectory:		
	Male gender	
Significant baseline predictors of less favourable trajectory:		
	ACPA positive	ACPA positive
	Fatigue	Fatigue
		Higher BMI

ACPA, anti-citrullinated peptide antibodies; BMI, body mass index; YEAR, Yorkshire Early Arthritis Register.

To some extent the findings from the present Chapter have confirmed previously published findings, for example, that male gender is associated with better outcome and that social deprivation is associated with worse outcome. The additional finding that high BMI predicted a less favourable disease course in YEAR C is also in keeping with prior results. However, fatigue as a predictor of disease activity is not commonly reported. The next chapter will address how HAQ-DI changes with time, using the same techniques reported here, before the effects of change in DAS28 on change in HAQ-DI are examined.

Chapter 5 Change in disability over time

5.1 Introduction

This Chapter focuses on factors influencing change in HAQ-DI in early RA. Functional capacity is part of the 'core set' of outcomes for clinical trials in RA identified in order to standardise outcome reporting in RA studies (Boers *et al.*, 1994) and HAQ-DI was the chosen method of measuring this in YEAR. The importance of disability as a sequelae of RA was highlighted in patients from ERAS, in whom functional impairment at baseline was associated with future requirement of joint replacement surgery and the necessary instalment of devices and adaptations to facilitate activities of daily living, such as wheel chair use (Young *et al.*, 2000). Results in this Chapter are presented in the same sequence as Chapter 4 with the cross-sectional analysis of factors influencing change in HAQ-DI after 6 and 12 months presented first, followed by an examination of the growth curve of change in HAQ-DI over time, then identification of trajectories of change in HAQ-DI over time within the cohort. Finally, factors predicting trajectory class membership were explored in the whole cohort, and then in a sub analysis of YEAR C, using the additional covariates available in YEAR C but not YEAR B, which were smoking, BMI, and presence or absence of comorbidities. As in the analyses involving DAS28, MI was used to account for missing data in the cross sectional analysis and maximum likelihood estimation was used for the longitudinal analyses of change in HAQ-DI over time.

The present analyses were enhanced by the use of HAQ-DI as a continuous variable, which is possible because of its Rasch transformation performed by Dr Elizabeth Hensor (described in Section 2.5.1). In comparison, previously published work has used HAQ as a categorical, or even dichotomous variable (as discussed in 1.8.3). This new approach may add more information.

5.2 Baseline predictors of change in disability after six months

In the cross sectional linear regression analysis of predictors of change in HAQ-DI, male gender was associated with greater reduction in HAQ-DI, whilst greater baseline fatigue and age at baseline predicted a lesser reduction in HAQ-DI after both 6 and 12 months. On average, HAQ-DI reduced by 2.02 units after 6 months (SE 0.12), according to the estimated mean change obtained from the imputed data. The constant from the model of change in HAQ-DI after 6 months, which was -2.03 (negative change indicated fall in HAQ-DI), was consistent with this estimate. The complete case linear regression model explained only 13% of the variance in change in HAQ-DI, so factors not included in the current model may better explain this variance. The growth curve analysis described in 5.4 explored change in HAQ-DI with time and permitted deviation from the linear change described by the present regression model. Table 5-1 shows the results of the linear regression model of change in HAQ-DI after 6 months. HAQ-DI improved (reduced) by an average of 0.82 units more for males than females (SE 0.24, p 0.001) and on average, reduction in HAQ-DI after 6 months was 0.23 units less per 10 years of age (SE 0.10, p 0.024). Each cm of baseline fatigue VAS predicted a reduction in HAQ-DI that was 0.10 units less after 6 months (SE 0.04, p 0.023). There were no significant interactions in the model. The Wald test indicated that the effects of the interactions between YEAR cohort and categories of EMS duration were non- significant, for both the MI analysis (F statistic 0.52, 363 df, p 0.6699) and the complete case analysis (F statistic 0.84, 539 df, p 0.4696). Therefore the effects of baseline predictors were the same for YEAR B and C.

Table 5-1 Predictors of change in function from baseline to six months in Yorkshire Early Arthritis Register

		Multiple imputation analysis N=1416			Complete case analysis N=564		
		Coefficient (β)	SE	p	Coefficient (β)	SE	p
YEAR C		-0.26	0.24	0.281	0.38	0.36	0.385
Male gender		**-0.82**	**0.24**	**0.001**	-0.47	0.37	0.207
Age[†]		**0.23**	**0.10**	**0.024**	-0.05	0.13	0.702
SD		0.03	0.03	0.279	0.03	0.04	0.448
RF positive		-0.16	0.39	0.695	-0.27	0.45	0.547
ACPA positive		0.72	0.42	0.098	0.38	0.43	0.382
Pain VAS		-0.11	0.06	0.053	-0.13	0.08	0.084
Fatigue VAS		**0.10**	**0.04**	**0.023**	0.10	0.06	0.100
EMS	40-75 min	0.18	0.31	0.559	0.47	0.46	0.310
	90-210 min	-0.59	0.55	0.280	0.39	0.50	0.434
	≥220 min	-1.35	0.86	0.114	-0.71	0.57	0.213
DAS28		0.05	0.10	0.659	-0.08	0.16	0.616
HAQ-DI		**-0.34**	**0.03**	**<0.0001**	**-0.29**	**0.05**	**<0.0001**
Constant		**-2.03**	**0.55**	**<0.0001**	**-2.05**	**0.50**	**<0.0001**

Results of linear regression analysis. Outcome variable was change in HAQ-DI after 6 months (HAQ-DI at 6 months – baseline HAQ-DI).
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
[†]Age was entered into the model (as age in years)/10.
For EMS, the referent category was 0-35 minutes.
Independent variables were measured at baseline.
ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score from counts of 28 joints; EMS, early morning stiffness duration; HAQ-DI, disability component of health assessment questionnaire; min, minutes; N, number (of cases); p, (statistical) probability; RF, rheumatoid factor; SD, symptom duration; SE, standard error; VAS, visual analogue score (measured in centimetres); YEAR, Yorkshire Early Arthritis Register.

As described for the analyses of change in DAS28 (4.3 and 4.4), the MI analysis was compared to analysis of cases with complete data (complete case analysis), which is shown alongside the MI results in Table 5-1. Although the effect of cohort was not statistically significant in either model, the coefficients suggested opposite effects: compared to YEAR B, YEAR C cases' HAQ-DI fell by 0.26 units more according to the MI model but decreased by 0.38 units less according to the complete case model. Mean HAQ-DI after 6 months was lower in YEAR C when all available data were considered: mean HAQ-DI from 1113 cases was 8.06 (SE 0.22) in YEAR B and 7.43 in YEAR C (SE 0.21), which explains why the MI analysis suggested that YEAR C cases' HAQ-DI fell more over 6 months than YEAR B cases. Conversely, when only the 564 cases with complete data were considered, HAQ-DI at 6 months was higher for YEAR C than YEAR B (7.87, SE 0.31 and 7.66, SE 0.30, respectively.) This discrepancy highlights the potential pitfalls encountered by losing data when incomplete cases are disregarded. Another difference in the analyses is found in the coefficients relating to the effect of age on change in HAQ-DI: the MI analysis suggested that increasing age at baseline was associated with less of a reduction in HAQ-DI after 6 months, whilst the complete case analysis indicated that increasing baseline age was associated with a slightly greater fall in HAQ-DI after 6 months, of 0.05 units per 10 years of age at baseline (SE 0.13, p 0.702). Scatterplots shown in Figures 5-1 and 5-2 illustrate why these results differed: when all available data were taken into account (Figure 5-1), there was a very slight positive change in HAQ-DI associated with increasing baseline age. Conversely, when only the cases used in the complete case analysis were considered (Figure 5-2), the effect of baseline age was in the opposite direction, that is, increasing baseline age was associated with a slight fall in HAQ-DI after 6 months.

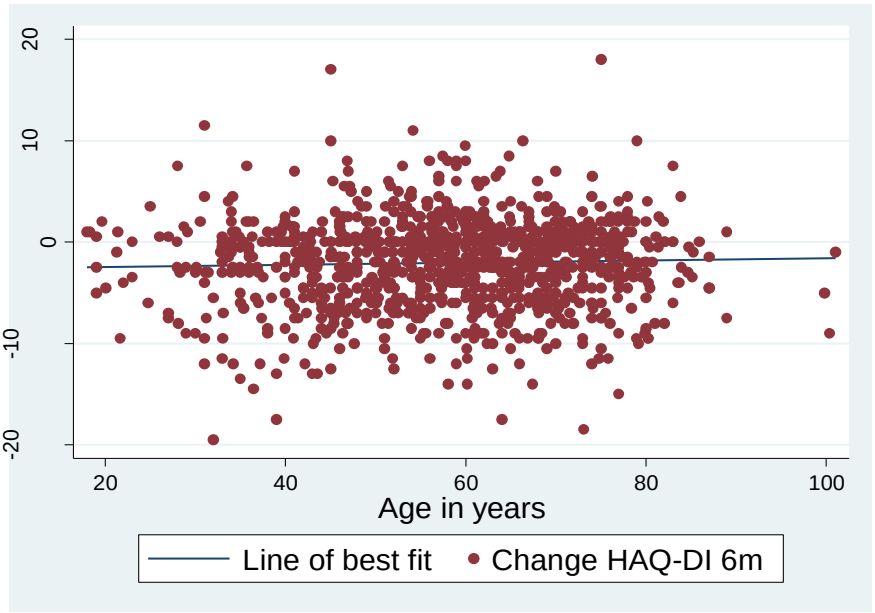

Figure 5-1 Scatterplot with line of best fit to show how change in function after 6 months varies with baseline age in all cases from Yorkshire Early Arthritis Register

Close inspection of the line of best fit indicates that change in HAQ-DI is slightly more positive (that is, reduction in HAQ-DI is less) with increasing age at baseline. 6m, 6 months; HAQ-DI, disability index component of health assessment questionnaire.

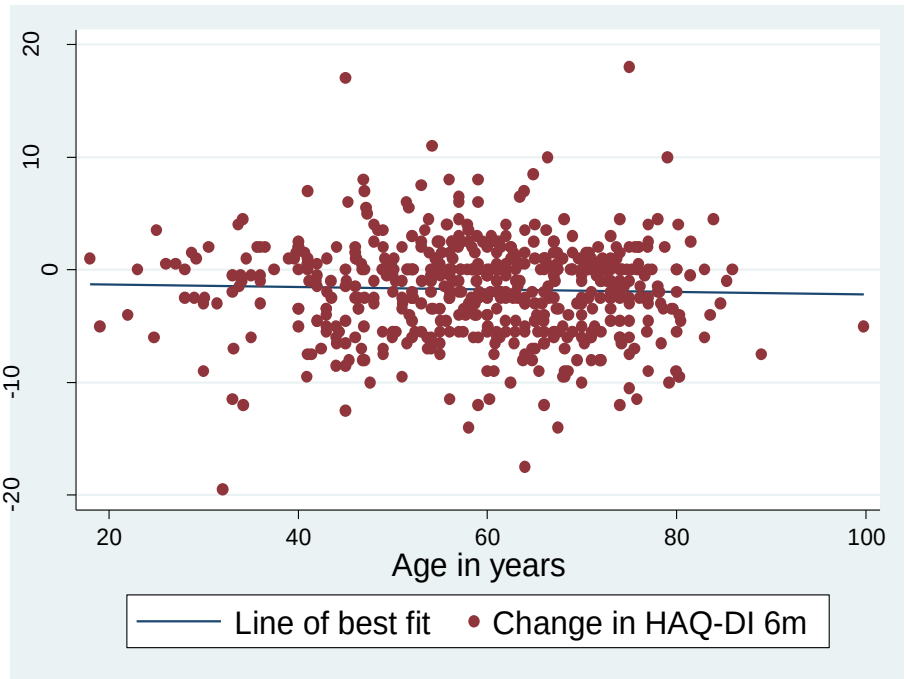

Figure 5-2 Scatterplot with line of best fit to show how change in function after 6 months varies with baseline age in Yorkshire Early Arthritis Register cases included in complete case analysis of change in function after 6 months

Close inspection of the line of best fit reveals that change in HAQ-DI is slightly more negative (that is, greater reduction in HAQ-DI) with increasing age at baseline. 6m, 6 months; HAQ-DI, disability index component of health assessment questionnaire.

As for the analyses of change in DAS28 presented in 4.3 and 4.4, fit of the linear regression model was assessed. Figure 5-3 is a scatterplot of the residual versus fitted values from the model of change in HAQ-DI after 6 months. There is no pattern to the points on the plot, which excludes deviation from the assumption of homoscedasticity. Figure 5-4 is a histogram depicting the distribution of the residuals, which were approximately normally distributed with a mean close to zero. However, there were three cases where the residuals' values were outside the range of -3.3 to 3.3. These values were -3.97, 3.58 and 4.45, suggesting that these cases could be outliers in the model. The three cases were deleted and the model was re-applied to the resulting dataset, however, this had little impact on the regression coefficients and standard errors, and therefore the three outlying cases were considered not to affect the results and were retained in the dataset.

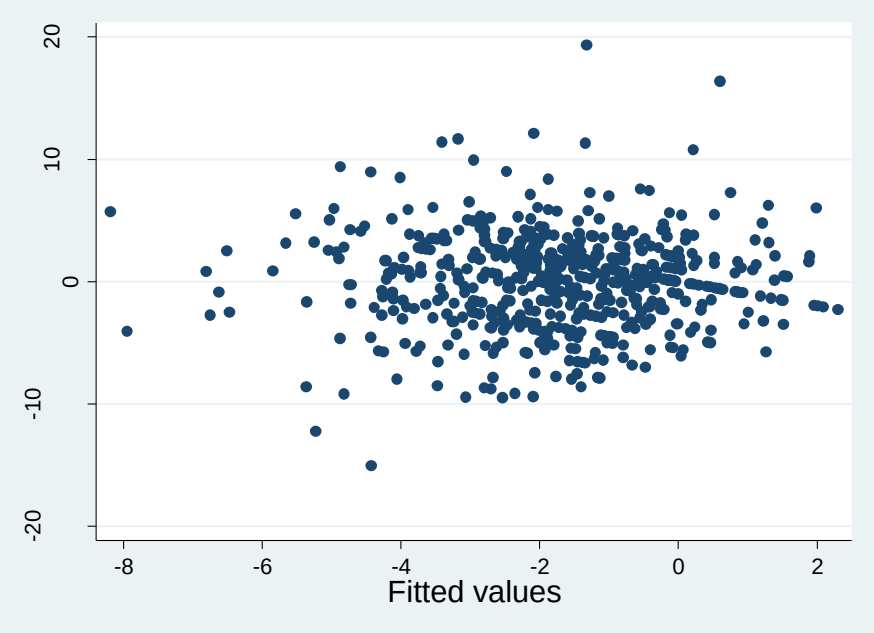

Figure 5-3 Residual versus fittted plot for the linear regression model of change in function according to Disability Index component of the Health Assessment Questionnaire (HAQ-DI) after 6 months for participants of Yorkshire Early Arthritis Register

Residual values represented the difference between observed change in HAQ-DI and change in HAQ-DI predicted by the model, whilst fitted values are those predicted by the model.

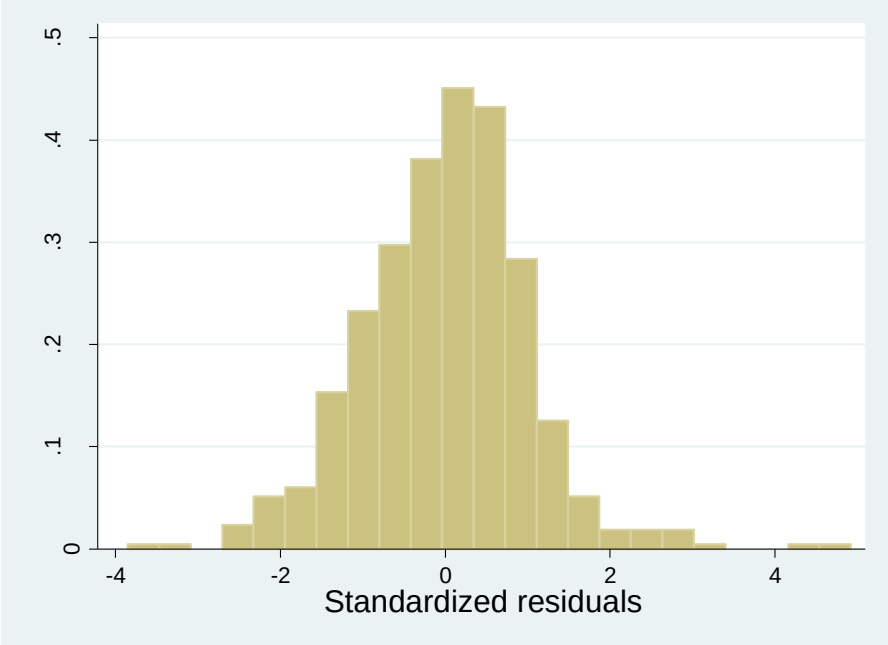

Figure 5-4 Histogram to show distribution of residuals from the linear regression analysis of change in function according to Disability Index component of the Health Assessment Questionnaire (HAQ-DI) after 6 months in Yorkshire Early Arthritis Register
Residual values represent the difference between actual change in HAQ-DI and change in HAQ-DI predicted by the model.
Range of standardised residual values (equal to actual residual divided by its standard error): -3.97 to 4.45.

5.3 Baseline predictors of change in disability after twelve months

Mean reduction in HAQ-DI after 12 months, calculated from the MI dataset, was 2.57 (SE 0.14). The constant from the linear regression analysis of change in HAQ-DI after 12 months (representing the change in HAQ-DI for the 'baseline patient', see Paragraph 4.3) approached this value, at -2.36. The complete case model explained only 18% of the variability in change in HAQ-DI after 12 months (adjusted R square value). The results are shown in Table 5-2. As for the model of change in HAQ-DI after 6 months, fall in HAQ-DI was greater for males than females: HAQ-DI improved (reduced) by an average of 0.89 units more after 12 months (SE 0.26, p 0.001). Similarly, greater age at baseline predicted less improvement in function (reduction in HAQ-DI): on average, reduction in HAQ-DI after 12 months was 0.28 units less per 10 years of age (SE 0.10, p 0.004). Furthermore, each cm of

baseline fatigue VAS predicted a reduction in HAQ-DI that was 0.11 units less after 12 months (SE 0.05, p 0.017). It is also noteworthy that in this model, the main effect of cohort approached statistical significance, with YEAR C patients having a 0.48 unit greater fall in HAQ-DI than YEAR B patients (SE 0.26, p 0.072). This may reflect the differences between treatment strategies in YEAR B (SSA) and YEAR C (MTX). Duration of EMS also approached statistical significance, and patents who reported ≥220 minutes of EMS at baseline achieved a fall in HAQ-DI that was on average 0.68 units more than cases reporting 0-35 minutes of stiffness at baseline (SE 0.38, p 0.075). There were no significant interaction effects in the MI model, so coefficients relating to the independent variables can be applied across both YEAR cohorts. The results of the Wald test for a significant interaction between cohort and EMS duration were negative when applied for both MI and complete case models (MI: F statistic = 0.22, df 763, p= 0.8850 and complete case model: F statistic 0.01, df 525 and p= 0.9985).

Table 5-2 Predictors of change in function from baseline to twelve months in Yorkshire Early Arthritis Register

		Multiple imputation analysis N=1416			Complete case analysis N=550		
		Coefficient (β)	SE	p	Coefficient (β)	SE	p
YEAR C		-0.48	0.26	0.072	-0.09	0.38	0.803
Male gender		**-0.89**	**0.26**	**0.001**	**-1.35**	**0.39**	**0.001**
Age†		**0.28**	**0.10**	**0.004**	0.25	0.14	0.072
SD		0.02	0.04	0.528	0.06	0.04	0.152
RF positive		0.08	0.35	0.811	-0.20	0.48	0.679
ACPA positive		0.56	0.34	0.107	0.87	0.46	0.057
Pain VAS		-0.02	0.07	0.716	0.11	0.11	0.297
Fatigue VAS		**0.11**	**0.05**	**0.017**	**0.14**	**0.06**	**0.024**
EMS	40-75 min	-0.04	0.32	0.912	0.31	0.19	0.530
	90-210 min	0.04	0.35	0.919	0.52	0.86	0.547
	≥220 min	-0.68	0.38	0.075	-1.69	1.33	0.207
DAS28		-0.05	0.11	0.641	-0.14	0.17	0.395
HAQ-DI		**-0.43**	**0.03**	**<0.0001**	**-0.39**	**0.05**	**<0.0001**
Interaction effect:							
Cohort*Pain VAS		Not included in model			-0.23	0.13	0.076
Constant		**-2.36**	**0.35**	**<0.0001**	**-3.11**	**0.88**	**<0.0001**

Results of linear regression analysis. Outcome variable was change in HAQ-DI after 12 months (HAQ-DI at 12 months – baseline HAQ-DI).
Statistically significant (p<0.05) coefficients are highlighted in **bold.**
†Age was entered into the model (as age in years)/10.
*Indicates an interaction effect between 2 variables.
For EMS, the referent category was 0-35 minutes.
Independent variables were measured at baseline.
ACPA, anti-citrullinated peptide antibodies; DAS28, disease activity score from counts of 28 joints; EMS, early morning stiffness duration; min, minutes; N, number (of cases); p, (statistical) probability; RF, rheumatoid factor; SD, symptom duration; SE, standard error; VAS, visual analogue score (measured in centimetres); YEAR, Yorkshire Early Arthritis Register.

Table 5-2 also includes results from the analysis of complete cases, which shows a significant interaction effect indicating that the effect of baseline pain VAS was different for YEAR B and C participants. Whilst YEAR B cases experienced a 0.11 unit lesser fall in HAQ-DI per cm of baseline pain VAS, YEAR C cases experienced a 0.23 unit greater fall in HAQ-DI per cm of baseline VAS, which is an effect in the same direction as the coefficient for pain VAS produced by the MI model. Another difference between the MI and complete case models is that the coefficients corresponding to the effect of RF were in opposite directions. In the MI analysis, the regression coefficient suggested that RF positive patients saw a lesser improvement (reduction) in HAQ-DI than the RF negative patients (0.08, SE 0.35 p 0.811), whilst analysis of the complete cases suggested that RF positive patients saw a 0.20 unit greater decline in HAQ-DI than RF negative patients (SE 0.48, p 0.679). As with previous discrepancies between the MI and complete case models, the explanation can be found by inspection of the data: the mean change in HAQ-DI was slightly greater for RF positive patients amongst complete cases, but not when all cases were analysed, as shown in Table 5-3.

Table 5-3 Comparison of mean twelve month change in Disability Index component of Health Assessment Questionnaire (HAQ-DI) for rheumatoid factor positive and negative cases, in all cases and those included in the complete case linear regression analysis

		All cases where data were available*	Cases included in complete case analysis
		N=974	N=550
Change in HAQ-DI	RF negative	-2.73	-2.63
	RF positive	-2.57	-2.67

Change in HAQ-DI was calculated by subtracting baseline HAQ-DI from that at 12 months.
*All cases included those with available data including baseline RF, HAQ-DI and 12 month HAQ-DI.
HAQ-DI, disability index component of the health assessment questionnaire; N, number (of cases); RF, rheumatoid factor.

Model fit was assessed in the same manner as the previous linear regression models. Figure 5-5 is a plot of the residual versus fitted values, showing that there was no discernible pattern. This is reassuring that the assumption of homoscedasticity was met. A histogram representing the distribution of the standardised residuals is shown in Figure 5-6, which reveals an approximately normal distribution with a mean close to zero. The spread of the values of the standardised residuals was within the range of -3.3 to 3.3, which is reassuring that there were no outliers.

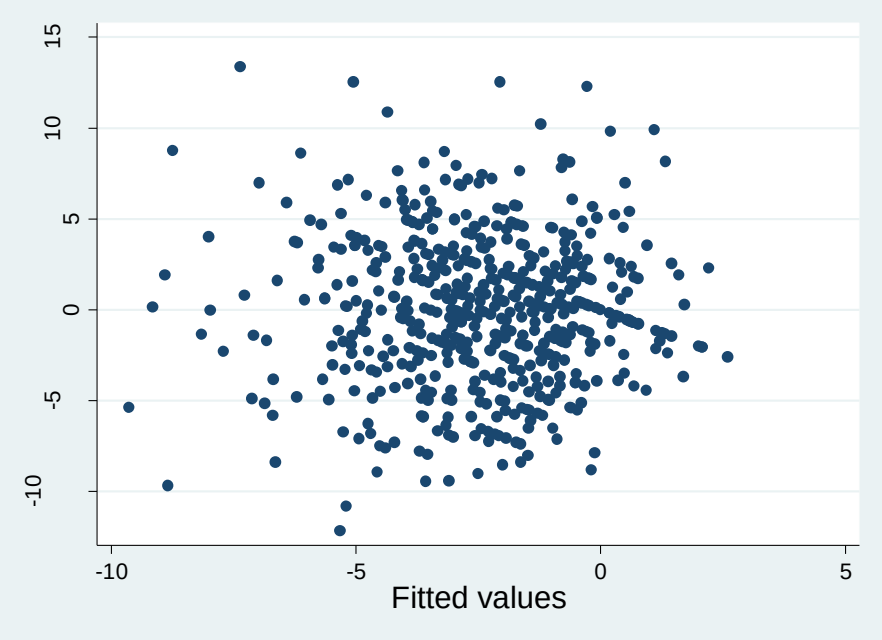

Figure 5-5 Residual versus fittted plot for the linear regression model of change in function according to Disability Index component of the Health Assessment Questionnaire (HAQ-DI) after 12 months for participants of Yorkshire Early Arthritis Register

Residual values represented the difference between observed change in HAQ-DI and change in HAQ-DI predicted by the model, whilst fitted values are those predicted by the model.

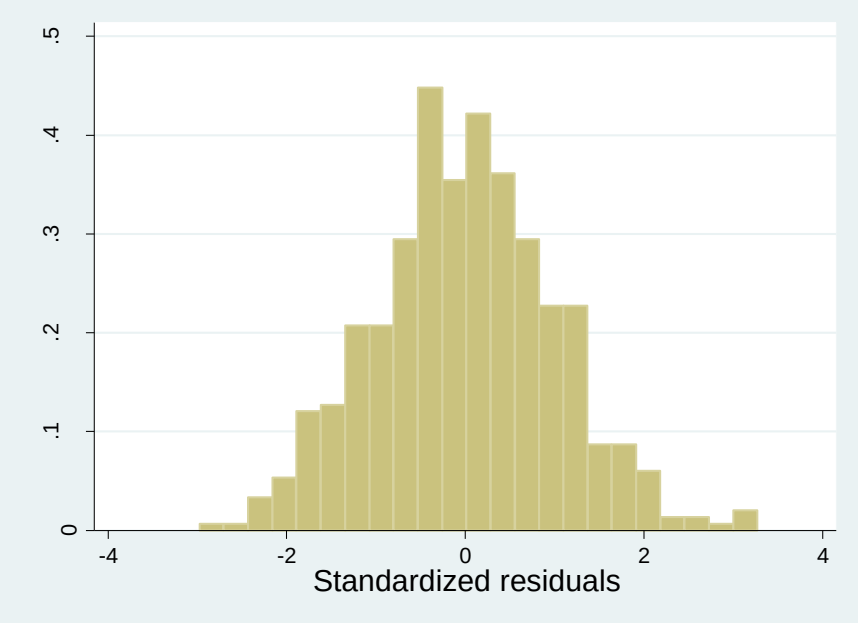

Figure 5-6 Histogram to show distribution of residuals from the linear regression analysis of change in function according to Disability Index component of the Health Assessment Questionnaire (HAQ-DI) after 12 months in Yorkshire Early Arthritis Register

Residual values represent the difference between actual change in HAQ-DI and change in HAQ-DI predicted by the model.

Range of standardised residual values (equal to actual residual divided by its standard error): -2.97 to 3.27.

5.4 Latent growth curve model of change in disability

5.4.1 Mean disability over time

Table 5-4 gives mean values of HAQ-DI at each data collection visit for the YEAR cohort as a whole, and also for YEAR B and C separately. HAQ-DI decreased with time, with the greatest reduction after the initial 6 months. It then continued to decline, but at a slower rate.

Table 5-4 Means and standard errors of Disability Index component of the Health Assessment Questionnaire (HAQ-DI) in Yorkshire Early Arthritis Register

	Mean HAQ-DI (SE)		
Time	YEAR (whole cohort)	YEAR B	YEAR C
Baseline	9.81 (0.12)	10.21 (0.17)	9.41 (0.18)
6 months	7.73 (0.15)	8.06 (0.22)	7.43 (0.21)
12 months	7.13 (0.15)	7.59 (0.22)	6.73 (0.21)
18 months	6.93 (0.16)	7.42 (0.25)	6.55 (0.22)
24 months	6.71 (0.16)	7.34 (0.25)	6.22 (0.22)

HAQ-DI, disability index component of health assessment questionnaire ; SE, standard error; YEAR, Yorkshire Early Arthritis Register.

5.4.2 Linear growth curve model of change in disability

As HAQ-DI was never captured for 7 individuals, the growth curve analyses of HAQ-DI included 1409 cases from YEAR. The linear model was a poor fit to the data, suggested by the χ^2 value of 385.711, df=13, p<0.0001, the CFI of 0.898 and RMSEA of 0.143 (90%CI 0.131, 0.156). This was expected, as the pattern of fall in mean HAQ-DI did not appear to follow a linear trend (Table 5-4), however, the linear growth curve is described here and in Table 5-5 so that it can be compared to subsequent models. The mean intercept, which represented the mean HAQ-DI at baseline estimated by the model, was 9.31 out of a total possible HAQ-DI of 24 (SE 0.18, p<0.001). However, the variance of this estimate was considerable: (13.67, SE 0.81, p<0.001), suggesting that there was a lot of inter-individual variation in this value. The mean linear slope was -0.54 (SE 0.05, p<0.001), which implied that on

average, HAQ-DI reduced by 0.54 units per 6 months: much lower than expected. (Subtraction of mean 6 month HAQ-DI from mean baseline HAQ-DI suggested a change of 2.08 units, Table 5-4.) The model implied a difference in intercept between the 2 cohorts, which was 9.31 for YEAR B and 8.40 for YEAR C (0.91 units lower, SE 0.24, p<0.001). Examination of the mean baseline HAQ-DI values shown in Table 5-4 reveals that whilst the value for YEAR C is indeed lower (9.41, compared to 10.21 in YEAR B), the model estimated values are less than expected. The model implied that the difference in rate of change in HAQ-DI between the 2 cohorts was not significant (-0.01, SE=0.07, p=0.911). The growth curve is illustrated in Figure 5-7, which compares change in mean HAQ-DI described by the model to observed mean HAQ-DI values.

Table 5-5 Parameters estimated by the linear growth curve model of change in Disability Index component of the Health Assessment Questionnaire (HAQ-DI) over time in Yorkshire Early Arthritis Register

Parameter	Estimate	(SE)	p
Mean intercept	9.31	0.18	<0.001
Intercept variance	13.67	0.81	<0.001
Mean linear slope	-0.54	0.05	<0.001
Linear slope variance	0.35	0.06	<0.001
Intercept/ linear slope covariance	0.65	0.17	<0.001
Regression of parameters on YEAR C cohort			
Mean intercept on YEAR cohort	-0.91	0.24	<0.001
Mean linear slope on YEAR cohort	-0.01	0.07	0.911

p, (statistical) probability; SE, standard error; YEAR, Yorkshire Early Arthritis Register.

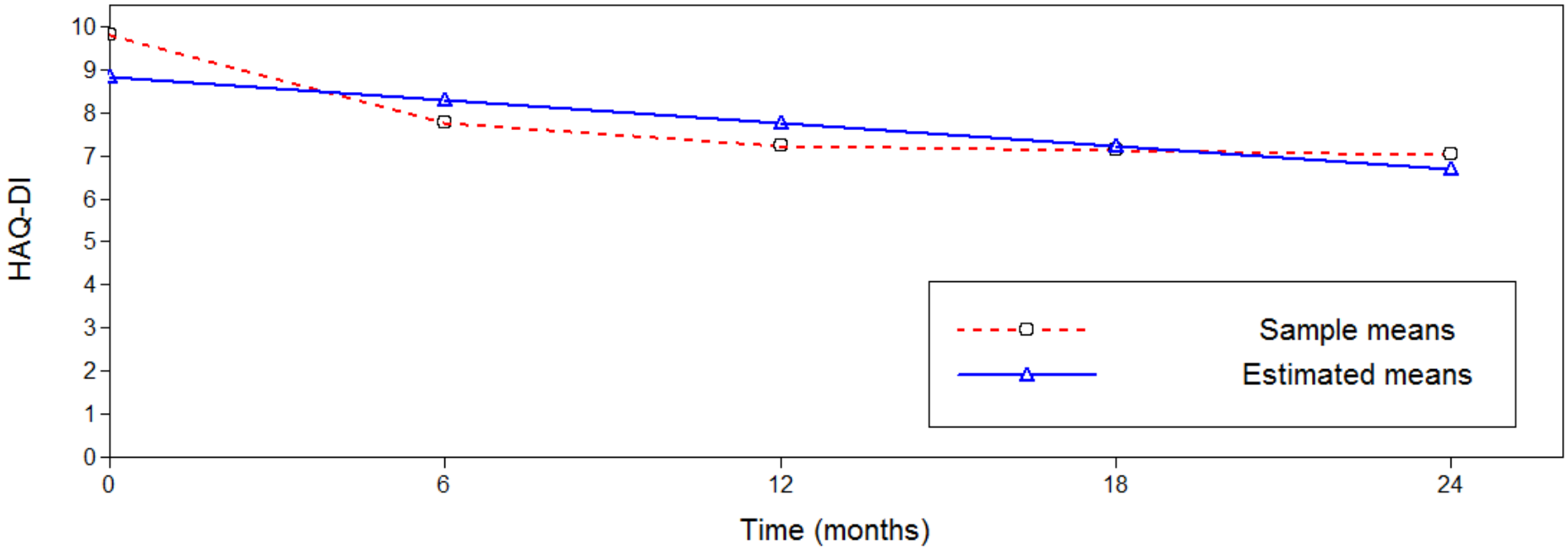

Figure 5-7 Graph to show how the sample mean Disability Index component of the Health Assessment Questionnaire (HAQ-DI) changed with time, compared to the means estimated by the linear growth curve model of change in HAQ-DI in Yorkshire Early Arthritis Register

HAQ-DI, disability index component of health assessment questionnaire.

5.4.3 Quadratic growth curve model of change in disability

This model was specified with an additional quadratic component, to allow for non-linear change in HAQ-DI with time. There was improved model fit compared to the linear model, as indicated by the following indices: $\chi^2 = 70.2$, df= 8, p<0.0001; CFI 0.983, RMSEA 0.074 (90% CI 0.059, 0.091). Table 5-6 gives the model estimated parameters that describe this growth curve. The mean intercept estimated by the model, representing mean baseline HAQ-DI, was 10.08 (SE 0.18, p<0.001), which is much closer to the actual mean HAQ-DI value for YEAR B of 10.21 shown in Table 5-4. The model implied a statistically significant difference in this value across the cohorts, with the intercept value for YEAR C being 9.20 (0.88 units lower than for YEAR B, SE 0.24, p<0.001), which was lower than the actual mean value of 9.41 shown in Table 5-4. Mean linear slope was -1.80, suggesting that mean HAQ-DI fell by an average of 1.80 units per 6 months initially, however, the relatively large variance of this parameter (5.79, SE 0.80, p<0.001) indicated variation within the cohort. There was no statistically significant difference between cohorts for this parameter. The mean quadratic slope value of 0.30 (SE 0.03, p<0.001) indicated that the rate of decline in HAQ-DI reduced with time, and again, this effect was not statistically different between YEARs B and C. Covariances between intercept and linear slope and between intercept and quadratic slope were non-significant, suggesting the rate of change in HAQ-DI did not vary according to baseline HAQ-DI. There was a significant covariance of - 1.14 between linear and quadratic slope (SE 0.17, p<0.001), indicating that a lesser initial fall in HAQ-DI was associated with a greater subsequent rate of fall in HAQ-DI. Whilst the overall quadratic slope (0.30) implied that the rate of fall in HAQ-DI slowed with time, this covariance suggested that for cases with lesser initial fall in HAQ-DI (or a more positive linear slope value), HAQ-DI should fall more quickly with time. The growth curve is represented graphically in Figure 5-8, which compares model- estimated means to observed mean values from the cohort. Whilst this curve appears to fit the data better, there is potential for the model to be improved. Therefore, a freed loading model was tested and is described in Paragraph 5.4.4.

Table 5-6 Parameters estimated by the quadratic growth curve model of change in Disability Index component of the Health Assessment Questionnaire (HAQ-DI) in Yorkshire Early Arthritis Register

Parameter	Estimate	(SE)	p
Mean intercept	10.08	0.18	<0.001
Intercept variance	13.31	1.04	<0.001
Mean linear slope	-1.80	0.16	<0.001
Linear slope variance	5.79	0.80	<0.001
Mean quadratic slope	0.30	0.03	<0.001
Quadratic slope variance	0.25	0.04	<0.001
Intercept/ linear slope covariance	-0.01	0.77	0.989
Intercept/ quadratic slope covariance	-0.03	0.15	0.848
Linear slope/ quadratic slope covariance	-1.14	0.17	<0.001
Regression of parameters on YEAR C cohort			
Mean intercept on YEAR cohort	-0.88	0.24	<0.001
Mean linear slope on YEAR cohort	0.02	0.21	0.916
Mean quadratic slope on YEAR cohort	-0.01	0.05	0.804

p, (statistical) probability; SE, standard error, YEAR, Yorkshire Early Arthritis Register.

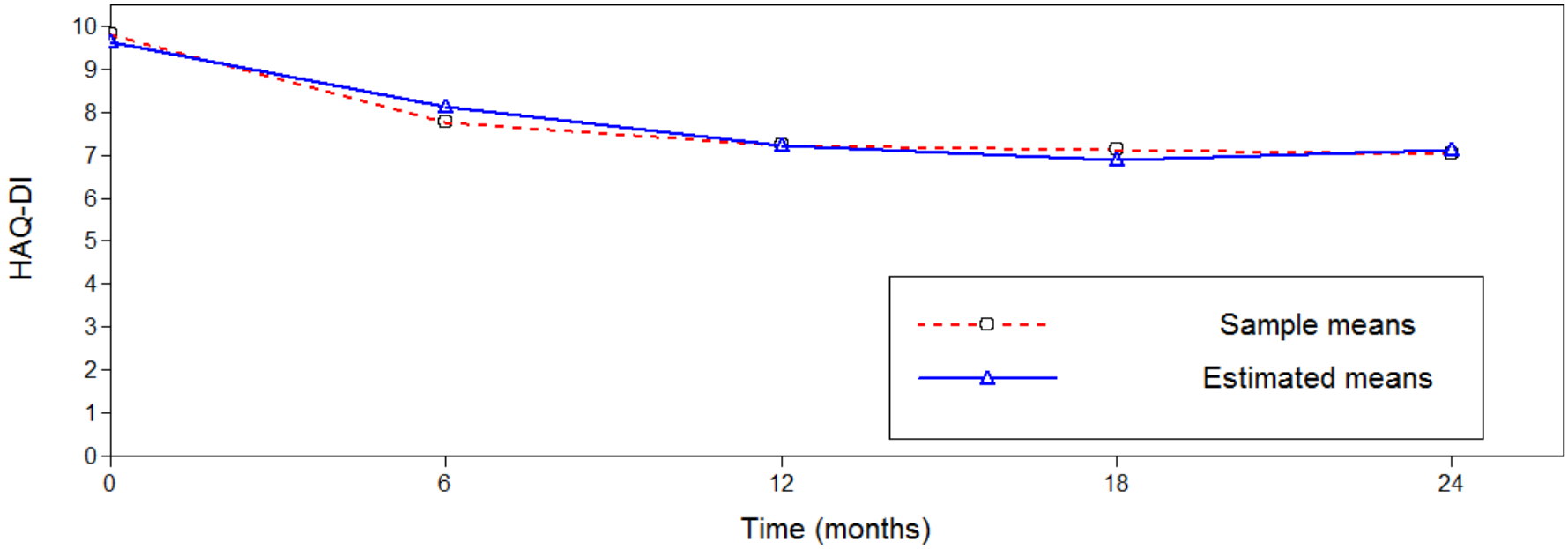

Figure 5-8 Graph to show how the sample mean Disability Index component of the Health Assessment Questionnaire (HAQ-DI) changed with time, compared to the means estimated by the quadratic growth curve model of change in HAQ-DI in Yorkshire Early Arthritis Register

HAQ-DI, disability index component of health assessment questionnaire.

5.4.4 Freed loading model of change in disability

Improvement of this model over the previous two was indicated by the preferable indices of fit : χ^2 52.347, df 16, p<0.0001; CFI 0.988; RMSEA 0.055 (90% CI 0.041, 0.070). The mean intercept estimated by the model implied that HAQ-DI at baseline was 10.24 in YEAR B and 9.36 in YEAR C (a difference of 0.88, SE 0.25, p<0.001). These estimates are closer to the observed mean values shown in Table 5-4 (10.21 and 9.41, respectively) than those obtained in the linear and quadratic models. However, there was substantial variance related to this estimate (17.49, SE 2.04, p<0.001), reflecting the wide range of HAQ-DI scores recorded at baseline. Mean linear slope, mean change in HAQ-DI per unit time (one unit of time was specified as 24 months in this model), was -2.64 (SE 0.19, p<0.001). Again there was substantial variance related to this estimate (13.92, SE 2.10, p<0.001). There was no significant difference in mean linear slope between the YEAR cohorts. Linear slopes at 6, 12 and 18 months were freely estimated by the model and their respective values were 0.76, 0.99, and 1.02. This implies that most (76%) of the overall fall in mean HAQ-DI had occurred by 6 months and the lowest value was reached by 18 months. Mean HAQ-DI then rose slightly from 18 to 24 months. Covariance between intercept and linear slope was statistically significant and indicated that cases with higher baseline HAQ-DI saw a steeper initial rate of decline in HAQ-DI (by 4.98 units of HAQ-DI per 24 months per unit of baseline HAQ-DI, SE 2.03, p=0.014). This is in keeping with expected results, as a higher baseline score has greater potential to decline. The growth curve is illustrated graphically in Figure 5-9, which compares observed and predicted means and shows a close fit to the data.

Table 5-7 Parameters estimated by the freed loading model of change in Disability Index component of the Health Assessment Questionnaire (HAQ-DI) in Yorkshire Early Arthritis Register

Parameter	Estimate	SE	p
Mean intercept	10.24	0.18	<0.0001
Intercept variance	17.49	2.04	<0.0001
Linear slope at baseline	0.00		
Linear slope at 6m	0.76	0.03	<0.0001
Linear slope at 12m	0.99	0.03	<0.0001
Linear slope at 18m	1.02	0.03	<0.0001
Linear slope at 24m	1.00		
Mean linear slope	-2.64	0.19	<0.0001
Linear slope variance	13.92	2.10	<0.0001
Intercept/ linear slope covariance	-4.98	2.03	0.014
Regression of parameters on YEAR C cohort			
Mean intercept on YEAR cohort	-0.88	0.25	<0.0001
Mean linear slope on YEAR cohort	-0.03	0.25	0.895

P, statistical probability; SE, standard error, YEAR, Yorkshire Early Arthritis Register.

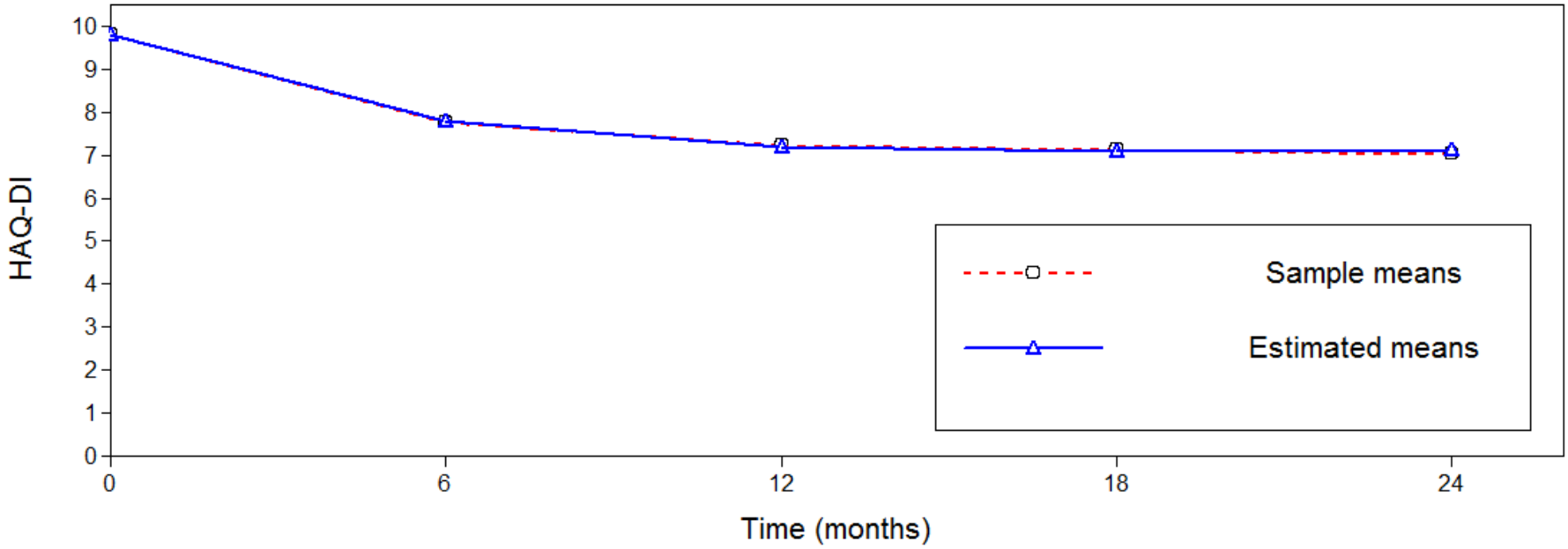

Figure 5-9 Graph to show how mean Disability Index component of the Health Assessment Questionnaire (HAQ-DI) changed with time, compared to the means estimated by the freed loading growth curve model of change in HAQ-DI in Yorkshire Early Arthritis Register

HAQ-DI, disability index component of health assessment questionnaire.

5.5 Identification of latent trajectories of change in disability

A LCGA was conducted, using the freed loading growth curve model described in Section 5.4.4. This analysis was similar to the one performed for DAS28, described in Chapter 4, Section 4.6. Table 5-8 gives the fit indices for models containing successive numbers of trajectories together with the numbers of cases included in each trajectory class. Based upon this information, the 2 class model was selected. This is because for the 3 class model, lowest log-likelihood values were not equal indicating that the solution was a local maximum and furthermore, the value for BIC was only a modest improvement compared to that of the 2 class model. Although Entropy was preferable for the 3 class model compared to 2 class one (0.646 compared to 0.502, respectively), the 3 class LMR-LRT was not statistically significant (p= 0.0681), indicating that this model did not fit the data as well.

The 2 trajectory classes are illustrated in Figure 5-10. The first class, which encompassed just under half (47%) of the cohort, could be described as 'high HAQ-DI', because after an initial slight fall in HAQ-DI, its value remains above 11 for the duration of follow up. The average probability that the most likely latent class membership was class 1 for cases grouped into trajectory class 1 by the model was 0.84 (and therefore the average probability that such cases were most likely to be in the other latent class was 0.16). The remainder of the cohort (53% of cases) fell into class 2, or 'low HAQ-DI'. In this trajectory class, mean HAQ-DI (equivalent to the intercept) was 8.05 at baseline and then fell until it reached its lowest value at 18 months (102% of the mean fall in HAQ-DI at 24 months), before increasing slightly from 18 to 24 months. Within this class, the average probability of most likely latent class membership being class 2 was also 0.84, and 0.16 that the most likely latent class was class 1.

Table 5-8 Fit indices and numbers of cases in each trajectory for models of change in disability with increasing numbers of trajectory classes

Number of trajectory classes in model	Number of cases assigned to each class, based on the estimated model (%)			AIC	BIC	Adjusted BIC	LMR-LRT p-value	BLRT p-value	Entropy
1	Trajectory 1	1409	(100)	34045	34176	34096			
2	Trajectory 1	664	(47)	28805	28899	28842	0.0060	<0.0001	0.502
	Trajectory 2	745	(53)						
3*	Trajectory 1	203	(14)	28760	28870	28803	0.0681	<0.0001	0.646
	Trajectory 2	537	(38)						
	Trajectory 3	669	(48)						

*For the 3 class model, log-likelihood values were not equal, indicating that the solution was possibly a local maximum.
AIC, Akaike information criteria; BIC, Bayesian information criteria; BLRT, Bootstrap likelihood ratio test; LMR-LRT, Lo, Mendell and Rubin likelihood ratio test; p, (statistical) probability.

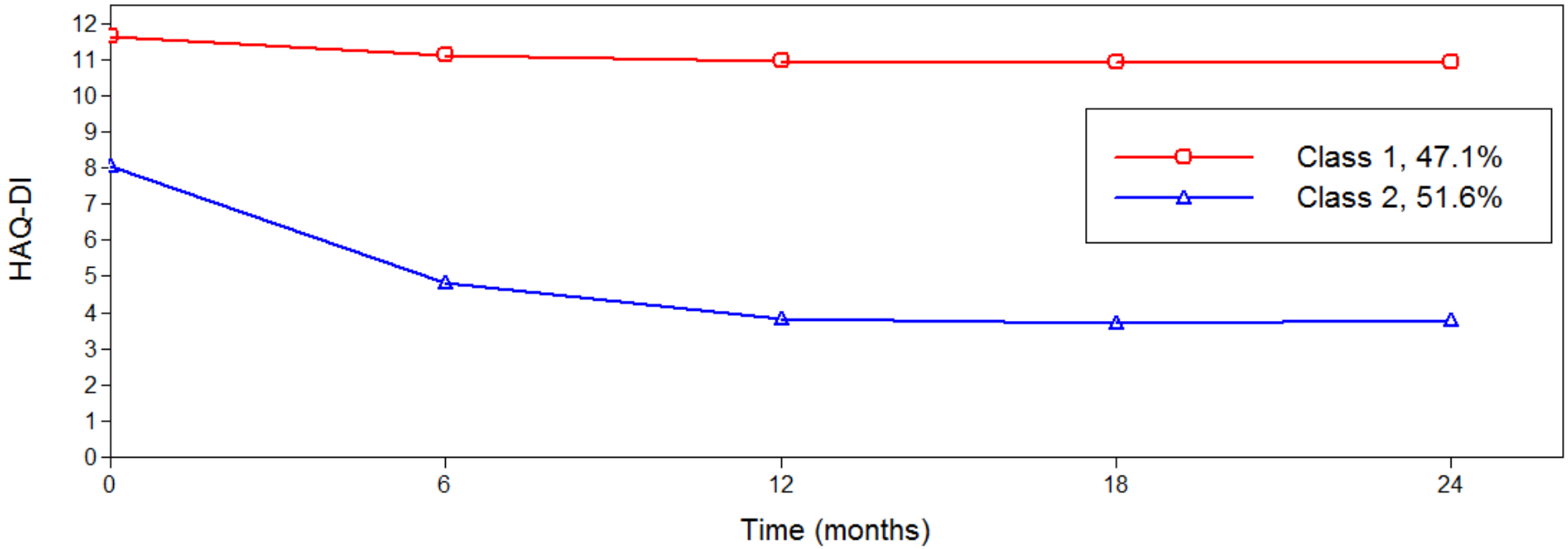

Figure 5-10 Illustration of the two latent trajectory classes of change in Disability Index of the Health Assessment Questionnaire (HAQ-DI)

The proportion of cases assigned to each trajectory class is given as a percentage of the whole cohort.
HAQ-DI, disability index component of health assessment questionnaire.

5.6 Predictors of disability trajectory class membership

Predictors of membership of the 'high HAQ-DI' trajectory class, which was the worst prognostic group, were similar to predictors of the 'high DAS28' trajectory class (Chapter 4, Section 4.7 and Table 4-9). Specifically, men were less likely to be classed in the 'high HAQ-DI' group (OR 0.51, 95% CI 0.42, 0.63, p<0.001) and those from more socially deprived areas were more likely to be classed in this group, compared to those from the least socially deprived 4th quartile. The OR for IMD quartile 1 was 2.66, (95% CI 2.01, 3.51; p <0.001) and OR for IMD quartile 2 was 1.59, (95% CI 1.21, 2.08; p=0.005), but the OR for IMD quartile 3 was not significantly different to that of quartile 4. Other statistically significant predictors of HAQ-DI trajectory class were consistent with those described in the linear regression analyses of change in HAQ-DI (Sections 5.2 and 5.3): fatigue VAS and age. The OR for membership of the high HAQ-DI trajectory class was 1.02 (95% CI 1.02, 1.03; p<0.001) for age, suggesting that the odds of membership of class 2 increases by 2% per year of age at baseline. Furthermore, the OR relating to fatigue VAS was 1.12 (95% CI 1.09, 1.16; p<0.001), indicating that for every 1cm increase in fatigue VAS at baseline, the odds of class 2 membership increased by 12%. These results are shown in Table 5-9.

In order to further explore these findings and to see whether the significant effects of age and SES could be explained by smoking, alcohol use, obesity or comorbidities, a further analysis using only cases from YEAR C was conducted and is presented in Section 5.6.1.

Table 5-9 Results of multinomial logistic regression analysis of predictors of class 1 trajectory ('high HAQ-DI') membership

Predictor	Coefficient	Odds ratio	(95% CI)	p
YEAR C cohort	0.06	1.07	(0.88, 1.29)	0.582
Male gender	**-0.67**	**0.51**	**(0.42, 0.63)**	**<0.001**
Age	**0.02**	**1.02**	**(1.02, 1.03)**	**<0.001**
RF positive	-0.03	0.98	(0.74, 1.29)	0.882
ACPA positive	0.21	1.23	(0.90, 1.68)	0.286
Shared epitope positive	0.07	1.08	(0.90, 1.29)	0.503
IMD quartile 1	**0.98**	**2.66**	**(2.01, 3.51)**	**<0.001**
2	**0.46**	**1.59**	**(1.21, 2.08)**	**0.005**
3	0.11	1.12	(0.85, 1.47)	0.507
Fatigue VAS	**0.12**	**1.12**	**(1.09, 1.16)**	**<0.001**

Results of multinomial logistic regression analysis.
Outcome variable was membership of class 1 trajectory, described in 5.4.
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
For IMD, the referent category was the 4th quartile, which was the least deprived group: higher levels of deprivation were represented by reducing quartile number .
Independent variables were measured at baseline.
ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; IMD, index of multiple deprivation; p, probability (statistical significance); RF, rheumatoid factor; VAS, visual analogue scale; YEAR, Yorkshire Early Arthritis Register.

5.6.1 Sub analysis of Yorkshire Early Arthritis Register C cases

5.6.1.1 Latent growth curve model of change in disability in Yorkshire Early Arthritis Register C

There were no recorded HAQ-DI values for 2 cases in YEAR C, so this sub-analysis used data from 723 participants. In order to select the optimal growth model to fit the data, the process of fitting linear, quadratic and then freed loading models, described in Section 5.4 for the whole YEAR cohort, was repeated for this selection of the data. As expected, the freed loading model was the best fit according to the fit indices, which are displayed in Table 5-10. There was reasonable model fit, with χ^2 =26.5, df = 7, p = 0.0004, CFI=0.991 and RMSEA 0.062.

Table 5-10 Fit statistics for successive models of change in disability in Yorkshire Early Arthritis Register C

Model	χ^2	df	p	CFI	RMSEA
Linear	217.3	10	<0.0001	0.907	0.169
Quadratic	37.6	6	<0.0001	0.986	0.085
Freed loading	26.5	7	0.0004	0.991	0.062

CFI, comparative fit index; df, degrees of freedom; p, (statistical) probability; RMSEA, root mean square error of approximation; χ^2 Chi-square.

The freed loading model of change in HAQ-DI in YEAR C is described by parameters displayed in Table 5-11. According to this model, mean HAQ-DI at baseline was 9.36 in YEAR C, which is slightly different to the mean value of 9.41 estimated directly from the data (Table 5-4). The variance of this intercept value was large: 17.49 (SE 2.37), reflecting significant inter-individual variability. The mean change in HAQ-DI for YEAR C was -2.73 units per 24 months, where the negative value represents a mean fall in HAQ-DI, however the variance of this value was also large: 13.11 (SE 2.50, p <0.001). The model indicated that the greatest fall in HAQ-DI occurred in the first 6 months, as 73% of the total mean fall in HAQ-DI over 24 months had occurred by this point. A further reduction in mean HAQ-DI was implied by the model and by 12 months, 99% of the mean total fall in HAQ-DI over 24 months had been achieved.

Table 5-11 Parameters estimated by the freed loading growth curve model of change in disease activity over time in Yorkshire Early Arthritis Register C

Parameter	Estimate	SE	p
Mean intercept	9.36	0.18	<0.001
Intercept variance	17.49	2.37	<0.001
Mean linear slope	-2.73	0.18	<0.001
Linear slope variance	13.11	2.50	<0.001
Linear slope at baseline	0.00		
Linear slope at 6m	0.73	0.04	<0.001
Linear slope at 12m	0.99	0.03	<0.001
Linear slope at 18m	0.99	0.03	<0.001
Linear slope at 24m	1.00		
Intercept/ linear slope covariance	-4.32	2.33	0.064

m, months; SE, standard error; p, (statistical) probability.

5.6.1.2 Identification of latent trajectories of change in disability in Yorkshire Early Arthritis Register C

Fit indices for models with successive numbers of trajectory classes are shown in Table 5-12. This time the 3 class model was selected as the most suitable because the addition of a further class yielded unequal highest log-likelihood values, which suggested that the solution was a locum maximum. Furthermore, the LMR-LRT value was not statistically significant for the 4 class model. Compared to the 2 class model, there was an improvement in Entropy value and BIC was smaller (although the difference in BIC between the 2 and 3 class models was modest). The 3 trajectory classes are illustrated in Figure 5-11. Class 1 describes a 'middle HAQ-DI' trajectory, where the baseline HAQ-DI value is just over 10, it then reduces to between 8 and 9 and stays at this level for the remainder of follow up. Class 2 ('low HAQ-DI') describes the most favourable trajectory because baseline HAQ-DI is the lowest of the 3, HAQ-DI reduces the most and stays lowest compared to the other 2 trajectories. Class 3 ('high HAQ-DI') is the least favourable trajectory because HAQ-DI starts high (13.5) and remains high throughout follow up.

Table 5-12 Fit indices and numbers of cases in each trajectory for models with increasing numbers of trajectory classes of disability in Yorkshire Early Arthritis Register C

Number of trajectory classes in model	Number of cases assigned to each class, based on the estimated model (%)			AIC	BIC	Adjusted BIC	LMR-LRT p-value	BLRT p-value	Entropy
1	Trajectory 1	723	(100)	17437	17529	17465			
2	Trajectory 1	364	(50)	15133	15209	15156	0.0024	<0.0001	0.619
	Trajectory 2	359	(50)						
3	Trajectory 1	318	(44)	15098	15185	15125	0.0277	<0.0001	0.714
	Trajectory 2	287	(40)						
	Trajectory 3	118	(16)						
4*	Trajectory 1	161	(22)	15084	15184	15115	0.2258	<0.0001	0.747
	Trajectory 2	267	(37)						
	Trajectory 3	275	(38)						
	Trajectory 4	20	(3)						

*For the 4 class model, log-likelihood values were not equal, indicating that the solution was probably a local maximum.
AIC, Akaike information criteria; BIC, Bayesian information criteria; BLRT, Bootstrap likelihood ratio test; LMR-LRT, Lo, Mendell and Rubin likelihood ratio test; p, (statistical) probability.

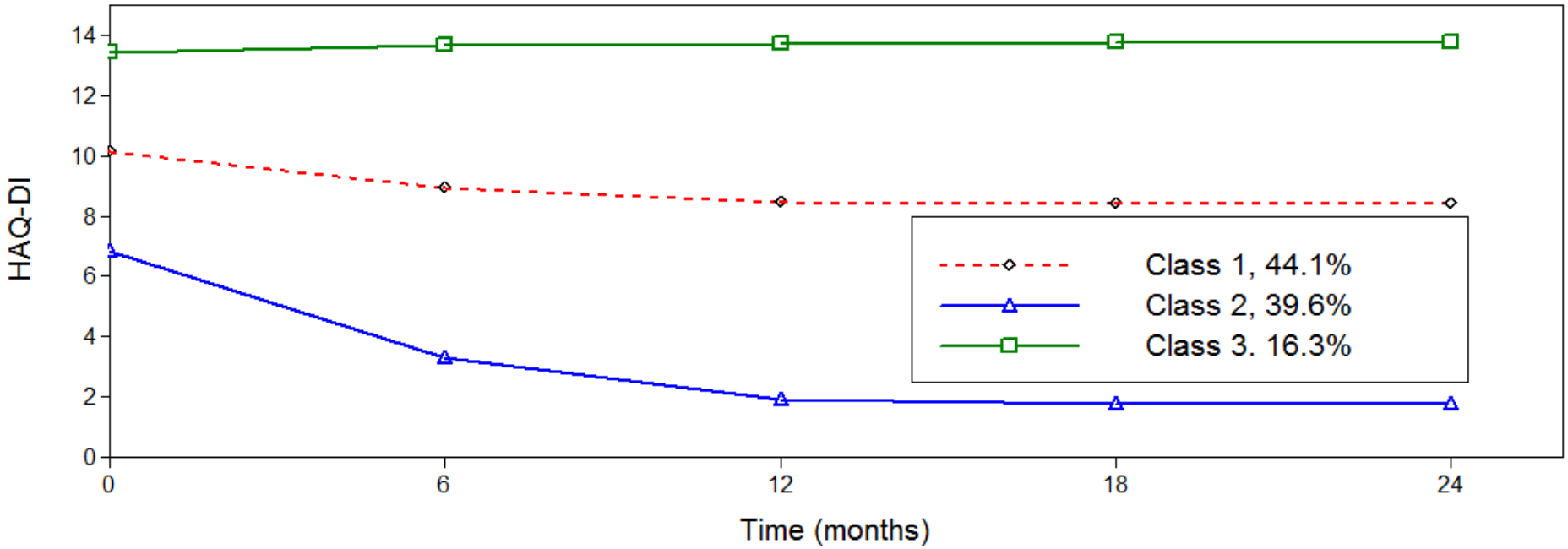

Figure 5-11 Illustration of the three latent trajectory classes of change in Disability Index component of Health Assessment Questionnaire (HAQ-DI) in Yorkshire Early Arthritis Register C

The proportion of cases assigned to each trajectory class is given as a percentage of the whole cohort.
HAQ-DI, disability index component of health assessment questionnaire.

5.6.1.3 Predictors of disability trajectory class membership in Yorkshire Early Arthritis Register C

A multinomial logistic regression model was used to determine predictors of membership of trajectory classes 1 (middle HAQ-DI) and 2 (low HAQ-DI), compared to class 3 (high HAQ-DI). Consistent with the analysis of the whole YEAR cohort (section 5.6), males were more likely to be in the most favourable class (2) (OR 3.54; 95% CI 2.15, 5.82; p<0.001) than the least favourable class (3) and membership of the low HAQ-DI class 2 was less likely than membership of the high HAQ-DI class in cases who were from the most deprived areas, represented by IMD quartile 1: OR 0.19; 95% CI 0.10, 0.36; p<0.001. Similarly, cases from IMD quartile 1 (the most deprived) were less likely to be in the middle HAQ-DI class (1) than the high HAQ-DI class (3): OR 0.45; 95% CI 0.25, 0.81, p= 0.024. Unlike the analysis of the whole YEAR cohort, there was no statistically significant difference between IMD quartiles 2 and 3 compared to quartile 4, however this may have been due to the reduction in statistical power in the present analysis, which included fewer cases than the previous. Fatigue VAS was another significant predictor of less favourable HAQ-DI trajectory in both the analysis of YEAR C and the whole cohort. In YEAR C, there was a 21% reduction in the odds of membership of class 2 (low HAQ-DI) compared to class 3 (high HAQ-DI) per cm of baseline fatigue (p<0.001) and a 12% reduction in the odds of membership of class 1 (middle HAQ-DI) compared to class 3 (p= 0.002).

Furthermore, consistent with predictors of DAS28 trajectory class in YEAR C (Chapter 4, Section 4.7.1.3), patients with higher BMI were more likely to fall into HAQ-DI trajectory class 3 (high HAQ-DI) than class 2 (low HAQ-DI): there was a 5% reduction in the odds of falling into the most favourable, compared to the least favourable trajectory class per Kg/m^2 of BMI (p= 0.031). Although age was not a statistically significant predictor of trajectory class membership, it did approach statistical significance as a predictor of membership of the low HAQ-DI class (2) compared the high HAQ-DI class (3): OR 0.98; 95% CI 0.97, 1.00; p=0.068. These results are displayed in Table 5-13.

Table 5-13 Results of multinomial logistic regression analysis of predictors of disability class trajectory membership for Yorkshire Early Arthritis Register C

Predictors of class 1 ('middle HAQ-DI') compared to class 3 ('high HAQ-DI)

Predictor	Coefficient	Odds ratio	(95% CI)	p
Male gender	0.32	1.38	(0.85, 2.21)	0.271
Age	-0.01	0.99	(0.97, 1.01)	0.256
RF positive	-0.06	0.95	(0.54, 1.65)	0.871
ACPA positive	-0.52	0.59	(0.31, 1.30)	0.183
Shared epitope positive	-0.05	0.96	(0.72, 1.28)	0.799
IMD quartile 1	**-0.80**	**0.45**	**(0.25, 0.81)**	**0.024**
2	-0.45	0.64	(0.35, 1.18)	0.227
3	-0.06	0.94	(0.49, 1.83)	0.884
BMI (Kg/m^2)	-0.03	0.98	(0.95, 1.00)	0.124
Smoking (pack years)	0.00	1.00	(0.99, 1.01)	0.521
Comorbidities	0.40	0.67	(0.43, 1.05)	0.139
Fatigue VAS (cm)	**-0.13**	**0.88**	**(0.82, 0.94)**	**0.002**

Predictors of class 2 ('low HAQ-DI') compared to class 3 ('high HAQ-DI')

Predictor	Coefficient	Odds ratio	(95% CI)	p
Male gender	**1.26**	**3.54**	**(2.15, 5.82)**	**<0.001**
Age	-0.02	0.98	(0.97, 1.00)	0.068
RF positive	-0.10	0.99	(0.54, 1.83)	0.979
ACPA positive	-0.68	0.51	(0.25, 1.02)	0.111
Shared epitope positive	-0.21	0.82	(0.59, 1.12)	0.293
IMD quartile 1	**-1.68**	**0.19**	**(0.10, 0.36)**	**<0.001**
2	-0.554	0.57	(0.30, 1.10)	0.158
3	-0.05	0.95	(0.48, 1.89)	0.903
BMI (Kg/m^2)	**-0.06**	**0.95**	**(0.91, 0.99)**	**0.031**
Smoking (pack years)	-0.10	0.99	(0.98, 1.00)	0.114
Comorbidities	-0.49	0.61	(0.37, 1.00)	0.099
Fatigue VAS (cm)	**-0.23**	**0.79**	**(0.74, 0.85)**	**<0.001**

Results of multinomial logistic regression analysis.
Outcome variable was membership of class 3 trajectory, described in 5.6.1.2.
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**

For IMD, the referent category was the 4th quartile, which was the least deprived group: higher levels of deprivation were represented by reducing quartile number.
Independent variables were measured at baseline.
One pack year was the equivalent of smoking 20 cigarettes per day for one year.
Comorbidities were classified as present /absent.
ACPA, anti-citrullinated peptide antibodies; BMI, body mass index; CI, confidence interval; cm, centimetres; IMD, index of multiple deprivation; Kg/m^2, kilograms per metre square; p, (statistical) probability; RF, rheumatoid factor; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register.

5.7 Summary of predictors of change in disability

As in Chapter 4, which explored change in disease activity, the present Chapter investigated predictors of change in function, measured by HAQ-DI, using both cross sectional (linear regression) and longitudinal (latent growth curve and LCGA) statistical techniques. Again, missing data were managed using MI in the linear regression analyses and maximum likelihood estimation in the longitudinal analyses, so that bias in the estimates as a result of missing data could be minimised and statistical power retained by including all cases where possible.

The results of the analyses of change in HAQ-DI are summarised in Table 5-14. The linear regression analysis revealed a greater mean reduction in HAQ-DI from baseline to 6 and 12 months in male patients compared to females and that HAQ-DI reduced less in older patients and those with higher baseline fatigue VAS. Change in HAQ-DI was described by growth curve models (Section 5.4.2 to 5.4.4) and then LCGA identified 2 latent trajectory classes within the cohort: high HAQ-DI and low HAQ-DI (Section 5.5). Membership of the least favourable, high HAQ-DI trajectory class was more likely with greater age at baseline, lower area-level SES and greater baseline fatigue VAS. It was less likely for male patients to fall into this trajectory class than females. A sub analysis, using data from YEAR C cases only, was conducted to examine the effects of predictors not collected in YEAR B. In this sub analysis, 3 trajectory classes of HAQ-DI were identified: high, middle and low HAQ-DI. Contrary to the results of the whole cohort analysis, age was not a significant predictor of trajectory class membership. This may have been due to a loss of statistical power owing to the smaller number of cases in the sub analysis. Otherwise, significant predictors were the same in YEAR C as in the whole cohort, with the

addition of BMI: higher BMI measured at baseline was associated with lower odds of membership of the low HAQ-DI, compared to the high HAQ-DI trajectory class.

Table 5-14 Summary of results of analyses of change in disability

	Linear regression analysis of change in HAQ-DI from baseline to:		Multinomial logistic regression analyses of predictors of trajectory class:		
	6 m	12 m		Whole cohort	YEAR C
Model characteristics:					
Mean HAQ-DI change from baseline	2.02	2.57	High HAQ-DI class: N	664 (47%)	118 (16%)
Variation in HAQ-DI explained by model	13%	18%	Middle HAQ-DI class: N	Not applicable	318 (44%)
			Low HAQ-DI class: N	745 (53%)	287 (40%)
Significant baseline predictors of more favourable (greater) reduction in HAQ-DI:					
	Male gender	Male gender		Male gender	Male gender
	HAQ-DI	HAQ-DI			
Significant baseline predictors of less favourable (lesser) reduction in HAQ-DI:					
	Age	Age		Social deprivation	Social deprivation
	Fatigue	Fatigue		Age	
				Fatigue	Fatigue
					BMI

BMI, body mass index; HAQ-DI, disability index component of health assessment questionnaire; m, months; N, number (of cases); VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register.

There were similarities between the predictors of change in DAS28 (summarised in Chapter 4, Tables 4-14 and 4-15), and predictors of change in HAQ-DI. Specifically, greater baseline fatigue, female gender and lower area level SES were associated with less favourable course in terms of both DAS28 and HAQ-DI and furthermore, in both YEAR C sub analyses of DAS28 and HAQ-DI trajectory class predictors, greater BMI was also associated with less favourable outcome. However, there were some differences in baseline predictors of change in DAS28 and HAQ-DI. For example, increasing baseline age was a significant predictor of less favourable outcome in some of the models of change in HAQ-DI but not of change in DAS28. Furthermore, some predictors of change in DAS28 were different between YEARs B and C (summarised in Chapter 4, Section 4.8) and cases from YEAR B had a lower mean reduction in DAS28 after 6 months than YEAR C cases, whereas predictors of change in HAQ-DI were the same for YEAR B and C and there was no significant difference in change in HAQ-DI between the 2 cohorts. Therefore, whilst some factors influencing DAS28 and HAQ-DI in early RA were the same, the differences will be taken into account in the final analysis of the relationship between DAS28 and HAQ-DI.

Chapter 6 The relationship between disease activity and disability over time

6.1 Introduction

The results presented so far have revealed that baseline predictors of change in DAS28 in the YEAR cohort were gender, social deprivation, fatigue, and BMI (summarised in Chapter 4, Section 4.8). Furthermore, some of the analyses suggested that YEAR cohort affected change in DAS28, although it is not possible to determine whether this was due to baseline differences between the 2 cohorts, or an effect of the different treatment regimes. One of the analyses also found that higher baseline EMS was associated with greater fall in DAS28. The analyses of change in HAQ-DI, summarised in Chapter 5, Section 5.7, indicated that baseline predictors relevant to change in DAS28 were also significant for HAQ-DI, with some differences (discussed in Chapter 5, 5.7), such as age as a predictor of change in HAQ-DI. This Chapter focuses on how change in DAS28 influenced change in HAQ-DI. It is expected that as disease activity falls with treatment for RA, disability should also reduce. However, as other factors, such as co-morbidity, age and psychosocial differences can influence disability, the relationship between DAS28 and HAQ-DI may not be straightforward.

In this Chapter the relationship between DAS28 and HAQ-DI was described using a parallel process growth curve model (described in Section 2.5.4.2 and illustrated in Figure 2-6) and then a dual process trajectory model (described in Chapter 2, Section 2.5.4.3).

6.2 Correlation between disease activity and disability

An initial examination of the correlations between DAS28 and HAQ-DI at each time point, shown in Table 6-1, reveals that all Pearson correlations between these variables were statistically significant ($p<0.0001$). The correlation between DAS28 and HAQ-DI was lowest at the baseline visit (0.44 for the overall YEAR cohort) and highest at 6 months in the overall YEAR cohort (0.62) and at 12 months for YEAR C (0.63).

Table 6-1 Pearson correlations between disease activity scores from a count of 28 swollen and tender joints (DAS28) and Disability Index components of Health Assessment Questionnaire (HAQ-DI)

Time	Overall YEAR (N)	YEAR B (N)	YEAR C (N)
Baseline	0.44 (1219)	0.41 (617)	0.45 (602)
6 months	0.62 (938)	0.62 (447)	0.62 (491)
12 months	0.57 (967)	0.50 (444)	0.63 (523)
18 months	0.59 (798)	0.56 (339)	0.61 (459)
24 months	0.54 (811)	0.50 (344)	0.56 (467)

Values represent Pearson correlations between DAS28 and HAQ-DI at the time points indicated.
DAS28, disease activity score based upon count of 28 tender and swollen joints and C-reactive protein; HAQ-DI, disability index component of the health assessment questionnaire; N, number (of cases with data available); YEAR, Yorkshire Early Arthritis Register.

6.3 Parallel process growth curve model of change in disease activity and disability over time

This analysis included 1415 YEAR cases for whom there was at least one recorded value for DAS28 or at least one HAQ-DI. The freed loading models of change in disease activity and change in function (described in Sections 4.5.4 and 5.4.4, respectively) were selected for combination in a parallel process growth model. The resulting model approached adequate fit to the data, with fit indices as follows: χ^2 783.62, df= 64, CFI = 0.907, RMSEA = 0.089. Table 6-2 gives the estimates obtained. As expected, linear slope for DAS28 and HAQ-DI did not change or were with 0.01 of those estimated by the previous freed loading models of change in DAS28 and HAQ-DI. Differences in intercepts and

slopes between YEAR B and C cohorts were also similar to those previously reported and furthermore, estimates of covariances between intercept and slope for DAS28 and between intercept and slope for HAQ-DI were within 0.1 of those reported for the respective singular models. The covariances between DAS28 and HAQ-DI intercepts and slopes were pertinent to revealing how HAQ-DI changed with DAS28. The covariance between intercepts was 2.87 (SE 0.15, $p<0.001$), which implied that baseline HAQ-DI increased by 2.87 per unit of baseline DAS28. Between the slopes, covariance was 3.51 (SE 0.25, $p<0.001$), so mean HAQ-DI changed in the same direction as mean DAS28 and fell by 3.5 units per unit fall in DAS28. Increased baseline DAS28 (or intercept), was associated with a 1.16 unit greater decline in HAQ-DI (or slope) over 24 months. This is likely because greater baseline DAS28 was associated with greater baseline HAQ-DI and therefore increased potential reduction in this value. The relationship between baseline HAQ-DI and rate of change in DAS28 was indicated by the covariance between HAQ-DI intercept and DAS28 slope, of -1.61 (SE 0.22, $p<0.001$). Thus, increased baseline HAQ-DI was associated with greater reduction in DAS28. The explanation for this is similar to that of the covariance between baseline DAS28 and HAQ-DI slope, and is also likely to be because higher baseline HAQ-DI occurred in cases with higher DAS28 and therefore increased potential to decline with time.

Table 6-2 Parameters estimated by parallel process model of change in disease activity and function over time in Yorkshire Early Arthritis Register

Parameter	Estimate	SE	p
Mean DAS28 Intercept	5.30	0.06	<0.001
Mean DAS28 slope	-1.97	0.07	<0.001
Linear DAS28 slope at baseline	0.00		
Linear DAS28 slope at 3m	0.68	0.02	<0.001
Linear DAS28 slope at 6m	0.75	0.02	<0.001
Linear DAS28 slope at 12m	0.95	0.02	<0.001
Linear DAS28 slope at 18m	0.98	0.02	<0.001
Linear DAS28 slope at 24m	1.00		
Mean HAQ-DI Intercept	10.24	0.18	<0.001
Mean HAQ-DI slope	-2.66	0.19	<0.001
Linear HAQ-DI slope at baseline	0.00		
Linear HAQ-DI slope at 3m	0.59	0.04	<0.001
Linear HAQ-DI slope at 6m	0.75	0.03	<0.001
Linear HAQ-DI slope at 12m	0.97	0.03	<0.001
Linear HAQ-DI slope at 18m	1.01	0.03	<0.001
Linear HAQ-DI slope at 24m	1.00		
Covariances between latent variables			
Slope DAS28 with intercept DAS28	-0.83	0.15	<0.001
Intercept HAQ-DI with intercept DAS28	2.87	0.19	<0.001
Intercept HAQ-DI with slope DAS28	-1.61	0.22	<0.001
Slope HAQ-DI with intercept DAS28	-1.16	0.19	<0.001
Slope HAQ-DI with slope DAS28	3.51	0.25	<0.001
Slope HAQ-DI with intercept HAQ-DI	-3.64	1.03	<0.001
Regression of parameters on YEAR C cohort			
Intercept DAS28	-0.62	0.08	<0.001
Slope DAS28	0.18	0.09	0.054
Intercept HAQ-DI	-0.89	0.25	<0.001
Slope HAQ-DI	-0.08	0.25	0.741

DAS28, disease activity score based upon counts of 28 joints and C-reactive protein; HAQ-DI, disability index component of health assessment questionnaire; m, months; p, statistical probability; SE, standard error, YEAR, Yorkshire Early Arthritis Register.

6.4 Dual trajectory analysis of change in disease activity and disability

This model, which simultaneously estimated trajectories for DAS28 and HAQ-DI, identified trajectories similar to those previously described by the LCGAs in Sections 4.6 and 5.5, respectively. The dual trajectory analysis classified 24% of the cohort into the high DAS28 category and 76% into the low DAS28 category, which is similar to the 26% and 74%, respectively, classified by the earlier model. Furthermore, the dual trajectory analysis found that 49% and 51% of the cohort were categorised into high and low HAQ-DI trajectories, respectively, which is comparable to the 47% and 52% of cases classified into these respective categories by the earlier model. As there were 2 trajectory classes for both DAS28 and HAQ-DI, 4 combinations of trajectories, or dual trajectory groups, were possible. These are described in Table 6-3. The least favourable dual trajectory group was group 1, in which both DAS28 and HAQ-DI trajectories were 'high'. As anticipated, group 2 was small because very few individuals who followed the high DAS28 trajectory also followed the low HAQ-DI trajectory (20 cases, representing 1% of the cohort). Most cases were classified into the most favourable group 4, in which both DAS28 and HAQ-DI were low. However, just over one quarter of the cohort followed a high HAQ-DI category, despite following a low DAS28 trajectory.

Table 6-3 Description of dual trajectory groups

Group	Percentage of cohort	DAS28 trajectory	HAQ-DI trajectory
1	23	High DAS	High HAQ-DI
2	1	High DAS	Low HAQ-DI
3	26	Low DAS28	High HAQ-DI
4	50	Low DAS28	Low HAQ-DI

DAS28, disease activity score based upon counts of 28 joints and C-reactive protein; HAQ-DI, disability index component of health assessment questionnaire.

Table 6-4 gives the probabilities of membership of each HAQ-DI trajectory, conditional on DAS28 trajectory. This confirms that cases from the high DAS28 trajectory were most likely to be in the high HAQ-DI trajectory, p=0.94, but not very likely to be associated with low HAQ-DI, p=0.06. Although cases from the low DAS28 trajectory were more likely to follow the low HAQ-DI trajectory (p=0.66), a significant number followed the High HAQ-DI trajectory (p=0.34).

Table 6-4 Probability of disability trajectory conditional on disease activity trajectory

	HAQ-DI trajectory:	
DAS28 trajectory:	High	Low
High	0.94	0.06
Low	0.34	0.66

DAS28, disease activity score based upon counts of 28 joints and C-reactive protein; HAQ-DI, disability index component of health assessment questionnaire.

6.5 Predictors of disease activity and disability trajectory groups

Predictors of group membership were considered, but as only 20 individual cases were assigned to group 2, they were excluded from the analysis. Baseline DAS28-P(CRP) was calculated as described in Chapter 2, Section 2.5.4.3.1, and added as a covariate in the regression analysis of predictors of DAS28/ HAQ-DI dual trajectory class. The spread of values of this variable was similar to DAS28-P described by McWilliams *et al.* (2012), with a median of 0.50 and an inter-quartile range of 0.44 to 0.54. Correlation between baseline values of DAS28-P and DAS28 was also similar to the correlation between these values reported by McWilliams *et al*: 0.39. As its values were small, DAS28-P(CRP) was multiplied by 10 before it was entered into the model so that the results could be interpreted more easily.

Results of the multinomial logistic regression analysis are shown in Table 6-5. Compared to membership of the most favourable group 4, cases were more likely to be assigned to the least favourable group 1 if they resided in the most socially deprived area compared to the least socially deprived (OR 1.52; 95% CI 1.00, 2.31; p =0.049), reported more fatigue at baseline and had a higher

DAS28 at baseline. There was a 6% increase in odds of being in group 1 compared to group 4 per cm of baseline fatigue VAS (p=0.020) and the odds of being in group 1, compared to group 4, were increased by 75% per unit of DAS28 at baseline (p<0.001). Men were less likely than women to be in group 1 compared to group 4 (OR 0.70; 95% CI 0.52, 0.95; p<0.001), and cases from YEAR C were also less likely than YEAR B cases to be in group 1: OR 0.70; 95% CI 0.52, 0.95, p=0.020. Although the effect of RF on membership of group 1 was not statistically significant, the effect of ACPA positivity approached significance, such that a positive antibody increased the odds of being in this less favourable category: OR=1.17, 95% CI 0.99, 2.82, p=0.056.

Dual trajectory group 3 followed the 'low DAS28' trajectory and 'high HAQ-DI' trajectories, so it is possible that factors other than RA were contributing to the disability measured by HAQ-DI in this group. Predictors of membership of this group were different to predictors of group 1 membership and included increasing age, with increased odds of group 3 compared to group 4 membership of 3% per year of age at baseline (p< 0.001). Cases were also more likely to be in group 3 if they were included in IMD quartile 1 compared to IMD quartile 4 (OR 2.15; 95% CI 1.44, 3.20; p< 0.001), and classification into IMD quartile 2 compared to IMD quartile 4 was almost statistically significant: OR for group 3 membership was 1.47 (95% CI 0.99, 2.20, p=0.058). Other predictors of group 3 membership were higher baseline DAS28-P(CRP) and increased fatigue at baseline: a 1cm increase in fatigue VAS at baseline was associated with increased odds of group 3 compared to group 4 membership by 9% (p=0.001) whilst a 10 fold increase in DAS28-P(CRP) was associated with an increase in odds of group 3 compared to group 4 membership of 35% (p<0.001). Again, males were less likely than females to be in the less favourable group 3 than group 4: OR 0.54; 95% CI 0.40, 0.73; p<0.001. Cohort (YEAR B or C) had no significant effect on membership of this group and neither did baseline DAS28.

Table 6-5 Results of multinomial logistic regression analysis of predictors of trajectory group membership

Predictors of group 1 membership ('high DAS28 and high HAQ-DI) compared to group 4 ('low DAS28 and low HAQ-DI) membership

Predictor	Coefficient	Odds ratio	(95% CI)	p
YEAR C cohort	**-0.36**	**0.70**	**(0.52, 0.95)**	**0.020**
Male gender	**-0.58**	**0.56**	**(0.41, 0.77)**	**<0.001**
Age (years)	0.00	1.00	(0.99, 1.01)	0.781
RF positive	0.15	1.17	(0.74, 1.83)	0.510
ACPA positive	0.51	1.67	(0.99, 2.82)	0.056
Shared epitope positive	0.17	1.18	(0.89, 1.57)	0.252
IMD quartile 1	**0.42**	**1.52**	**(1.00, 2.31)**	**0.049**
2	0.25	1.28	(0.84, 1.93)	0.248
3	-0.01	0.99	(0.65, 1.51)	0.965
Fatigue VAS (cm)	**0.06**	**1.06**	**(1.01, 1.12)**	**0.020**
DAS28-P(CRP)*	0.15	1.16	(0.95, 1.41)	0.145
DAS28	**0.56**	**1.75**	**(1.53, 2.00)**	**<0.001**

Predictors of group 3 membership ('low DAS28 and high HAQ-DI) compared to group 4 ('low DAS28 and low HAQ-DI) membership

	Coefficient	Odds ratio	95% CI	p
YEAR C cohort	-0.02	0.98	(0.74, 1.31)	0.901
Male gender	**-0.62**	**0.54**	**(0.40, 0.73)**	**<0.001**
Age (years)	**0.03**	**1.03**	**(1.02, 1.04)**	**<0.001**
RF positive	-0.10	0.90	(0.61, 1.34)	0.610
ACPA positive	0.25	1.28	(0.81, 2.01)	0.289
Shared epitope positive	0.14	1.15	(0.89, 1.49)	0.290
IMD quartile 1	**0.77**	**2.15**	**(1.44, 3.20)**	**<0.001**
2	0.39	1.47	(0.99, 2.20)	0.058
3	0.08	1.09	(0.72, 1.64)	0.691
Fatigue VAS (cm)	**0.09**	**1.09**	**(1.04, 1.14)**	**0.001**
DAS28-P(CRP)*	**0.30**	**1.35**	**(1.17, 1.57)**	**<0.001**
DAS28	-0.03	0.97	(0.86, 1.10)	0.649

Results of multinomial logistic regression analysis.
*DAS28-P(CRP) was multiplied by 10 before entry into the model.

Outcome variables were membership of trajectory groups 1 and 3 and the referent group was 4, as described in Table 6-3.
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
For IMD, the referent category was the 4th quartile, which was the least deprived group: higher levels of deprivation were represented by reducing quartile number .
Independent variables were measured at baseline.
ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; cm, centimetres; DAS28, disease activity score based upon counts of 28 joints; DAS28-P(CRP), pain index component of DAS28, calculated using CRP; IMD, index of multiple deprivation; p, probability (statistical significance); RF, rheumatoid factor; VAS, visual analogue scale; YEAR, Yorkshire Early Arthritis Register.

Although data on comorbidities were not complete, with approximately 50% of this information missing in YEAR B and 10% in YEAR C (as described in Chapter 3, Section 3.4), a crude analysis was undertaken to determine whether there was a heavier burden of comorbidity in group 3 compared to the other groups. There were more YEAR B cases in group 1 than groups 3 and 4: 59% of group 1 were from YEAR B, compared to 45% and 46% in groups 3 and 4, respectively. Therefore, comorbidity data were missing more often for group 1 and could not be compared to the other groups easily. However, there were similar numbers of YEAR B cases in groups 3 and 4 and, as shown in Table 6-6, all comorbidities except renal disease were more frequent in group 3 than group 4. The average number of comorbidities in group 3 was greater than for group 4: 0.55 compared to 0.32, respectively.

Table 6-6 Percentage of cases reporting comorbidities by trajectory group

Group	YEAR B: % of cases	HT	IHD	DM	COPD	Renal disease	CVD	PVD	Chronic liver disease	Average number of comorbidities
1	59	16	6	5	8	2	2	0	0	0.29
3	45	23	15	7	13	1	4	3	1	0.55
4	46	16	5	3	9	2	2	2	1	0.32

Numbers shown are percentages of the whole group.
%, percent; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HT, hypertension; IHD, ischaemic heart disease; PVD, peripheral vascular disease; YEAR, Yorkshire Early Arthritis Register.

6.6 Summary

This final Chapter of results is the first description of a longitudinal analysis of the relationship between disease activity and disability in which both DAS28 and HAQ-DI were analysed as continuous variables. The advantage of this type of analysis is that change over time has been captured, which can be useful when considering outcomes of disease; and furthermore, as HAQ-DI was not broken down into categories, statistical power was retained. The parallel process model of change in disease activity and disability confirmed that HAQ-DI and DAS28 both reduced over time and that the baseline values for both variables were lower in YEAR C than YEAR B. The dual trajectory analysis identified 4 different dual trajectory groups and half of the YEAR cases were classified within the most favourable group, with lower DAS28 and HAQ-DI trajectories. As expected, very few cases from the high DAS28 trajectory were classified within the low HAQ-DI trajectory.

Just under one quarter of the cases from YEAR were within the least favourable group, where both DAS28 and HAQ-DI trajectories were high. Membership of this least favourable, compared to the most favourable group, was more likely in females, YEAR B cases, patients from more deprived areas and cases reporting higher fatigue and with higher DAS28 at baseline. The association between DAS28 at baseline and membership of this group suggests that for these individuals, inflammation due to RA was greater than for cases in the low DAS28/ low HAQ-DI group. This is supported by the finding that DAS28-P(CRP) , representing non-inflammatory components of DAS28, was not a significant predictor of membership of this group.

The majority of the remaining cases, representing 26% of the cohort, fell within the group characterised by low DAS28 and high HAQ-DI. Membership of this group compared to the most favourable group was also more likely in females, older patients, those from more deprived areas, and those reporting higher levels of fatigue; but membership of this group was not influenced by YEAR cohort (B or C). A crude comparison of the numbers of comorbidities in the different trajectory groups implied that pre-existing medical conditions probably contributed to the disability reported by this group. It is likely that disability in

this group was also influenced by symptoms of RA unrelated to inflammation. This hypothesis is supported by the influence of DAS28-P(CRP) at baseline: odds of membership of the 'low DAS28 /high HAQ-DI' trajectory increased by 35% per 10 units of baseline DAS28-P(CRP) ($p<0.001$, Table 6-5), implying that the higher level of disability reported by this group is related to the non-inflammatory components of the DAS28 at baseline: TJC and patient VAS.

The findings of all results chapters are discussed further in Chapter, 7.

Chapter 7 Discussion

7.1 Introduction

This chapter addresses the main findings of the Thesis, including the significance of fatigue as a predictor of outcome in Section 7.2.1. Findings from the Thesis are put in the context of the recent literature in Section 7.3, before strengths and limitations of this study are discussed (Section 7.4), including recruitment to YEAR, management of RA in YEAR compared to modern practice and the statistical methodology used. Directions for further research are proposed throughout and expanded in Section 7.5.

7.2 Summary of main Thesis findings

Recent decades have seen great progress in the treatment of RA and this was reviewed in Chapter 1, Section 1.6. The importance of suppression of inflammation during early disease is now widely recognised and patients are managed using a 'treat to target' approach (also reviewed in Section 1.6). Pharmacological therapy may include biological agents which are more expensive than synthetic DMARDs such as MTX and SSA, and in addition, are more immune-suppressive, leaving the patient at greater risk of infection. Therefore, to ensure that benefits of treatment outweigh its risks, an ideal therapeutic approach would be stratified so that aggressive drugs are targeted towards patients most likely to benefit from suppression of inflammation.

The work in this Thesis has identified one potential deficiency in the contemporary approach to management of RA in the UK and provided additional evidence for two further problems which have been described previously. Furthermore, as well as adding to evidence of the importance of fatigue as a significant symptom in RA, baseline fatigue was demonstrated as a consistent predictor of outcome. The clinical implications of this finding require further investigation and are discussed in greater detail in Section 7.2.1. The novel finding of this work came from the dual trajectory analyses, which identified four different disease activity / disability trajectory groups in the YEAR

cohort, the least favourable of which were the high DAS28 / high HAQ-DI and the low DAS28/ high HAQ-DI groups. The former group is likely to include patients with persistent inflammation resulting in disability, whereas the latter represented patients who reported disability despite suppression of inflammation. Membership of this group was more likely in cases with a greater proportion of baseline DAS28 attributable to its subjective components, but was not predicted by actual DAS28 at baseline. This suggests that therapies directed at non-inflammatory manifestations of RA should be explored as they may have a positive influence on future disability. This is an area of interest for future research, which may include investigations into the impact of interventions such as improving coping strategies, or non-pharmacological management of pain for patients with early RA.

The second problem with RA management in the UK highlighted in this Thesis is that it is guided by the DAS28. As described above and in Section 1.8.1, this parameter can be affected by co-existent problems in RA, such as fibromyalgia, via its subjective components TJC and VAS. Cases with a greater proportion of baseline DAS28 attributable non-inflammatory components (that is, those with higher DAS28-P) were more likely to follow a high HAQ-DI trajectory. This suggests that for such patients a treatment regime based upon DAS28 does not address the full impact of RA and consideration should be given to non-inflammatory manifestations. A more suitable marker of disease activity for guidance of pharmacological treatment would accurately reflect inflammation, as this is the target of such therapy.

Further work is required to determine the safety and cost-effectiveness of using biologic agents in patients with persistent inflammation due to RA, using an alternative to DAS28 to define whether such treatments are used. For example, application of the recently developed modified disease activity score (m-DAS28), described by Baker *et. al*., (2014). The m-DAS28 measured at baseline included SJC, CRP and a physician's assessment of disease activity scored using a VAS, but not TJC or patient's assessment of disease activity. It performed better than baseline DAS28 in the prediction of radiographic progression at 52 weeks amongst the clinical trial participants involved in the study. Therefore, the m-DAS28 may be a truer measure of inflammation due to

RA than the DAS28 and is possibly a superior value on which to base treatment decisions.

The impact of 'moderate DAS28' is the third deficiency in contemporary RA management highlighted in this Thesis and is illustrated by cases following the high DAS28 / high HAQ-DI trajectory. As shown in Section 4.6, mean disease activity in the high DAS28 group was >4.7 throughout follow up, but remained below the threshold of 5.1 stipulated by NICE as a requirement for the commencement of biologic agents (discussed in Chapter 1, Section 1.6). Therefore, there was inadequate suppression of inflammation in this group, which was likely to have contributed to persistent disability, but may not have been supressed by escalation of treatment under current UK guidelines.

7.2.1 Fatigue as a predictor of outcome in rheumatoid arthritis

Baseline fatigue VAS was a statistically significant predictor of worse outcome in all prediction models. That is, greater baseline fatigue VAS was associated with lesser improvement in DAS28 after 6 and 12 months and worse DAS28 trajectory (summarised in Table 4-14 and 4-15, respectively), as well as lesser improvement in HAQ-DI after 6 and 12 months and worse HAQ-DI trajectory (summarised in Table 5-14). It also predicted membership of both high DAS28/ high HAQ-DI and low DAS28/ high HAQ-DI trajectory groups, compared to the more favourable low DAS28/ low HAQ-DI trajectory group. This latter result is of interest, as baseline fatigue predicted membership of both groups. That is, the group with disability attributable to persistent disease activity and the group with persistent disability despite suppression of disease activity. This finding likely reflects the probable multiple reasons behind the symptom of fatigue in RA, as proposed by Hewlett's conceptual model (discussed in Section 1.5.2.6). Whilst biological consequences of active RA such as anaemia and persistent inflammation could have driven fatigue in the high DAS28 / high HAQ-DI group, the psychosocial drivers of fatigue (depression and poor social support) may have been more prominent for the low DAS28/ high HAQ-DI group.

In a study from NOAR, reviewed in Chapter 1, Section 1.8.4.3, learned helplessness was associated with worse HAQ. Further work from this cohort

showed that baseline learned helplessness (measured using the rheumatology attitudes index) also predicted HAQ, fatigue and pain after 2 years (Camacho *et al.*, 2013). Learned helplessness was not measured in YEAR, but may have been a factor underlying the observed relationship between fatigue and worse outcome, especially in the low DAS28/ high HAQ-DI trajectory group. Further evidence to demonstrate the impact of psychosocial factors on fatigue in RA came from BRASS (a cohort which was described in Chapter 1, Section 1.7.1) in a study that used cluster analysis to describe 3 groups of patients characterised according to SJC, pain, sleep disturbance, fatigue, depression, illness burden (including symptoms such as impaired concentration and memory, migraine and headache) and pain catastrophising (Lee *et al.*, 2014). One group, which included 57 of the 169 patients in the study, had low disease activity, yet the highest fatigue (measured using the fatigue numeric rating scale component of the multidimensional HAQ), pain catastrophising and patient global health VAS. The authors concluded that in this group of patients, factors other than inflammation due to RA, such as chronic pain, were contributing to the high levels of fatigue and pain.

It would be possible to test which factors contribute to fatigue amongst the two adverse trajectory groups in YEAR by extending the structural equation model described by Nicassoio (2012), discussed in Section 1.5.2.6. Additional variables should be considered, including the presence of anaemia, level of co-morbidity, learned helplessness and social support. The model could then be tested to see whether the impact of these variables on fatigue are different across the two trajectory groups. If this hypothesis is confirmed, it could aid future stratification of therapy for RA: the group with fatigue driven by inflammation would be expected to benefit more from corticosteroid and DMARD treatment, whilst the group with fatigue driven predominantly by psychological and social factors may benefit from additional treatment, such as cognitive behavioural therapy. The impact of such treatment on future disability could be assessed.

The findings of the present study have reinforced previous work by Zink and Zink (2010), which demonstrated that fatigue is associated with worse outcome in RA. In a study including 1057 patients with RA and symptom duration <24

months, greater fatigue at baseline was associated with worse global health score after 8 years (OR= 1.82; 95% CI 1.21, 2.75), as well as increased likelihood of study drop-out due to all causes including death (OR= 2.3; 95% CI 1.3, 4.2) and frailty (OR= 2.3, 95% CI 1.2, 4.5). Although fatigue is recognised as a significant and troublesome symptom of RA, further research is required in order to fully understand its aetiology, clinical significance and successful treatment, before this symptom can usefully guide clinical decisions.

7.3 Comparison of Thesis findings to published evidence

RA disease registers are valuable research tools which have enabled the study of RA epidemiology and outcomes. Despite common underlying principles and purposes of such RA registers, the cohorts described are heterogeneous. Of the UK registers, the YEAR cases included in the present study are most similar to ERAS and ERAN, as these cohorts recruited patients during a similar time-period, from multiple centres with a consultant made diagnosis of RA whose symptom duration was less than 24 months (described in Table 1-2). YEAR was also similar to this cohort in terms of proportion of female patients and those who were ACPA and RF positive (described in Section 3.2). YEAR is different to NOAR, where cases were recruited based upon persistent swelling of joints and therefore included patients with undifferentiated inflammatory arthritis. The cohort from the Leiden clinic in the Netherlands also included patients with 'recent onset' (less than 2 years) arthritis, but not specifically RA (van Aken *et al.*, 2003). Cases from this cohort were selected for inclusion in some analyses if they met RA classification criteria (van den Broek *et al.*, 2012, van der Woude *et al.*, 2012, van Nies *et al.*, 2010). Other international registers described in Table 1-2 used different criteria for inclusion, such as meeting 1987 ACR criteria (BARFOT), or persistent synovitis with other clinical variables (CATCH); or included a cross section of cases with RA with variable symptom durations (BRASS). These differences should be borne in mind when comparing results to those from YEAR.

Some findings from YEAR, such as better outcomes amongst male patients and the association of increasing age at baseline with greater disability, were expected and in keeping with previous studies, as discussed in Sections 1.8.2

and 1.8.4. However, there were some differences from previously published results, which are discussed here.

7.3.1 Comparison of latent class growth analyses of change in disease activity and disability

The findings of the disease activity LCGA were different to those of a Dutch study of 568 cases with early RA, with similar inclusion criteria to YEAR (Siemons *et al.*, 2013), which identified 3 trajectories of change in DAS28. Whilst the research question and statistical methodologies of the Dutch study were broadly similar to the present analysis, significant differences in the treatment protocols likely explain the different results. Participants of the Dutch study, which began recruitment in 2006, were treated according to a 'treat to target' approach, whereby patients were offered MTX at a dose of 15mg, then 25mg, and additional DMARDs were included if DAS28 <2.6 was not achieved. This included TNF inhibitors, which according to NICE, cannot be used in UK treated patients if DAS28 <5.1. It is therefore not altogether surprising that 83% of the Dutch study participants followed the 'fast response' trajectory, whereby sustained remission was achieved by 9 months. In this cohort, fewer patients would have maintained a 'moderate DAS28' (discussed in Section 7.3) than in YEAR. Interestingly, the 'poor outcome' trajectory, which represented 19 (3.3%) of Dutch cases, was a different shape to the trajectories described in YEAR, with an initial improvement, followed by a subsequent rise in DAS28 after 6 months that returned to the baseline level. A similar trajectory may have been present in YEAR, but was possibly not distinguishable from cases with persistently moderate DAS28. Other differences in the two studies that are likely to explain the disparate results include follow up length, which was 12 months in the Dutch study, and possibly the statistical approach, which was GMM using a quadratic model in the analysis by Siemons.

The disability LCGA applied to YEAR identified 2 trajectories of change in HAQ-DI and the analysis applied to YEAR C identified 3. Different numbers of trajectories have been identified in 2 other cohorts: in both ERAS and NOAR, 4 trajectories were identified using LCGA (Norton *et al.*, 2014). The difference between the present analysis and those from ERAS and NOAR is likely to be due to the follow-up time, which was 15 years in the latter 2 cohorts, compared

to only 2 in YEAR. Nevertheless, some predictors of adverse trajectory class membership, such as increased age at baseline and female gender, were similar in YEAR. More information could have been gained from longer follow up in YEAR, but outcomes at 12 months remain of interest as they have been shown to better predict disability at 5 years than baseline predictors (Wiles *et al.*, 2000)

7.3.2 The relationship between disease activity and disability

The parallel process growth curve model described in Section 6.3 implied that DAS28 and HAQ-DI changed in the same direction with time. In the subsequent dual trajectory analysis, very few patients (1%) fell into trajectory group 2, which was described by high DAS28 and low HAQ-DI trajectories. Examination of the raw data confirmed that in these 20 cases, the values of DAS28 and HAQ-DI were correct. It is possible that these individuals represent the previously described 'robustus' phenotype of RA (de Haas *et al.*, 1973), in which individuals have little pain and good retention of function, despite active inflammation due to RA.

It is likely that co-morbidity has a significant impact upon disability in the low DAS28/ high HAQ-DI trajectory group, and in fact the mean number of comorbidities was greater in this trajectory group compared to the low DAS28/ low HAQ-DI group and the high DAS28 / high HAQ-DI group (0.55, compared to 0.32 and 0.29, respectively). The 'co-morbidities present/ absent' variable was not included in the multinomial logistic regression model of predictors of trajectory group membership, as there would have been reduced statistical power when applied to the model of predictors of 3 different categories. As shown in Table 6-5, increased age at baseline predicted membership of this low DAS28/ High HAQ-DI trajectory group, with odds of this group, compared to the more favourable low DAS28 /low HAQ-DI, increased by 3% per year of age at baseline. This observation was probably attributable to the increased likelihood of comorbidity in older patients.

7.3.3 Autoantibodies did not predict outcome in Yorkshire Early Arthritis Register

The evidence reviewed in Chapter 1, Section 1.7.2.3 indicated that remission was less likely in patients with autoantibodies, such as RF and ACPA. In

YEAR, the presence of RF or ACPA did not predict a lesser reduction in DAS28 in the cross-sectional analyses of change in DAS28 after 6 and 12 months, but ACPA were associated with the less favourable DAS28 trajectory in the analysis that utilised DAS28 data from baseline to 24 months. It is possible that the results were affected by missing data, because ACPA status was missing in 46% and 33% of cases in YEAR B and C, respectively (Chapter 3, Table 3-2). However, the rates of missingness for RF status were relatively small: 4% and 8% in YEAR B and C, so this was an unlikely cause of the discrepancy between the results of the cross sectional analyses and those previously published. For these analyses, MI was used to minimise bias caused by missing data, and although the risk of bias increases with greater quantities of missing data, simulation studies have shown that this effect is worse if complete case analysis is used compared to MI (Janssen *et al.*, 2010). Indeed, the complete case analysis of change in DAS28 after 12 months, reported as recommended, to compare to the results obtained using MI (as explained in Chapter 2, Section 2.5.5.2), did show that ACPA predicted less improvement in DAS28: 0.32 units of DAS28, p=0.037: Chapter 4, Table 4-3. The major difference between the cross-sectional analyses of change in DAS28 and those reviewed in Chapter 1, Section 1.8.2.3 was that the YEAR analysis examined absolute change in DAS28 after 6 and 12 months, whereas the Leiden clinic data spanned 5 to 10 years, with sustained remission as the primary outcome of the analyses reported. Therefore, antibodies may have a more significant role as a predictor of long term disease activity than short term, and this may explain why the longitudinal DAS28 trajectory analysis, in which data from baseline to 24 months were utilised, identified an association between ACPA and worse outcome. There have been reports of associations between RF and ACPA positivity and disease activity, but in established RA, rather than early disease. In a study of 855 cases from the Veterans Affairs Rheumatoid Arthritis registry in the USA, which was mostly comprised of male participants with a mean disease duration of 11.8 years and variable follow up duration of at least 6 months, RF and ACPA were associated with greater area under DAS28 curve with regression coefficients of 0.17; p=0.025 and 0.23; p=0.003, respectively (Miriovsky *et al.*, 2010). Furthermore, a Moroccan cross-sectional study of 245

cases of RA with a mean disease duration of 9.6 years found that DAS28 (measured at a single visit) was higher in RF positive, compared to RF negative cases (6.6 compared to 5.8, respectively, p=0.002) and in ACPA positive, compared to ACPA negative cases (5.8 compared to 4.5, respectively, p=0.001) (Ibn Yacoub *et al.*, 2012). Whilst it is acknowledged that there are likely significant differences between these cohorts and YEAR; for example, the Veteran's cohort was mainly male and the Moroccan cohort had likely received different treatment and probably had greater disease activity than YEAR, indicated by the high DAS28 scores; it would be interesting to test the hypothesis that antibodies predict longer term disease activity by examining the relationship between antibody status and disease activity in YEAR cases after several year's follow up. Whilst there is evidence that antibodies predict bony erosion in RA and are associated with less likelihood of remission (reviewed in Chapter 1, Section 1.8.2.3), there are relatively few studies reporting the relationship between antibody status and disease activity in early RA, which may be as a result of publication bias (whereby publication in journals is less likely if studies yield negative results).

RF and ACPA did not predict change in HAQ-DI after 6 and 12 months, or HAQ-DI trajectory. In this respect, predictors of HAQ-DI trajectory in YEAR were similar to those reported in ERAS and NOAR, where RF was also not a significant predictor (Norton *et al.*, 2014). As discussed in Chapter 1, Section 1.8.4.2, reports of the influence of autoantibodies on functional outcome in RA have differed from study to study, but the relationship described in some studies may have been mediated by the development of erosions. Radiographic change has not been included in the present analysis, but is available for a proportion of YEAR cases. A future analysis could therefore examine the relationship between HAQ-DI and erosions in YEAR, by including radiographic erosion as a time-varying covariate in the model of change in HAQ-DI.

7.3.4 Shared epitope alleles as predictors of outcome

As part of YEAR data collection, information on whether or not cases carried the *HLA-DRB1* shared epitope was recorded. Available data included the number of alleles (that is, 0,1, or 2), but for the main analysis, a binary variable was entered into the statistical models to indicate presence or absence of at least

one copy of the *HLA-DRB1* shared epitope allele. This variable did not predict membership of DAS28 trajectory class and furthermore, when the number of shared epitope alleles was included in the model (as 1 or 2 alleles compared to no alleles), the effect was also not statistically significant (Chapter 4, Section 4.7). The number of alleles was only tested in the analysis of the whole cohort because inclusion of this ordinal variable in the model necessitated an additional predictor variable and as the number of cases in the analysis of YEAR C data was smaller, statistical power would have been diminished. These results appear to be contrary to the evidence presented in Chapter 1, Section 1.8.2.2 and Table 1-5, in which presence of shared epitope alleles was associated with more severe disease. However, a major difference between the reviewed articles and the present study was the outcome variable employed, which in the previous studies was more severe disease indicated by treatment failure and requirement of additional therapy to manage the disease. In two of these studies (Gonzalez-Gay *et al.*, 2002 and , Hider *et al.*, 2009), the decision to increase treatment was not based upon DAS28, but was decided by the physician, and furthermore, the paper by Hider (2009) was from NOAR, which included cases with early inflammatory arthritis rather than RA, so the population studied was different to YEAR. Therefore, the results from these studies are difficult to compare to those from YEAR. In the Japanese study conducted by Mori and colleagues (Mori *et al.*, 2010), DMARD failure and eligibility for biological therapy was indicated by presence of 6 or more tender and swollen joints and CRP ≥ 2mg/dl in 47 of 50 'non-responders' and evidence of progression of radiographic damage due to RA in 3 of 50 cases. Using the SJC, TJC and CRP noted by the authors of this study, the equivalent DAS28 indicative of treatment failure would be ≥4.62, which is similar to the 'high DAS28' trajectory described in Chapter 4, Section 4.6 and Figure 4-10. Thus, predictors of high DAS28 trajectory group membership would be expected to be similar to those of treatment failure in Mori's study. However, when applied to a logistic regression analysis, carriage of shared epitope alleles was not a significant predictor of treatment failure if non-*04 alleles were also included. This is therefore consistent with the findings in the present YEAR analysis, in

which the effects of different types of shared epitope allele were not investigated.

7.3.5 The impact of social deprivation on outcome

Area-level social deprivation, measured using IMD, was not a statistically significant predictor of DAS28 trajectory, but was almost significant in the analysis that involved only YEAR C cases (discussed in Chapter 4, Section 4.7.1.3). This analysis indicated that lower SES (higher deprivation) was associated with the less favourable DAS28 trajectory, which was expected: OR 0.83; 95%CI 0.99, 3.40; p=0.054. Interestingly, in a prior model that did not include fatigue VAS (shown in Appendix 7), IMD significantly predicted DAS28 trajectory in the whole cohort and in YEAR C (discussed in Chapter 4, Sections 4.7 and 4.7.1.3) and furthermore, male gender was significantly associated with more favourable DAS28 trajectory in the YEAR C analysis that did not include fatigue VAS. This suggests possible relationships between fatigue and SES, and fatigue and gender, and illustrates the importance of considering potential confounders for inclusion in statistical models. Table 8A in Appendix 8 shows that mean baseline fatigue VAS was lowest for cases from IMD quartile 4 (least deprived) and highest for IMD quartile 2. Mean baseline fatigue VAS was 1.08cm greater in women than men (Chapter 4, Section 4.7.1.3).

Cases classified into the most deprived quartiles of IMD were more likely to fall into the less favourable HAQ-DI trajectories (Chapter 5, Section 5.6 and 5.6.1.3). This finding was in keeping with the results from the ERAS and NOAR cohorts (Norton *et al.*, 2014), and the BROSG (Reviewed in Chapter 1, Table 1-6). Potential causes of this finding are numerous and may relate to increased co-morbidities in patients from more socially deprived areas, later presentation owing to reduced access to health care, reduced adherence to medication owing to cost of prescriptions, or poorer general health and wellbeing as a result of a lower level of education and poor lifestyle choices. Smoking is also an important consideration, but was controlled for in the analysis of YEAR C data, so is unlikely to have confounded the results, which are displayed in Section 5.6.1.3. Comorbidity was also controlled for in the analysis of YEAR C data, although the limitations of the comorbidity variable used have been noted (discussed in Section 7.3.8).

7.3.6 Smoking did not predict outcome in Yorkshire Early Arthritis Register

As explained in Chapter 2, Section 2.1, data on smoking were not available for YEAR B participants and therefore the effect of smoking on DAS28 and HAQ-DI trajectories was examined in YEAR C participants only. The smoking variable was entered into the models as the quantity smoked by the individual, measured in pack years (described in Chapter 2, Section 2.5.2). The quantity of cigarettes smoked was not a significant predictor of DAS28 or HAQ-DI trajectory, with OR close to 1.0 (shown in Table 4-13 in Chapter 4 and Table 5-13 in Chapter 5). This is contrary to the evidence presented in Chapter 1, Section 1.8.2.6, which suggested that disease activity may be worse in smokers and that there may be a possible dose effect, with increased disease activity associated with greater numbers of cigarettes smoked. SES was controlled for in the analysis of YEAR C data, which is a key difference between this analysis and the studies that found smoking predicted worse disease activity. It is possible that the association of SES with smoking could explain why the results from previous studies were different to those of the present study. Although the difference in pack years smoked across the quartiles of IMD in YEAR C was not significantly different according to a one-way between groups analysis of variance (shown in Appendix 8), the mean quantity of pack years smoked did reduce from IMD1 (most deprived) to IMD4 (least deprived): 16.8 to 11.4, respectively. The evidence reviewed in Chapter 1, Section 1.8.4.4, also indicated that functional outcome is worse in smokers; however, these studies included patients with established RA and did not consider bony erosions as a potential confounder of their results. Although the present analyses also did not include erosion as a covariate, the cases had early RA, so there should have been fewer erosions in this cohort.

The accuracy of the smoking variable depended upon the patient's correct recollection of the quantity of cigarettes they had smoked and the number of years they had smoked for. Studies utilising laboratory indicators of cigarette smoking have confirmed that use of tobacco products has been under-reported at interview, which is likely due to its association with adverse health outcomes (reviewed by Coughlin, 1990). Therefore, the smoking variable used in the

YEAR cohort could have been inaccurate and this may have influenced the results, however, this would similarly apply for most published studies.

7.3.7 Body mass index as a predictor of outcome

There is evidence of an association between higher BMI and worse disease activity in RA (reviewed in Chapter 1, Section 1.8.2.7) and the present analysis was in keeping with these results. In the analysis of YEAR C data, the odds of membership of the least favourable of the DAS28 trajectories increased by 4% per Kg/m^2 of baseline BMI, p=0.033, shown in Table 4-13. The present analysis did not investigate why higher BMI was associated with adverse outcome, but the potential for obesity to influence inflammatory markers, and therefore DAS28, has already been discussed (Chapter 1, Section 1.8.2.7).

Although the mean BMI of patients of the YEAR cohort was 27.3 (as reported in Chapter 3, Table 3-1), which is in the 'overweight' range, this was not unusually high for the UK population. Statistics published by the National Obesity Observatory estimated that 81% of men and 68% of women aged 55-64 in the 2009 health survey for England were overweight or obese (National Obesity Observatory, 2011).

An alternative mechanism linking BMI and DAS was proposed by Heimans and colleagues (2011), in a study from the BeSt cohort (Heimans *et al.*, 2013). In their study of 508 patients with RA, assigned to 4 different treatment regimes, mean TJC over 1 year was 1.4 joints greater in obese individuals (BMI ≥25) than non-obese (95% CI 0.6, 2.2), and mean VAS pain was 6.2mm greater (95% CI 3.0, 9.4), compared to SJC and CRP, which were not significantly different between the 2 groups (0.6 joints, 95% CI -0.02, 1.2 and 0.7 mg/L, 95% CI -1.5, 2.9, respectively). Thus, the authors suggested that DAS was greater in obese individuals from the BeSt cohort owing to its subjective components (that is, VAS and TJC), rather than objective measures of inflammation. The cause of this observation is not clear and it is possible that in the present study, increased pain and the influence of obesity on CRP may have had a compound effect resulting in elevated DAS28.

In the analysis of YEAR C data, increased BMI was associated with a reduction in the odds of falling into a more favourable HAQ-DI trajectory: 5% reduction in

odds per kg/m^2 BMI; p=0.031 (Chapter 5, Section 5.6.1.3). This finding is in keeping with results from NOAR (reviewed Chapter 1, Section 1.8.4.5). The cause of the association between BMI and HAQ-DI could be related to other co-morbidities, as although the presence of comorbidity was controlled for in the analysis, the limitations of this variable are noted (discussed in Section 7.3.8). The association between obesity and other conditions, such as osteoarthritis (which was not asked about as part of the YEAR protocol), could explain a reduced functional outcome in patients with higher BMI. The causal relationship could also be in the reverse direction: patients with worse RA are less able to exercise and therefore have a higher BMI; however, as BMI was measured at baseline in patients with early arthritis, this is less likely. A further possible explanation of the observed association may be pain: BMI was a predictor of persistence of chronic widespread pain after 11 years in a large cohort study of 27, 574 individuals resident in Norway (Mundal *et al.*, 2014). In this study, chronic widespread pain was present in 17% of individuals at the baseline assessment and was persistent in 53% of these after 11 years. In a multivariable logistic regression model adjusted for age, gender, depression, anxiety, smoking, alcohol intake, marital status, and presence of a chronic disease, individuals who were overweight and obese at baseline were more likely to have persistent widespread pain: OR (overweight, BMI 25-29.9) 1.18; 95% CI 1.01, 1.32; OR (obese, BMI ≥30.0) 1.66; 95% CI 1.37-2.01. Thus, increased BMI has been associated with presence and persistence of pain, and this, together with the pro-inflammatory nature of adipose, may explain the relationship between BMI and HAQ-DI.

Paradoxically, although predictive of worse disease activity, increased BMI has been associated with reduced erosive damage in RA (Baker *et al.*, 2014b). As data on BMI were only available for YEAR C, it was not added as a covariate in the regression analysis of predictor of DAS28/HAQ-DI trajectory, but this would have been of interest. Given the association with greater pain in RA, higher baseline BMI may be expected to predict membership of the low DAS28 / high HAQ-DI trajectory and be associated with higher DAS28-P.

7.3.8 Comorbidities and their impact on outcome

This study was not designed to examine the effect of comorbidities on disease activity in RA and different methods of data collection would have been adopted if this had been the original intention. Thus, although the presence of comorbidities did not predict DAS28 or HAQ-DI trajectory in YEAR C (Chapter 4, Section 4.7.1.3), it is recognised that this variable was not adequately measured. Comorbidity might have influenced disease activity in YEAR, because some illnesses may have precluded the use of certain DMARDs; for example, MTX could have been avoided in a patient with known pulmonary fibrosis. Results from ERAS indicated an association between adverse HAQ trajectory and greater comorbidity, although this relationship was observed after 3 and 5 years and not at baseline (Norton *et al.*, 2013). The dichotomous variable used in the analysis was a crude estimation of comorbidity and a different method of measuring comorbidities, such as the Charlson index of comorbidity (Charlson *et al.*, 1987), used by Norton *et.al*. (2013), may have been preferable. However, the Charlson index was designed to predict mortality amongst medical inpatients: an altogether different group of patients to the cohort in question. At present, there is no validated measure of the burden of comorbidity designed specifically for use in RA, although this is an area under development.

7.4 Strengths and limitations

YEAR aimed to capture data on patients newly diagnosed with RA and follow their progress over the first 2 years. Occasionally circumstances were encountered that may have adversely affected the quality of the data available for analysis. This Section outlines the strengths and limitations of the study and statistical analyses.

7.4.1 Yorkshire Early Arthritis Register and its relevance to contemporary practice

The YEAR cohort was established to investigate whether outcomes in RA could be predicted by “conventional prognostic factors” (as detailed in Chapter 2, Section 2.5.1). The participants of YEARs B and C were recruited between 1997 and 2009, during a period of evolution of the treatment of RA, bought

about by the emergence of biological therapies. YEAR cases were treated in the traditional 'step-up' fashion of adding or increasing DMARD therapy if disease activity was apparent, which is different to the modern practice of 'early and aggressive' therapy (reviewed in Chapter 1, Section 1.6). This difference to contemporary practice was more marked for YEAR B, which employed SSA rather than MTX, and did not include an intramuscular steroid injection at baseline in the protocol (although corticosteroids may have been given by the treating rheumatologist). Despite the differences between modern therapeutic approaches and YEAR treatment protocols, the information from this register may still be useful. YEAR shares one advantage with many other inflammatory arthritis registers: it captured data on patients treated within a realistic clinical setting and therefore the results are likely to be more generalizable than the results from clinical trials with rigid protocols. As NICE guidelines limit the use of biological therapies for UK patients with RA to those with DAS28 values of greater than 5.1 (shown in Chapter 1, Figure 1-2), patients with moderate disease activity must rely on synthetic DMARDs, such as MTX and SSA, for management of their arthritis. YEAR contains data on patients managed with these agents, so the results within this Thesis are relevant for such modern-day patients with early RA, including paharmacogenetics studies that will be dependent on access to cohorts treated with a single DMARD.

7.4.2 Cases excluded from Yorkshire Early Arthritis Register C

A limitation of the present study is that some cases with early RA were not included in the register and were instead recruited to randomised controlled trials, as discussed in Chapter 2, Section 2.2.5. As 367 cases of early RA patients were thus excluded from YEAR C, the data do not represent all incident cases of RA in the Yorkshire centres involved in the study and this must be borne in mind when interpreting the data and comparing to other cohorts. It is likely that this anomaly contributed to some of the baseline differences between YEAR B and C, which were highlighted in Chapter 3, Table 3-1. For example, mean baseline DAS28 and HAQ-DI were both higher in YEAR B because selection for two of these clinical trials depended upon cases having higher DAS28 and therefore some patients with more active disease were recruited into these studies instead of YEAR C (discussed in Chapter 3, Section 3.2).

Another difference between the 2 cohorts was that symptom duration was longer in YEAR C than in YEAR B. It was anticipated that this would be the other way around: awareness of the need for prompt secondary care referral of patients with signs and symptoms of early inflammatory arthritis by primary care physicians should have increased with time and therefore, YEAR C cases should have had a shorter symptom duration at baseline. The EMPIRE study (Nam *et al.*, 2014b) recruited 110 patients with symptom duration of 3 months or less, whilst IDEA (Nam *et al.*, 2014a) recruited 112 cases with symptoms for 3-12 months, which may explain the longer symptom duration YEAR C cases.

7.4.3 The definition of symptom duration

Owing to the importance of early therapeutic intervention in RA, the definition of symptom onset for clinical trials has received some interest. Historically, several different methods have been used to define symptom onset in RA, including the patient reported date of symptom onset (as in the YEAR cohort), date of first joint swelling, or date of meeting criteria for the definition of RA (Raza *et al.*, 2012). Recently, EULAR published recommendations on how to capture symptom onset in for RA research, which were as follows (Gerlag *et al.*, 2012):

1. Record the date of the first musculoskeletal symptom that the rheumatologist considered was attributable to RA,
2. Record the date of first joint swelling that persisted to presentation,
3. Record the date that either 1987 ACR, or 2010 ACR/EULAR criteria for RA were first met, according to the patient's history (that is, through information that may be obtained retrospectively),
4. Record the date that either 1987 ACR, or 2010 ACR/EULAR criteria for RA were first met, in the opinion of the rheumatologist.

Although IACON, the successor to YEAR, does capture these data, YEAR B and C were established before these recommendations were published, and symptom onset was defined by asking patients the date that their symptoms started. Therefore, the symptom duration variable used in analyses within this Thesis may have been inaccurate, as the data required each patient to recall

the information and may also have been subject to recall bias. The wording of this question likely explains why patients with symptom durations of greater than 12 months were included, despite the YEAR protocol, which specified that patients should have symptom durations less than 12 months. The decision to include subjects in YEAR was at the discretion of the rheumatologist, who may not have agreed that the patient's reported date of symptom onset was actually attributable to RA. Unfortunately, the clinical record form did not capture symptom duration in the opinion of the rheumatologist. Due to this potential discrepancy, patients with symptom durations of up to 24 months were included in the analyses. This duration was chosen as a cut-off as it allowed retention of the majority of cases. Furthermore, 12 months seemed a plausible discrepancy between patient and physician reported onset of symptoms, allowing for a possible 'sub clinical' period of arthralgia prior to diagnosis, which has been noted in some patients who subsequently develop clinically evident inflammatory arthritis (van Steenbergen *et al.*, 2014). In 36 and 25 cases in YEAR B and C, respectively, data were not included in the analysis as the symptom duration exceeded 24 months. During the data validation process, where possible, symptom onset was checked against the clinical notes for cases with symptom durations of greater than 24 months or missing. In some cases where the clinical notes were reviewed, the symptom onset recorded did seem in keeping with onset of RA, and some of these patients had already received treatment for inflammatory arthritis.

Some of the cases with symptom duration missing were also excluded from the analysis. The decision to omit these cases from the analysis, rather than use MI to allow for the missing values, was based upon the finding that subjects with symptom durations of up to 15 years had been recruited to YEAR (Chapter 3, Section 3.2). As the focus of this study was early RA, it was crucial to avoid including cases with longstanding disease. Although MI would have been useful to minimise bias in estimates due to missing symptom duration, it could not be used to distinguish between early and late RA.

7.4.4 Measurement of autoantibodies

Measurement of RF was at performed at baseline, 12 and 24 months in both YEAR B and C, but ACPA status was not measured at the time of data

collection. Instead, this test was performed retrospectively on stored samples and in some cases, patients were asked to provide a new blood sample after data collection was complete (described in Chapter 2, Section 2.2.4). The limitations associated with the timing of ACPA testing in YEAR was previously discussed in relation to another study (Morgan *et al.*, 2009) and evidence that a small proportion of patients who are ACPA-negative at baseline may become ACPA-positive with time, and vice-versa, has been acknowledged (Kastbom *et al.*, 2004, Meyer *et al.*, 2006). As the ACPA test is more widely applied in contemporary practice, future studies will have the advantage of a true baseline value.

7.4.5 Patient reported outcomes and their relationship to disease activity and disability

Previous analyses of predictors of outcome in early RA (such as those reviewed in Chapter 1, Sections 1.8.2 and 1.8.4) have focused on objective or semi-objective measurements like age at presentation, antibody status, smoking history and BMI. The cross sectional analyses of YEAR data evaluated the influence of 3 subjective measurements as predictors of outcome, which were EMS, fatigue and pain at baseline. The rationale for including these as predictors was that TJC and VAS components of DAS28 are subjective and may be influenced by non-inflammatory processes like chronic pain and fibromyalgia, so could contribute to an elevated DAS28 in cases with minimal inflammation. Therefore, higher levels of baseline pain, fatigue and EMS may be associated with higher DAS28 at 6 and 12 months, reflecting symptoms attributable to non-inflammatory causes.

In the cross sectional analyses of change in DAS28 and HAQ-DI, duration of EMS was applied as a categorical predictor variable. The question “for how long are your joints stiff in the morning?” can pose some difficulty for patients, who are unlikely to have noted the exact timing of improvement of joint stiffness. The value given by the patients is therefore an approximate one and furthermore, is not always specific to RA (reviewed by Sokka, 2011). Although it was not a statistically significant predictor of outcome, difficulties encountered in the measurement of stiffness would mean that it would be difficult to apply as an indicator of prognosis. Furthermore, as this question related stiffness in the

morning, EMS duration should not last beyond 5 or 6 hours (for example, stiffness all day should not be classified as EMS and may reflect a cause other than RA), so some cases reporting EMS >220 minutes (approximately 3.6 hours) may have been reporting stiffness that was unrelated to RA.

7.4.6 Data management

As described in Chapter 3, Section 3.4, there was a significant amount of missing data, with 22% of values unrecorded. To account for this, missing data management techniques were employed for the statistical analyses to minimise the impact of missingness. A superior approach would have been to employ a rigid system that would identify gaps in the dataset as they occurred, so that the data could then be obtained. As most of the missing values occurred because patients failed to attend appointments, this could have been achieved by regularly reminding patients of their missed appointments and offering an alternative date as close as possible to the missed visit. In practice, although the YEAR dataset was reviewed periodically, a more systematic approach may have been costly and difficult to achieve: contacting patients required the attention of a dedicated staff member and in addition, NHS clinic appointments are often booked well in advance, so that the next available appointment may be some months ahead of the missed one.

7.4.7 Outcome measures

The outcome measures used in this Thesis were DAS28 and HAQ-DI, which were discussed in Chapter 1, Sections 1.8.1 and 1.8.3, respectively. One advantage of the DAS28 is that it is a well recognised and comprehensible measure: it has been in use for almost 20 years and now forms part of UK guidelines on the management of RA (reviewed in Chapter 1, Table 1-3). However, more recently, the limitations of the DAS28 have been highlighted, including its elevation due to non-inflammatory pain and fibromyalgia (McWilliams *et al.*, 2012).

The HAQ-DI is also a well-established and recognised outcome measure, as discussed in Chapter 1, Section 1.8.3. There have been no previous descriptions of the use of a Rasch-transformed version of this variable as an outcome measure and Dr Hensor's work on this is currently unpublished. The

transformed HAQ-DI is a strength of the present analysis because the use of a continuous (rather than categorical or dichotomous) value retains statistical power.

7.4.8 The use of visual analogue scales

As the pain and fatigue variables are subjective, they can be difficult to quantify and the YEAR data collection protocol made use of a VAS to capture individual patient's perception of pain and fatigue, as described in Chapter 2, Section 2.2.2. Baseline VAS for pain and fatigue were applied to the regression models as predictor variables, whilst disease activity VAS was considered as an auxiliary variable in the management of missing data using MI or maximum likelihood estimation (Chapter 3, Sections 3.5.1 and 3.5.2, respectively). On each of these occasions, the VAS was used as an interval variable. Although often applied in quantitative analysis, data from VAS may not represent a true interval scale, so that the difference in the concept being measured may not be the same between 1 and 2 cm on the VAS, compared to 8 and 9 cm, for example. The use of VAS for this type of analysis has been the subject of much debate (for example, Franchignoni *et al.*, 2012, Harms-Ringdahl, 2012, Price *et al.*, 2012) and Rasch-transformed values have been suggested as preferable for use in parametric analyses (reviewed by Grimby *et al.*, 2012). More recently, a Rasch analysis of data from 221 cases with chronic musculoskeletal pain awaiting joint replacement surgery found that whilst mean pain VAS measured over 7 days at baseline was internally valid, unidimensional change in VAS from baseline did not represent a linear scale (Kersten *et al.*, 2014). This means that pain VAS as a raw variable, or change in VAS, is not suitable as an outcome variable in parametric analysis because measured change may under or over-represent actual change in pain. In this Thesis, pain VAS was used as a predictor rather than an outcome, so the resulting estimates may not have been affected by the problems with VAS discussed here. Much of the research on the suitability of VAS in parametric analysis has focused on pain, and I am not aware of any studies addressing similar issues relating to fatigue VAS. A 2007 review of fatigue measurement tools used for RA identified 5 different anchor statements to represent 0cm on fatigue VAS, and 7 different anchor statements to represent 10cm, from a total of 26 articles that used VAS

to measure fatigue (Hewlett *et al.*, 2007). Indeed, there was a difference in the wording used for the fatigue VAS in YEAR B and C (described in Chapter 2, Section 2.2.2) and although such heterogeneity can make comparisons between studies difficult, the fatigue VAS from YEAR B and C were grouped together for the purpose of the analyses that included data from both cohorts. Any differences in model estimates that may have occurred due to the wording of the fatigue VAS question would have been identified by the interaction term (between fatigue and YEAR cohort), but this was not significant in any of the models studied. Measurement of fatigue using a VAS was assessed using a cohort of 7760 patients with RA from the USA, in a study that compared VAS to 3 other scales used to measure fatigue: the vitality component of the short-form 36, brief fatigue inventory (previously used for cancer research), and multidimensional assessment of fatigue scale (Wolfe, 2004). Correlations with VAS were 0.71, 0.76 and 0.80, respectively. The authors also reported that the VAS was sensitive to change and concluded that it was quick to complete and suitable for use in clinical practice.

Another consideration is that the VAS were not normally distributed (shown in Appendix 6), with proportionally larger quantities of patients reporting pain VAS of 10cm and fatigue VAS of 0cm, as described in Chapter 3, Section 3.3. This was especially notable for fatigue, where 148 and 159 cases from YEAR B and C, respectively, reported no fatigue (or 0cm on fatigue VAS). This observation could have been due to the way in which this question was asked, as well as the nature of VAS. As described in Chapter 2, Section 2.2.2, only cases who responded positively to a question about whether or not they experienced abnormal fatigue (YEAR B), or felt unusually tired (YEAR C) were asked to complete the VAS. In this way, the opportunity to complete a fatigue VAS was removed from a significant number of cases. It is possible that people who responded ‘no’ to the initial question would have indicated a small amount of fatigue on the VAS, rather than zero, which is how their response was interpreted. Although a similar effect was seen for pain VAS, the modal value for this variable was 10cm and is therefore not explained by the question asked of YEAR C participants: “do you have any pain associated with your rheumatoid arthritis?”.

7.4.9 Measurement of social deprivation

As a marker of SES, IMD was obtained using the patient's postal code. Although this variable has the advantage of being a low-cost and easily obtainable estimate of SES, it has been associated with the following problems:

1. The IMD includes a 'health' domain (as described in Chapter 2, Section 2.5.2), which could potentially affect it's use as a predictor of outcome for health research. Although one study into the effect of removing the health domain from the 2004 IMD showed that the relationship between IMD and health outcomes identified in the 2004 census was not affected, the authors did recommend that the health domain be removed for research into other health outcomes that utilised the IMD (Adams and White, 2006). For the present analyses, the health domain of the IMD was not removed and may have therefore confounded the results.
2. The IMD is a measure of area-level, rather than personal level deprivation, and each LSOA could include a heterogeneous population of individuals with differing socio-economic statuses. This situation is a common problem for measures of area level deprivation and personal deprivation may be a more important indicator of some health outcomes (Sloggett and Joshi, 1998). IMD was selected for use in analyses of YEAR data because postcode was routinely collected at baseline, whereas personal indicators of SES were not recorded.
3. The IMD 2007 was used for the present analyses, but this index is based upon census data and subsequent ranking of LSOA, which are both subject to change over time. Therefore, the IMD rank in 2007 may not be an accurate representation of area-level deprivation for all of the patients in YEAR, who were recruited between 1997 and 2009.
4. Another previously recognised problem with area-level deprivation is that the health outcome studied may have influences SES (reviewed by Mackie *et al.*, 2012). However, this was an unlikely cause of the observations from analyses of YEAR data, because the cases all had early RA and postcode at baseline was used as an indicator of SES.

This association of SES and poor outcome, consistent with previous reports, is important as it may indicate a potential target group for intervention to improve outcome in RA. However, in order for this information to be used, a better understanding of the cause of this relationship is required, and further study is warranted.

7.4.10 The differences between Yorkshire Early Arthritis Register B and C

In order to allow for the differences between YEAR B and C, 'cohort' was included as a covariate in all statistical models and furthermore, in the cross sectional analyses, interaction terms between 'YEAR cohort' and other predictor variables were included. Fall in DAS28 after 6 months was 0.21 units greater for YEAR C cases (p=0.026), but there was no statistically significant difference in fall in DAS28 after 12 months between YEAR B and C. Although change in HAQ-DI after 6 and 12 months was not statistically significantly different between YEAR B and C, change after 12 months approached significance. For YEAR C, fall in HAQ-DI was 0.48 units greater than for YEAR B patients (p=0.072). Furthermore, there was a 30% increase in the odds of membership of the high DAS28/ high HAQ-DI trajectory group for YEAR B cases, compared to the low DAS28 / low HAQ-DI group.

The effect on change in DAS28 after 6 months may be attributable to the corticosteroid given as part of the treatment protocol at baseline in YEAR C. An improved treatment strategy over time and the preferential use of MTX in YEAR C may have influenced these results; however, it was not possible to fully examine the effects of the different DMARDs used. Although there were often deviations from the treatment protocols (described in Chapter 2, Section 2.3) due to individual patient preference, or where treatment was not tolerated, or suspended due to infective illness, the majority of YEAR B cases were offered SSA as an initial treatment, whilst MTX was usually offered fist-line in YEAR C. Therefore, some of the differences in outcome between YEAR B and C might be due to these different initial treatments. Unfortunately, it was not possible to test this further because there was considerable inter-individual variation in treatment received. For example, there was variation in the doses of each drug prescribed, whether or not drugs were given in combination, and whether

DMARDs had to be suspended for clinical or personal reasons. Consistent with the rest of the dataset, missing information was also a problem relating to the treatment received. During the period of time that YEAR C recruitment was ongoing, the use of biological therapies for RA was emerging. There were only 7 cases for whom TNF inhibitors were prescribed: for 6 of these, biological therapy began after the 12 month visit and in the other case, it was started 9 months after baseline. A higher quantity of patients offered biologic therapy may have been expected, but the exclusion of some potential YEAR patients due to recruitment into clinical trials (described in Chapter 2, Section 2.2.5) may have influenced this number. Thus, as only 7 patients were known to have used biological therapy during YEAR follow up, this treatment is unlikely to have affected the results.

Other possible causes for better outcome in YEAR C may be that there was closer follow up of these cases, with an additional scheduled visit at 3 months. Furthermore, some YEAR C cases with higher baseline DAS28 were excluded so that they could participate in clinical trials (discussed in 7.4.1), and those remaining in the register may have had milder disease.

7.4.11 Longitudinal data analysis

Latent growth curves were used to describe change in DAS28 and HAQ-DI over time and LCGA was used to identify trajectories of change within the cohort. Although these techniques of analysing longitudinal data with repeated measures of the same variable were developed decades ago, their application to RA research is emerging. The strengths of longitudinal analysis versus cross sectional techniques were outlined in Chapter 1, Section 1.7.2.1. For the present analyses of change in DAS28 and HAQ-DI trajectories, LCGA was chosen in preference to latent class-GMM because of its simplicity and ease of application. There appears to be no evidence of superiority of either approach. The main difference between these 2 techniques is that for LCGA, all cases within a given trajectory are presumed to follow that trajectory and the variance is therefore zero, whilst latent class-GMM allows for inter-individual variation and variance of trajectory groups is provided within the results. These 2 techniques were amongst 5 different methods of classifying trajectories

compared in a recent study that included data manipulated to follow pre-determined trajectories (Twisk and Hoekstra, 2012). The results from this study implied that LCGA was preferable to latent class-GMM when the altered data followed linear trajectories, but neither performed well when the trajectories were quadratic. The authors suggested that whilst longitudinal methods appeared to be superior to cross sectional techniques, LCGA was likely to estimate a greater number of trajectories compared to latent class-GMM; however, the analysis of YEAR B and C data identified only 2 trajectories of DAS28 and HAQ-DI, which is a relatively small number and unlikely to be greater than that estimated by an alternative method.

7.4.12 Handling of missing data

Missing data is a common problem amongst longitudinal studies to which YEAR was particularly susceptible, with 22% of all observations required for the present analyses missing (detailed in Chapter 3, Section 3.4). In order to minimise the impact of missing variables, as many values absent from the database as possible were obtained through the data validation process described in Chapter 2, Section 2.4. Furthermore, statistical missing data management techniques including multiple imputation and maximum likelihood estimation were employed. As described in Chapter 1, Section 1.7.2.2, these methods require that the data are MAR and therefore this was an assumption of all of the analyses in this Thesis. Sensitivity analysis was not conducted, but would have been useful to determine how the results would have been affected if the MAR assumptions were not met.

7.5 Future directions

Much research on predictors of outcome in RA has been conducted with an ultimate goal of developing personalised treatment strategies for individual patients and development within this area is ongoing. With this target in mind, the work in this Thesis has raised several areas of potential focus for future study.

If the purpose of treatment in early RA is to supress inflammation and improve physical function, then the results presented herein suggest that both of these

targets should be considered together: it is not enough to simply reduce inflammation and expect that disability will be improved or prevented. However, despite following a low DAS28 trajectory, there may have been ongoing synovial inflammation for some YEAR cases within this trajectory group. Therefore, in order to describe the relationship between disease activity and disability more accurately, a study to determine the level of disability amongst cases for whom inflammation is fully suppressed (as far as possible with modern treatments) would be necessary. This may involve a study of patients with RA for whom DMARD treatment is escalated whenever there is apparent synovial inflammation. For this to be possible, a true biomarker of synovial inflammation is required. Currently used indicators of RA disease activity, such as the DAS28, are influenced by factors other than inflammation, such as chronic pain (as discussed in Section 1.8.1) and alternative measures may perform better (such as the m-DAS28, described in Section 7.2). A longitudinal observational study to evaluate the presence and causes of disability despite full suppression of inflammation in early RA would add to current knowledge in several ways. Firstly, an observational study would reflect actual clinical practice and the results would be more readily applicable to everyday patient management. There is also much to learn from cases for whom full suppression of inflammation is not achievable. These may be patients who cannot take certain DMARDs due to co-morbidity, or cases who fail to attend their appointments or adhere to medication (there may be myriad reasons for this, such as drug side effects, caring responsibilities, poor literacy or financial reasons). It is essential to understand why RA disease activity cannot be controlled for every patient during this era of biological therapies. Inequalities in health across socioeconomic groups are well recognised, but despite free access to healthcare provided by the NHS in the UK, little progress has been made to improve health of individuals from poor social backgrounds.

It is not clear why disability persisted in some YEAR cases despite apparent suppression of inflammation, but this could be due to the impact of comorbid conditions on physical function. As discussed in Section 7.3.8, there is currently no measure of comorbidity specifically for use in outpatients with RA, however this is an area that does require development. Large research databases

containing anonymised patient information from primary care consultations have been established and are likely to be of great value for investigating the impact of co morbidity in conditions such as RA. Through linkage of data between primary care and disease specific registers such as YEAR, co-morbidity as a factor contributing to disability can be explored. Other possible contributors to disability in early RA also deserve attention, including psychological parameters such as learned helplessness and social factors like level of education and social support.

As discussed in Section 7.2.1, the results presented in this Thesis support current evidence that fatigue in RA is driven by a multitude of factors, which are likely to be both biological and psychosocial. Fatigue at baseline also predicted worse outcome and although the reasons for this observation are unknown, they warrant exploration: it is possible that drivers of fatigue in RA could contribute to a tool that may be used to guide treatment of RA. For example, in a patient recently diagnosed with RA with severe fatigue, anaemia, high CRP and a large number of SJC, immediate treatment with a biological agent (for example) may be more suitable than for a different patient with recent onset RA who has severe fatigue at baseline, higher ratio of TJC to SJC, higher pain VAS, lower CRP and a history of depression. For the latter patient, suppression of inflammation may be satisfactorily achieved with MTX and SSA, whilst complementary therapies and patient support may play a more important role in management.

An initial probing analysis to test the hypothesis that drivers of fatigue are different for the two adverse trajectory classes in YEAR could be conducted using a structural equation model. The model should include 'biological drivers of fatigue' (CRP, anaemia, possibly m-DAS) and 'psychosocial drivers of fatigue' (SES, level of social support, anxiety and depression), as well as co-morbidity, in order to describe each component's contribution to fatigue. It would then be possible to show whether the different 'drivers of fatigue' influence this outcome equally across the 2 trajectory groups.

7.6 Concluding comments

Through analysis of data obtained from YEAR, the work in this Thesis showed that half of patients followed a good prognostic trajectory group (low DAS28/ low HAQ-DI). The remainder either demonstrated evidence of continued inflammation and poor function, or poor function despite suppression of inflammation. This indicates that treatment with synthetic DMARDs alone may not be adequate to suppress inflammation and maintain function in a subgroup of patients with RA. Furthermore, for some individuals, non-inflammatory aspects of RA may be a significant factor contributing to continued disability. Further research is required to determine whether additional therapeutic intervention can benefit such individuals. The impact of comorbidity in these cases remains of interest and is another area for future study, which is likely to be possible through linkage to data from primary care research databases.

Fatigue at baseline consistently predicted adverse outcome and was associated with both persistent disability related to ongoing inflammation and persistent disability despite suppression of inflammation. The reasons underlying these findings are likely to be multi-factorial, but the key contributors to fatigue may differ between the two groups, with psychological and social factors more prominent in those whose inflammation was supressed, but who had ongoing disability. Understanding specific drivers of fatigue for individual patients may help to inform treatment decisions in early RA and this is an area of interest for future research.

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Appendix 1 Health Assessment Questionnaire

Tick the one response which best describes your usual abilities over the past week.

	Without ANY difficulty (0)	With SOME difficulty (1)	With MUCH difficulty (2)	Unable to do (3)
1. DRESSING & GROOMING **Are you able to:**				
• Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
• Shampoo your hair?	☐	☐	☐	☐
2. RISING **Are you able to:**				
• Stand up from an armless straight chair?	☐	☐	☐	☐
• Get in and out of bed?	☐	☐	☐	☐
3. 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)?	☐	☐	☐	☐
4. 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

Walking stick ☐
Walking frame ☐

Devices used for dressing (button hook, zipper pull, long-handled shoe horn) ☐

Built up or special utensils ☐

Crutches ☐

Wheelchair ☐

Special or built up chair ☐

Other (Please specify) ☐

Please tick any categories for which you usually need help from another person.

Dressing and grooming ☐ Rising ☐ Eating ☐ Walking ☐

Tick the one response which best describes your usual abilities over the past week.

	Without ANY difficulty (0)	With SOME difficulty (1)	With MUCH difficulty (2)	Unable to do (3)
5. HYGIENE **Are you able to:**				
• Wash and dry your entire body?	☐	☐	☐	☐
• Take a bath?	☐	☐	☐	☐
• Get on and off the toilet?	☐	☐	☐	☐
6. REACH **Are you able to:**				
• Reach and get down a 5lb object (eg a bag of potatoes) from just above your head?	☐	☐	☐	☐
• Bend down to pick clothing from the floor?	☐	☐	☐	☐
7. GRIP **Are you able to:**				
• Open car doors?	☐	☐	☐	☐
• Open jars which have previously been opened?	☐	☐	☐	☐
• Turn taps on and off?	☐	☐	☐	☐
8. ACTIVITIES **Are you able to:**				
• Run errands and shop?	☐	☐	☐	☐
• Get in and out of a car?	☐	☐	☐	☐
• Do chores such as vacuuming, housework or light gardening?	☐	☐	☐	☐

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

Raised toilet seat ☐ Bath rail ☐ Bath seat ☐ Long-handled appliances for reach ☐

Jar opener (for jars previously opened) ☐ Other (please specify) ☐

Please tick any categories for which you usually need help from another person.

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

Appendix 2 Joint count from Yorkshire Early Arthritis Register B clinical record form

Swollen/Tender Joint count: Complete ALL joint count

(Indicate with a tick or cross the swollen/tender joints present)

T=Tender
S=Swollen

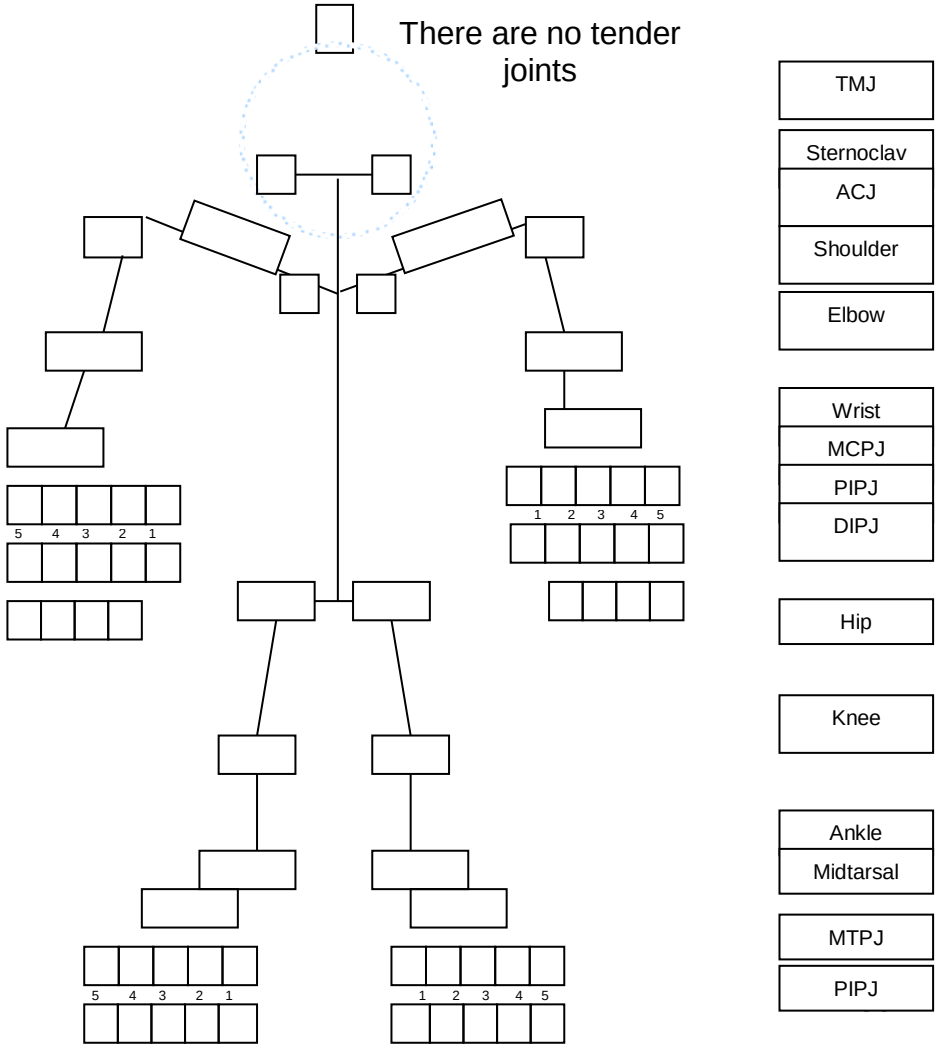
Right			S	T		T	S			Left
					TMJ					
					Sternoclavicular					
					ACJ					
			*	*	Shoulder	*	*			
			*	*	Elbow	*	*			
			*	*	Wrist	*	*			
*	*	*	*	*	MCP tender	*	*	*	*	*
*	*	*	*	*	MCP swollen	*	*	*	*	*
*	*	*	*	*	PIP tender	*	*	*	*	*
*	*	*	*	*	PIP swollen	*	*	*	*	*
					DIP tender					
					DIP swollen					
					Hip					
			*	*	Knee	*	*			
					Ankle					
					Midtarsal					
					MTP tender					
					MTP swollen					
					PIP tender					
					PIP swollen					

*28 Swollen/Tender Joint Count

ACJ, Acromioclavicular joint; DIPJ, distal interphalangeal joint; MCPJ, metacarpophalangeal joint; MTPJ, metatarsal phanangeal joint; PIPJ, proximal interphalangeal joint; TMJ, temperomandibular joint.

Appendix 3 Joint count from Yorkshire Early Arthritis Register C clinical record form

Indicate which joints are ***tender***



TMJ

Sternoclav

ACJ

Shoulder

Elbow

Wrist

MCPJ

PIPJ

DIPJ

Hip

Knee

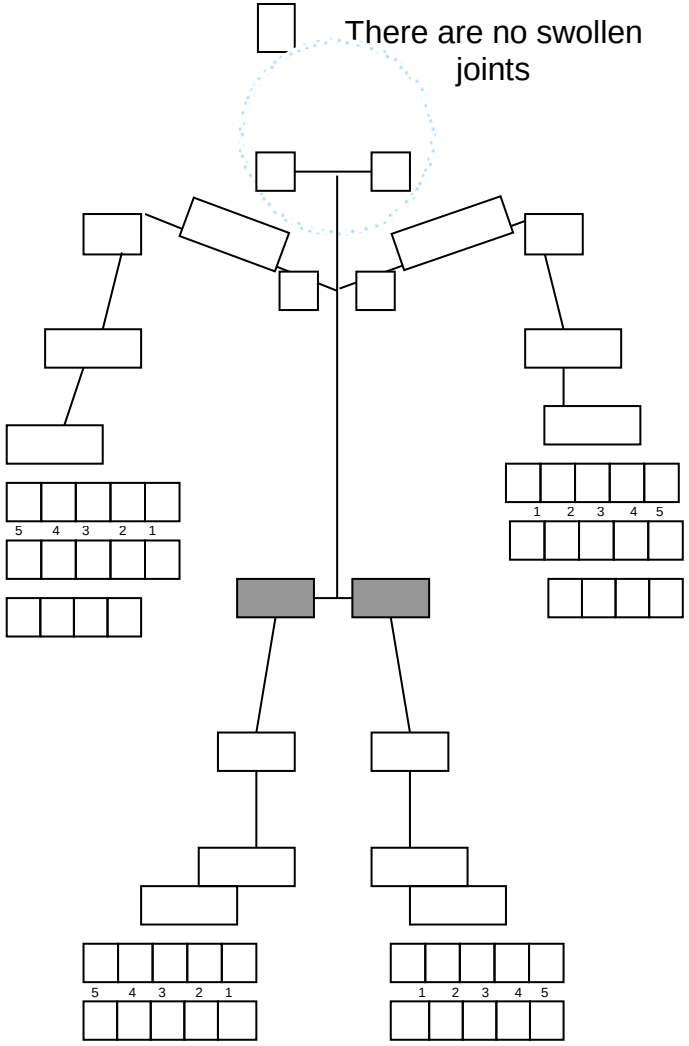
Ankle

Midtarsal

MTPJ

PIPJ

Indicate which joints are ***swollen***



Appendix 4 Medication record from Yorkshire Early Arthritis Register C clinical record form

DMARDs Commenced today

Have DMARDs been *commenced* today? ❑ No/NA

❑ Yes complete details

❑ **Methotrexate (MTX)**

- ❑ As per protocol guidelines (7.5mg/week for 4 weeks, 15 mg/week maintenance)
- ❑ Other please complete the following table

Initiation				Maintenance Week ……
Wk 1	Wk …….	Wk ……	Wk …….	
❑ 7.5mg	❑ 7.5mg	❑ 7.5mg	❑ 7.5mg	❑ 7.5mg
❑ 10 mg	❑ 10 mg	❑ 10 mg	❑ 10 mg	❑ 10 mg
❑ 12.5mg	❑ 12.5mg	❑ 12.5mg	❑ 12.5mg	❑ 12.5mg
❑ 15 mg	❑ 15 mg	❑ 15 mg	❑ 15 mg	❑ 15 mg
❑ ….mg	❑ ….mg	❑ ….mg	❑ ….mg	❑ …….mg

❑ **Sulphasalazine (SSA)**

Initiation				Maintenance Week……
Wk 1	Wk …….	Wk ……	Wk ……	
❑ 0.5g	❑ 1g	❑ 1.5g	❑ 2g	❑ 1g
❑ Other …….. g	❑ Other …….. g	❑ Other …….. g	❑ Other ……..g	❑ 1.5g ❑ 2g

❑ **Hydroxychloroquine (HCQ)**

- ❑ 200 mg daily
- ❑ 400 mg daily

DMARDs Prescribed in previous visit/Maintenance Dose

If the patient has been taking DMARDs, please complete the details for the appropriate DMARD

Methotrexate (MTX)

What is the maintenance dose?

❑ 5 mg	❑ 17.5 mg
❑ 7.5mg	❑ 20 mg
❑ 10 mg	❑ 22.5mg
❑ 12.5mg	❑ 25mg
❑ 15 mg	❑ Other ……..

❑ **Sulphasalazine (SSA)**

What is the maintenance dose?

❑1g ❑1.5g ❑2g ❑2.5g ❑3g

❑ **Hydroxychloroquine (HCQ)**

What is the maintenance dose?

❑200 mg/day ❑400 mg/day

DMARDs Side Effects

Has the patient reported any side effects with the DMARDS?

❑Yes ❑No

If yes, was this due to:

- ❑ Gastro-intestinal side effects
- ❑ Liver function test results
- ❑ Renal
- ❑ Skin rash
- ❑ Haematological abnormalities
- ❑ Other problems (please describe)

Appendix 5 Rasch transformation of the disability index of the Health Assessment Questionnaire

In order to use HAQ-DI as a continuous variable in all analyses, it was transformed using a Rasch model. This transformation was performed by Dr Elizabeth Hensor, the YEAR data analyst, using RUMM2030 (RUMM laboratory Pty ltd. 1998-2010).

Using baseline HAQ-DI values, subsets were selected so that there were 15 patients with each score from 0-23. Only 7 patients had a baseline HAQ-DI score of 24 and all were included. Estimates from this group were used (subjects with missing items were excluded), then anchored on reaching and rising in the entire dataset (including those with missing values), to obtain estimates for all cases. The summary statistics for the model are shown below:

Item location mean	0
Item location SD	0.672
Item Fit Residual mean	-0.242
Item Fit Residual SD	1.245
Person location mean	-0.103
Person location SD	2.384
Person Fit Residual mean	-0.302
Person Fit Residual SD	1.043
Total-Item Chi Square	63.532
Degrees of freedom	48
P=	0.066
PSI with extremes	0.91349
PSI without extremes	0.90829
CA with extremes	0.94365
CA without extremes	0.93251

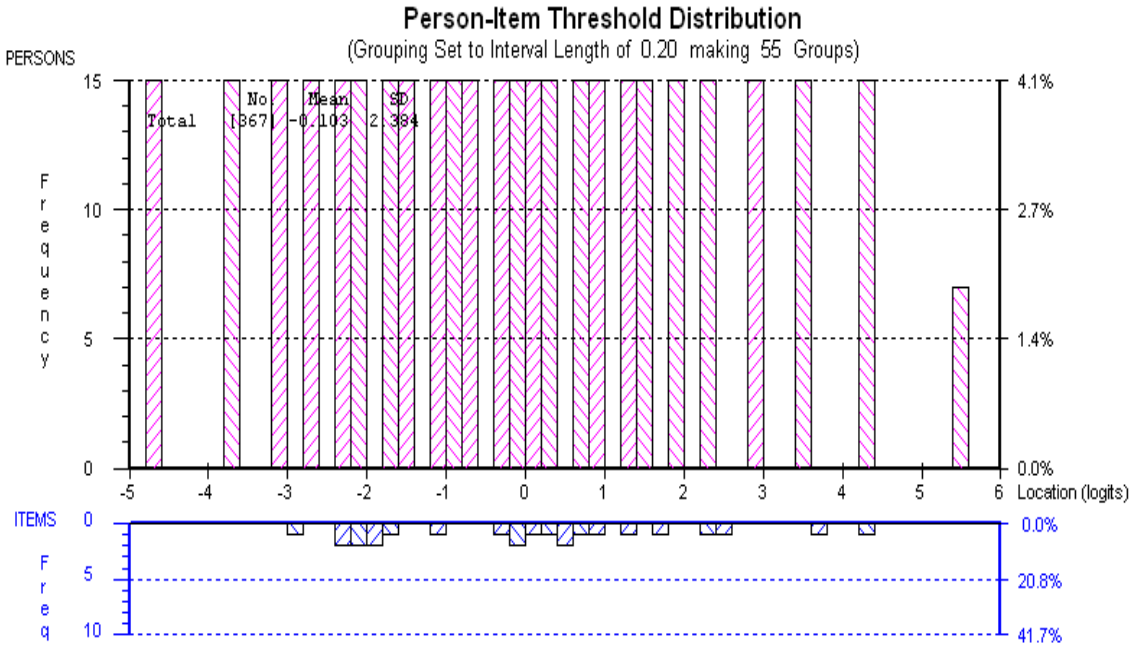
Where SD is standard deviation, P is probability PSI is person separation index and CA is Crohnbach's alpha.

Item fit details are shown in the following table:

HAQ Domain	Fit Residuals	Chi square Probability	F-statistic Probability	LD	DIF
Hygiene	0.46	0.132	0.182	NONE	NONE
Reaching	-1.474	0.356	0.128	NONE	NONE
Gripping	1.1	0.128	0.223	NONE	NONE
Activities	-2.069	0.099	0.019	NONE	NONE
Dressing	-1.321	0.382	0.184	NONE	NONE
Rising	0.573	0.414	0.353	NONE	NONE
Eating	-0.328	0.347	0.227	NONE	NONE
Walking	1.126	0.296	0.335	NONE	NONE

DIF, differential item functioning; LD, local dependency

Person-item threshold distribution is illustrated in the figure below:



Appendix 6 Variable distributions

Figure 6A Histograms to show distributions of age in Yorkshire Early Arthritis Register B and C

The upper figure (A) represents data from YEAR B. (Mode 67 years, median 59 years and mean 58 years.)

The lower figure (B) represents data from YEAR C. (Mode 61 years, median 58 years and mean 58 years.)

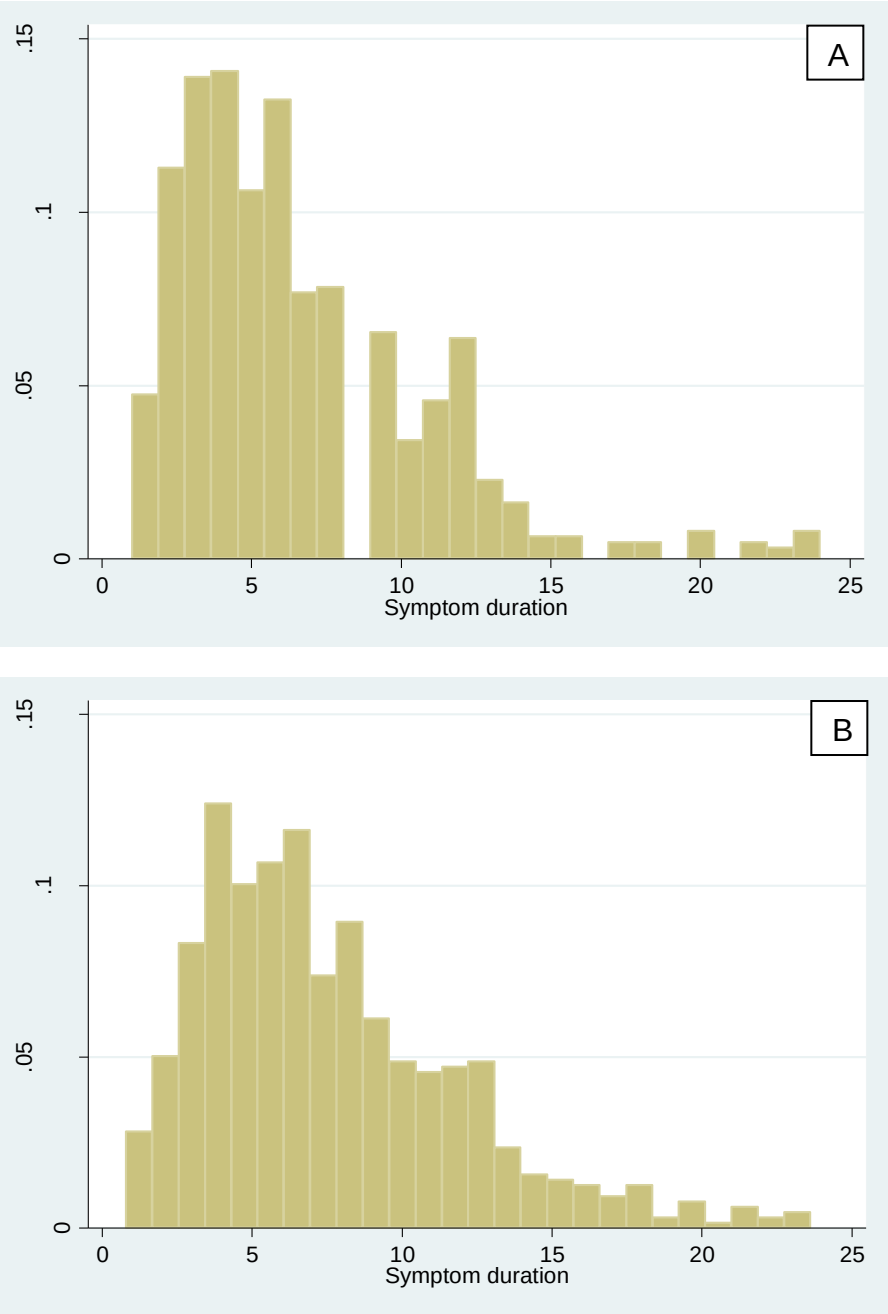


Figure 6B Histograms to show distributions of symptom duration **in Yorkshire Early Arthritis Register B and C**

The upper figure (A) represents data from YEAR B. (Mode 4.0 months, median 6.0 months and mean 6.5 months.)

The lower figure (B) represents data from YEAR C. (Mode 4.3 months, median 6.6 months and mean 7.5 months.)

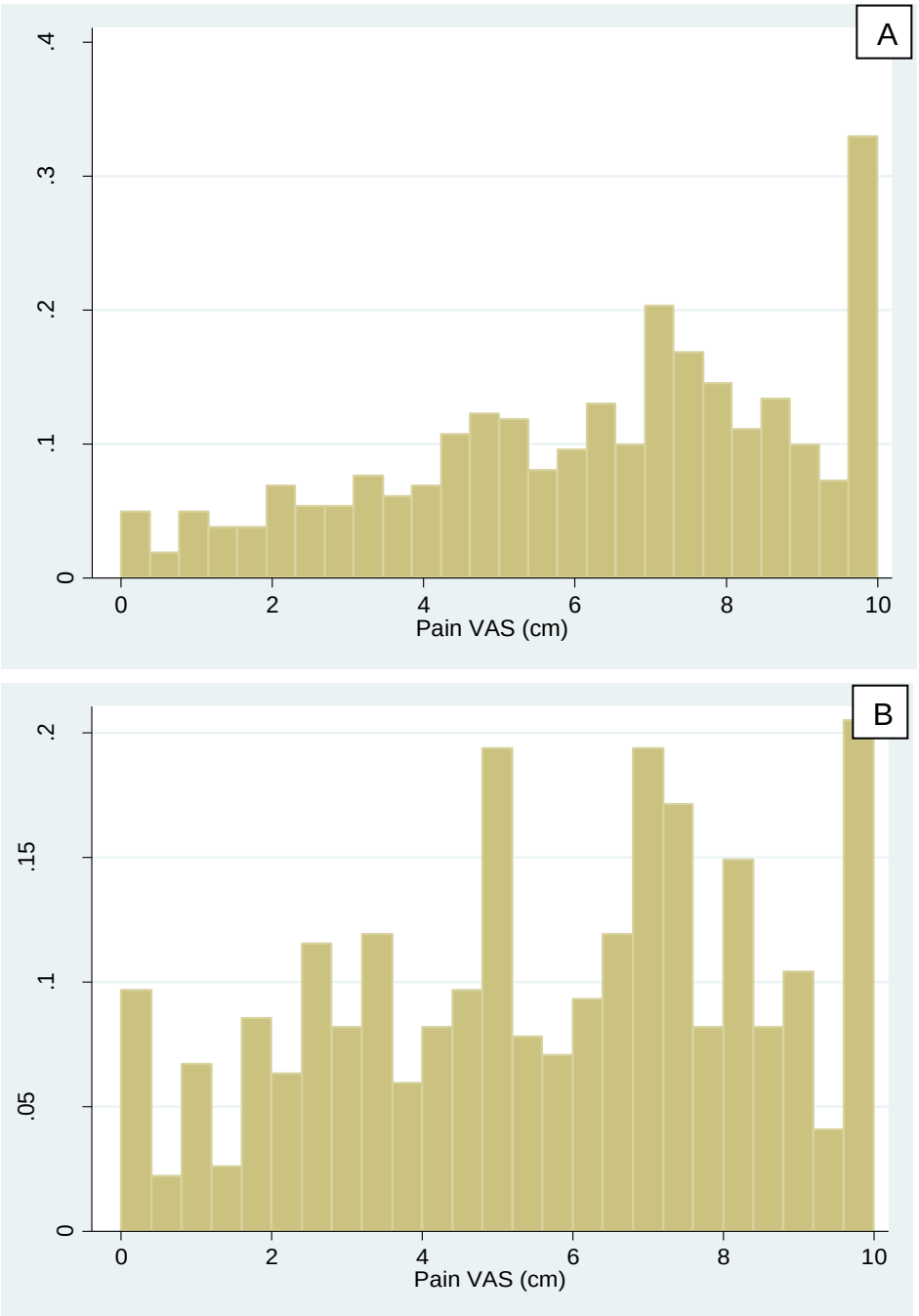


Figure 6C Histograms to show distributions of pain visual analogue score in Yorkshire Early Arthritis Register B and C

The upper figure (A) represents data from YEAR B. (Mode 10.0cm, median 6.8cm and mean 6.3cm.)

The lower figure (B) represents data from YEAR C. (Mode 10.0cm, median 5.9cm and mean 5.6cm.)

cm, centimetres.

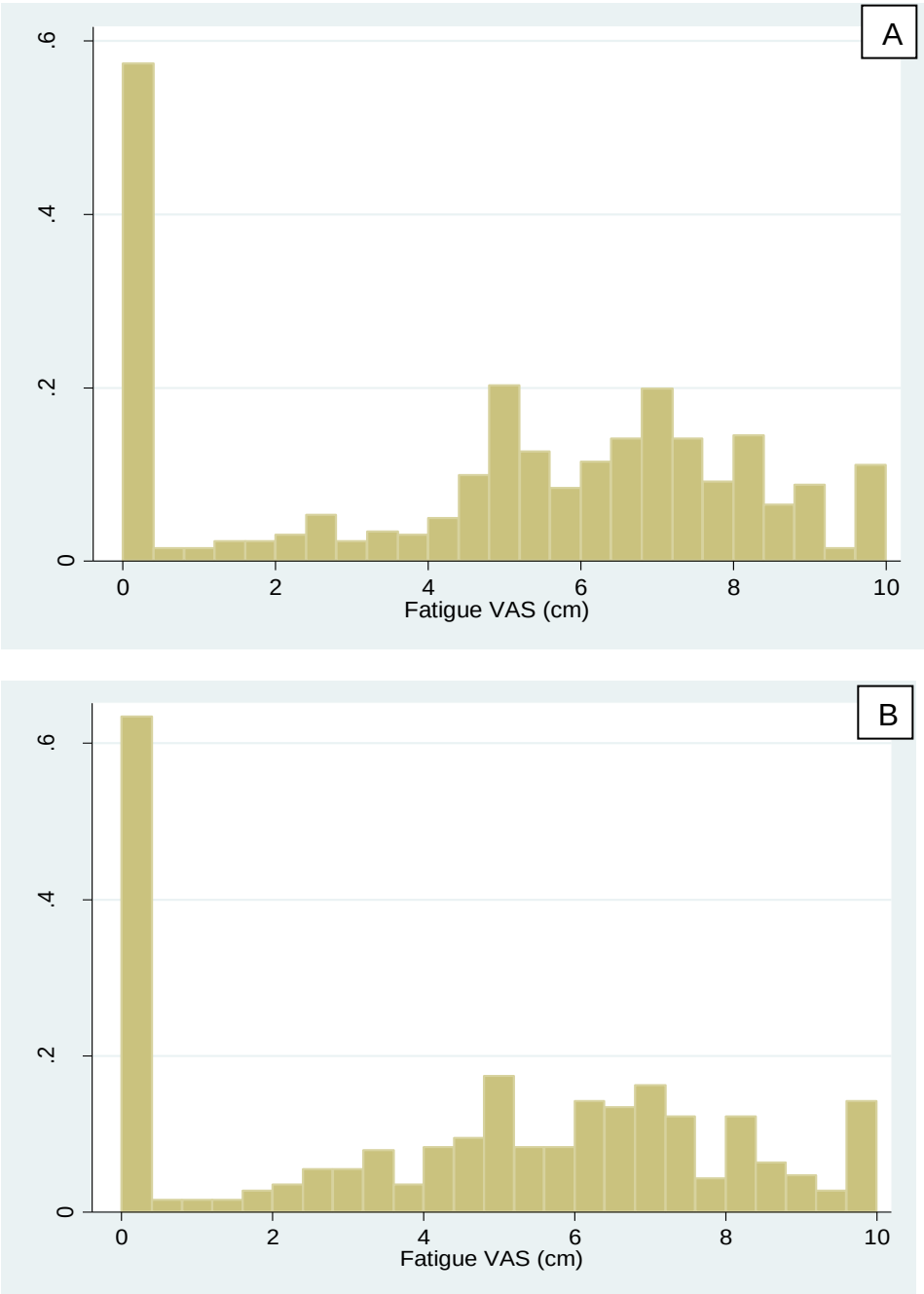


Figure 6D Histograms to show distributions of pain and fatigue visual analogue scores in Yorkshire Early Arthritis Register

The upper figure (A) represents data from YEAR B. (Mode 0.0cm, median 5.5cm and mean 4.8cm.)

The lower figure (B) represents data from YEAR C. (Mode 0.0cm, median 5.0cm and mean 4.0cm.)

cm, centimetres; VAS, visual analogue score.

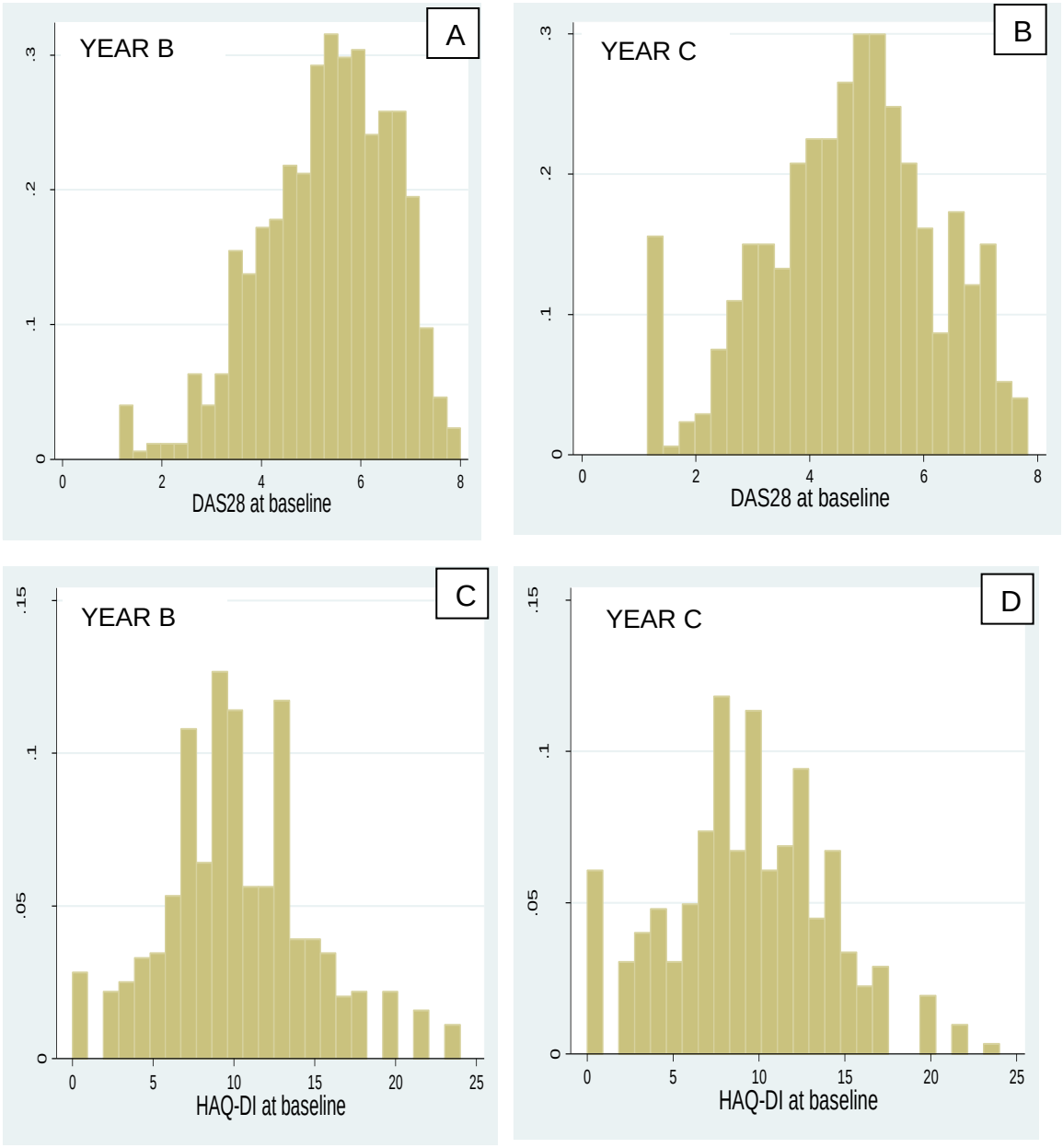


Figure 6E Histograms to show distributions of baseline disease activity scores from counts of 28 joints and health assessment questionnaire scores in Yorkshire Early Arthritis Register.

The upper left figure (A) represents baseline DAS28 from YEAR B. (Mode 5.4, median 5.4 and mean 5.3.)

The upper right figure (B) represents baseline DAS28 from YEAR C. (Mode 5.0, median 4.8 and mean 4.7.)

The bottom left figure (C) represents baseline HAQ-DI from YEAR B. (Mode 9.0, median 10.2, mean 10.2.)

The bottom right figure (D) represents baseline HAQ-DI from YEAR C. (Mode 8.0, median 9.5, mean 9.4.)

DAS28, disease activity score based upon count of 28 joints; HAQ-DI, disability component of the health assessment questionnaire; YEAR, Yorkshire early arthritis register.

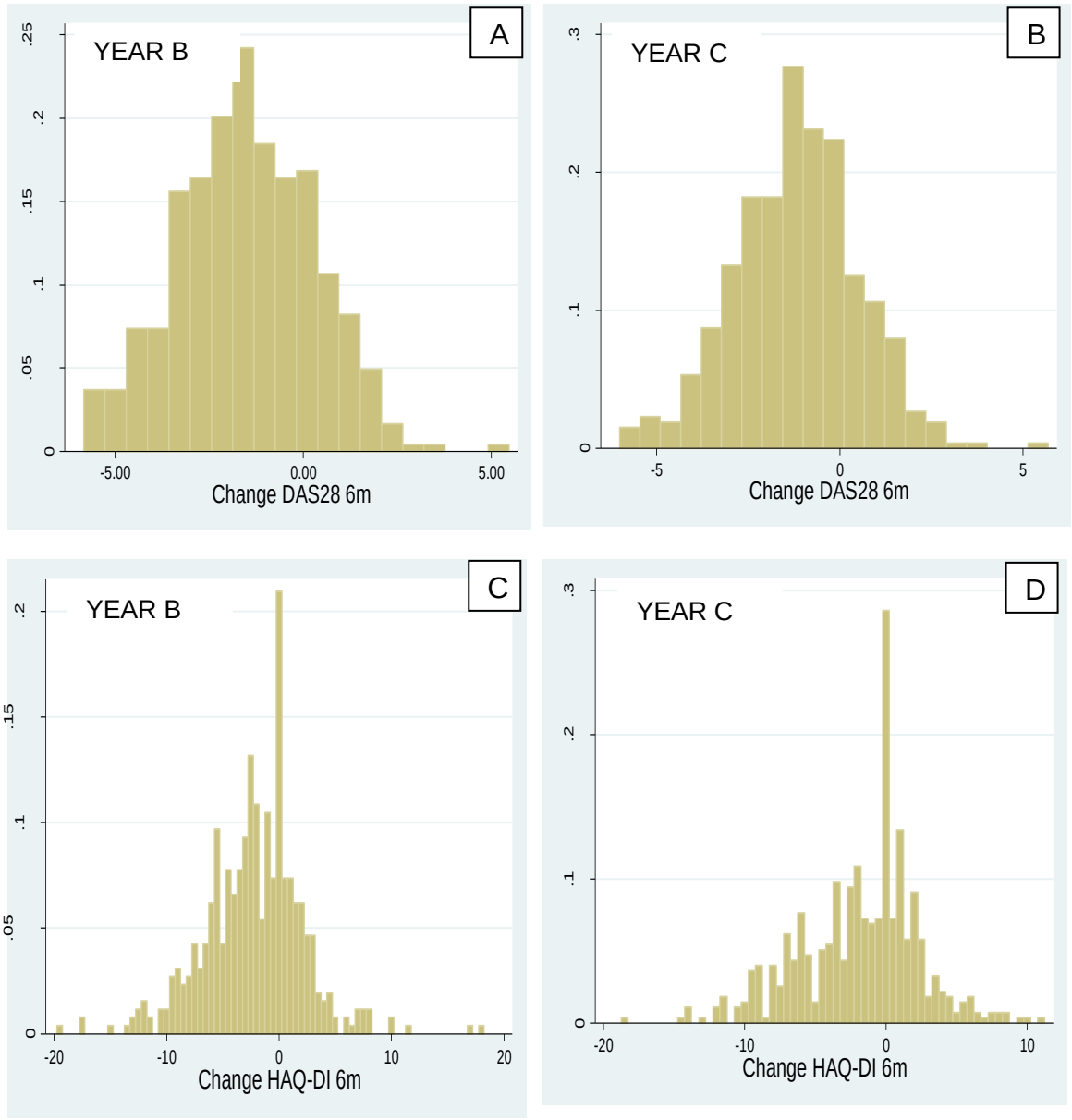


Figure 6F Histograms to show distributions change in disease activity scores from counts of 28 joints and health assessment questionnaire scores after six months in Yorkshire Early Arthritis Register

The upper left figure (A) represents change in DAS28 after 6 months in YEAR B. (Mode -1.6, median -2.0 and mean -1.5.)

The upper right figure (B) represents change in DAS28 after 6 months in YEAR C. (Mode -1.3 median -1.1 and mean -1.2.)

The bottom left figure (C) represents change in HAQ-DI after 6 months in YEAR B. (Mode 0.0 , median -2.0, mean -2.2.)

The bottom right figure (D) represents change in HAQ-DI after 6 months in YEAR C. (Mode 0.0, median -1.0, mean -1.9.)

Change in DAS28 and HAQ-DI were calculated by subtracting the scores at baseline from those at 6 months.

DAS28, disease activity score based upon count of 28 joints; HAQ-DI, disability component of the health assessment questionnaire; YEAR, Yorkshire early arthritis register.

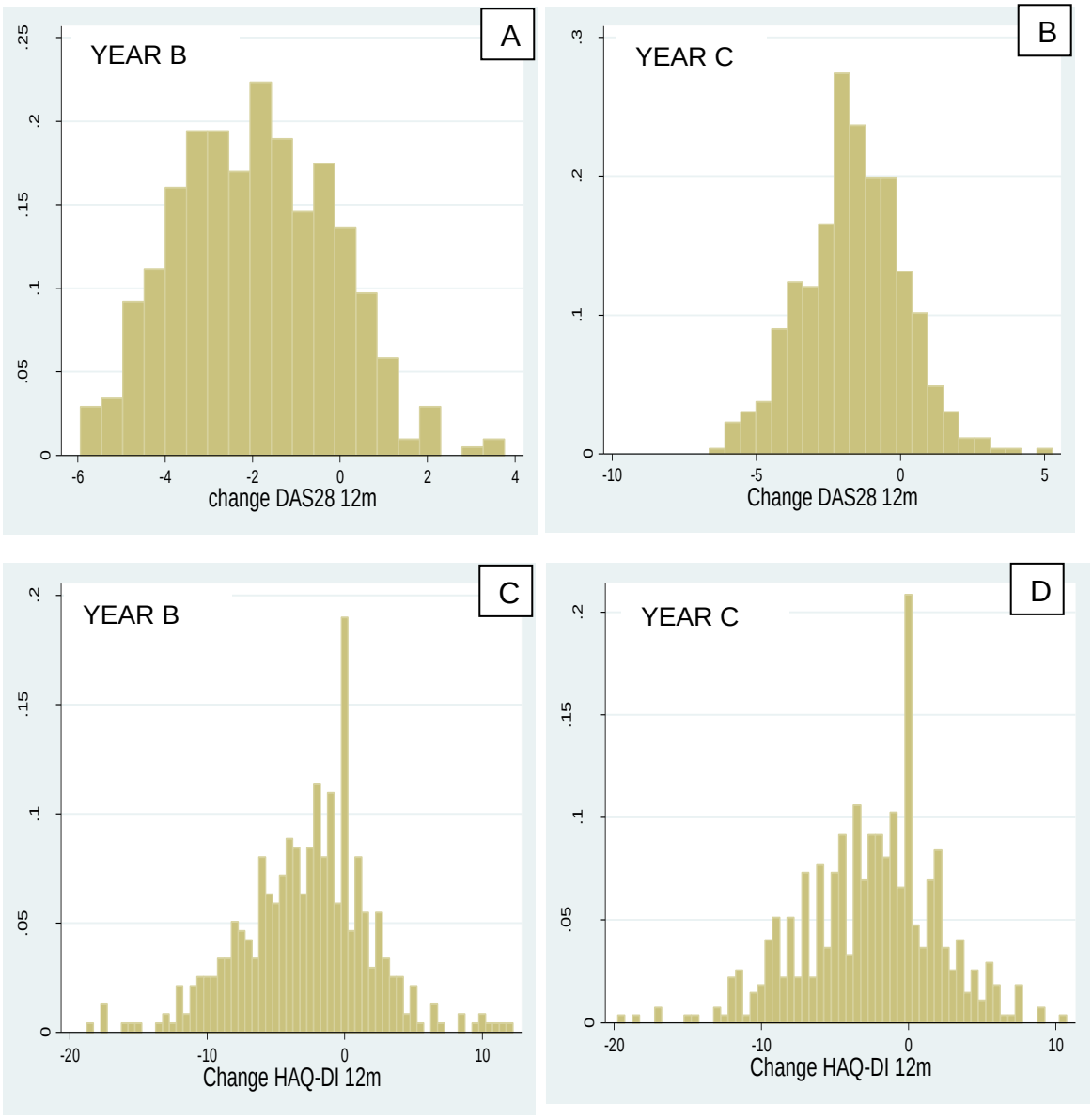


Figure 6G Histograms to show distributions change in disease activity scores from counts of 28 joints and health assessment questionnaire scores after twelve months in Yorkshire Early Arthritis Register

The upper left figure (A) represents change in DAS28 after 12 months in YEAR B. (Mode -1.84, median -1.95 and mean -1.93.)

The upper right figure (B) represents change in DAS28 after 12 months in YEAR C. (Mode -2.0 median -1.6 and mean -1.6.)

The bottom left figure (C) represents change in HAQ-DI after 12 months in YEAR B. (Mode 0.0, median -2.5, mean -2.8.)

The bottom right figure (D) represents change in HAQ-DI after 12 months in YEAR C. (Mode 0.0, median -2.0, mean -2.5.)

Change in DAS28 and HAQ-DI were calculated by subtracting the scores at baseline from those at 12 months.

DAS28, disease activity score based upon count of 28 joints; HAQ-DI, disability component of the health assessment questionnaire; YEAR, Yorkshire early arthritis register.

Appendix 7 Predictors of disease activity trajectory (fatigue excluded)

Table 7A Results of multinomial logistic regression analysis of predictors of class 2 trajectory ('low disease activity') membership

Predictor	Coefficient	Odds ratio	(95% CI)		p
YEAR C cohort	-0.05	0.95	(0.77,	1.19)	0.727
Male gender	**-0.53**	**0.59**	**(0.47,**	**0.75)**	**<0.001**
Age	0.00	1.00	(0.99,	1.01)	0.763
RF positive	0.17	1.19	(0.86,	0.64)	0.382
CCP positive	0.38	1.46	(1.01,	2.11)	0.094
Shared epitope positive	0.16	1.18	(0.96,	1.45)	0.184
IMD quartile 1	**0.41**	**1.50**	**(1.10,**	**2.04)**	**0.030**
2	0.29	1.33	(0.97,	1.82)	0.133
3	-0.11	0.90	(0.65,	1.24)	0.581

Results of multinomial logistic regression analysis using data from whole YEAR cohort. Outcome variable was membership of class 2 trajectory, described in Chapter 4, Section 4.6.
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
For IMD, the referent category was the 4th quartile, which was the least deprived group: higher levels of deprivation were represented by reducing quartile number .
Independent variables were measured at baseline.
CCP, cyclic citrullinated peptide antibody; CI, confidence interval; IMD, index of multiple deprivation; p, probability (statistical significance); RF, rheumatoid factor; YEAR, Yorkshire Early Arthritis Register.

Table 7B Results of multinomial logistic regression analysis of predictors of class 1 trajectory (more favourable) membership for Yorkshire Early Arthritis Register C

Predictor	Coefficient	Odds ratio	(95% CI)		p
Male gender	**0.75**	**2.13**	**(1.46**	**3.10)**	**0.001**
Age	0.00	1.00	(0.99	1.02)	0.719
RF positive	-0.06	0.94	(0.57	1.51)	0.831
CCP positive	-0.38	0.69	(0.41	1.53)	0.232
Shared epitope positive	-0.14	0.87	(0.69	1.10)	0.337
IMD quartile 1	**-0.63**	**0.54**	**(0.32**	**0.88)**	**0.039**
2	**-0.60**	**0.55**	**(0.34**	**0.90)**	**0.045**
3	-0.28	0.76	(0.45	1.26)	0.367
BMI (kg/m^2)	**-0.04**	**0.96**	**(0.93**	**0.99)**	**0.032**
Smoking (pack years)	-0.01	0.99	(0.99	1.00)	0.163
Comorbidities	-0.15	0.86	(0.58	1.29)	0.539

Results of multinomial logistic regression analysis.
Outcome variable was membership of class 1 trajectory, described in Chapter 4, section 4.7.1.3.
Statistically significant ($p<0.05$) coefficients are highlighted in **bold.**
For IMD, the referent category was the 4^{th} quartile, which was the least deprived group: higher levels of deprivation were represented by reducing quartile number .
Independent variables were measured at baseline.
One pack year was the equivalent of smoking 20 cigarettes per day for one year.
Comorbidities were classified as present /absent.
BMI, body mass index CCP, cyclic citrullinated peptide antibody; CI, confidence interval; IMD, index of multiple deprivation; p, probability (statistical significance); RF, rheumatoid factor.

Appendix 8 Comparison of baseline variables across quartiles of index of multiple deprivation scores

Table 8A Comparison of mean baseline variables across quartiles of index of multiple deprivation score

Mean baseline values by IMD quartile (SD)

	1		2		3		4		F*	P*
Age /years	56.2	(14.9)	56.9	(14.7)	58.5	(13.8)	58.9	(14.2)	2.30	0.030
DAS28	5.2	(1.4)	5.0	(1.5)	5.0	(1.4)	4.9	(1.4)	1.66	0.174
Fatigue VAS /cm	4.9	(3.2)	5.0	(3.3)	4.6	(3.3)	4.3	(3.2)	3.53	0.014
Number of PY	16.8	(20.4)	14.2	(24.4)	14.1	(18.6)	11.4	(18.9)	1.96	0.119
BMI	27.6	(6.6)	27.0	(6.6)	27.0	(4.7)	27.7	(6.1)	0.74	0.531
HAQ-DI	11.0	(4.8)	10.1	(4.6)	9.3	(4.5)	9.0	(4.2)	12.65	<0.001

*F-statistic and statistical probability, p refer to results of a one-way between groups analysis of variance.

BMI, body mass index (measured in kilograms per metre squared); cm, centimetres; DAS28, disease activity score based upon counts of 28 joints and C-reactive protein; HAQ-DI, disability index component of health assessment questionnaire (Rasch transformed variable used); IMD, index of multiple deprivation; PY, pack years; SD, standard deviation; VAS, visual analogue score.