The course of psychological distress and determinants of adjustment following diagnosis of rheumatoid arthritis

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Dedicated to my late grandfather Colonel David C. Munn.

His attitude towards life remains an inspiration.

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Abstract

Chronic physical illnesses, such as rheumatoid arthritis (RA), that are painful and disabling not only impact on a person's ability to complete normal daily activities (e.g. dressing, bathing, walking etc.) but may also have a negative impact on psychological well-being. Although a large number of prospective observational studies have examined psychological well-being in RA, none has used appropriate statistical techniques to examine variability in change over time at the individual level.

The overarching aim of this dissertation is to use advanced quantitative methods to examine how psychological well-being in RA changes over the course of the disease; and to identify demographic, clinical and psychosocial factors that influence how the disease affects psychological well-being. This aim is addressed via a programme of research with three objectives: (i) to describe patterns of change in psychological well-being during the RA disease course; (ii) to quantify the association between psychological well-being and somatic symptoms; and (iii) to investigate the impact of illness cognitions and coping on psychological well-being. The programme of research consists mainly of analysis of a subsample of data collected as part of the Early RA Study (ERAS, $N = 784$), an ongoing observational study of RA patients followed prospectively from first presentation to a rheumatologist.

A major problem relating to the assessment of psychological distress in individuals with chronic physical illness is the overlapping symptomatology with depression. An examination of the factorial validity of the Hospital Anxiety and Depression Scale (HADS), in the ERAS cohort, indicated the presence of a bifactor structure. Specifically, a general distress factor along with orthogonal (autonomic) anxiety and (anhedonic) depression factors was found to provide the optimal empirical explanation of the covariance in item responses. Further analysis, revealed that responses to one of the depression items were biased by disease severity. However, the magnitude of this bias was negligible, confirming the suitability of this tool in RA populations.

For the ERAS cohort, general psychological distress was observed to reduce rapidly early in the course of the disease, stabilising after around two to three-years. However, further analysis suggested that subgroups with distinct longitudinal patterns of distress were present within the sample. Confirm-

ing observations in other disease groups, four distinct longitudinal patterns of distress were identified: resilient, chronic distress, delayed distress and recovered. Interestingly, changes in distress were related to self-reported somatic symptoms but not serological markers of disease activity. Building on these findings, analyses that jointly modelled changes in psychological distress with changes in the common somatic symptoms of pain and functional limitation revealed strong cross-sectional and longitudinal associations. This extends the findings of previous research by showing the importance of considering the impact of the disease course on the underlying trajectory of distress.

Due to the lack of psychosocial data available in the ERAS cohort a further prospective study, involving 230 RA patients, was conducted to examine the influence of illness cognitions and coping on the affect of the disease on psychological well-being over a period of 6-months. Coping was not found to be related to changes in psychological well-being. Analysis revealed two groupings of patients with similar patterns of illness cognitions that were labelled *adapters* and *non-adapters*. Furthermore, cognitions concerning the attribution of symptoms to RA and the perceived personal consequences of their condition were related to changes in psychological distress, even after controlling for demographic and clinical characteristics; and there was some indication that a higher reported level of understanding of their condition was related to increased future positive outlook.

In conclusion, the findings of this programme of research highlight the need for the early identification and treatment of RA, not only to slow the progression of the disease but also to maintain or improve psychological well-being. Early treatment is currently focused on pharmaceutical interventions. A tailored psychosomatic approach to treatment involving the skills of a wide range of health professionals, such as nurses, physiotherapists, occupational therapists and psychologists is likely to improve outcomes in RA.

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List of abbreviations

A Anxiety

AIC Akaike's Information Criterion

AIMS Arthritis Impact Measurement Scale

AIMS Arthritis Impact Measurement Scale

BAI Beck Anxiety Inventory

BDI Beck Depression Inventory

BIC Bayesian Information Criterion

CAIC Consistent Akaike's Information Criterion

CFA Confirmatory Factor Analysis

CFI Confirmatory Fit Index

CRP C-reactive Protein

D Depression

DAPOS Depression Anxiety and Positive Outlook Scale

DAS Disease Acivity Score

DIF Differential item functioning

EFA Exploratory Factor Analysis

EMS Early Morning Stiffness

ERAS Early Rheumatoid Arthritis Study

ESR Erythrocyte Sedimentation Rate

EURIDISS European Research in Incapacitating Diseases and Social Support network

FIML Full Information Maximum Likelihood

G General distress

GBTM Group-Based Trajectory Model

GDS Geriatric Depression Scale

GHQ General Health Questionnaire

GMM Growth Mixture Model

HADS Hospital Anxiety and Depression Scale

HAM-A Hamiliton Anxiety Rating Scale

HAQ Health Assessment Questionnaire

IPQ-R Revised Illness Perception Questionnaire

IRDL Impact of Rheumatic Diseases on Health and Lifestyles

IRT Item Response Theory

KMO Kaiser-Meier-Olkin measure of sampling adequacy

LCM Latent Curve Model

LGCA Latent Class Growth Analysis

LVM Latent Variable Model

MADRS Montgomery Asberg Depression Rating Scale

MAR Missing At Random

MCAR Missing Completely At Random

MCS Mental Component Score

MG-CFA Multiple Group Confirmatory Factor Analysis

MHI Mental Health Inventory

MHQ Middlesex Hospital Questionnaire

MI Multiplie Imputation

ML Maximum Likelihood

NA Negative Affectivity

NMAR Not Missing At Random

OLS Ordinary Least Squares

PA Positive Affect

PCA Principle Components Analysis

PCS Physical Component Score

PHQ-9 Patient Health Questionnaire

PMM Pattern Mixture Model

QLSC Quality of Life Status and Change

RA Rheumatoid Arthritis

RMSEA Root Mean Square Error of Approximation

SCL-90 Symptom Check List

SD Standard deviation

SE Standard error

SEM Structural Equation Modelling

SES Socio-economic status

SF12 Short Form Health Survey (12item version)

SF36 Short Form Health Survey (36 item version)

SF-GDS Short Form Geriatric Depression Scale

SJC Swollen Joint Count

SRM Self Regulation Model of illness cognitions

STAI State-Trait Anxiety Inventory

TJC Tender Joint Count

TLI Tucker-Lewis Index

UCSF RA Panel University of California San Francisco Rheumatoid Arthritis Panel survey

VAS Visual Analogue Scale

VWLS Variance Weighted Least Squares

WLS Weighted Least Squares

WLSMV Robust Weighted Least Squares

Chapter 1

Introduction to the dissertation

1.1 Background

My interest in psychological well-being in chronic physical illness began when I worked in the Rheumatology department at St Albans City Hospital. I was fascinated and inspired by the resilience of some of the patients that Adam Young saw in his clinic to the adversity posed by the physical consequences of their condition. At the same time I recognised that others experienced far greater distress and reported far worse impact on their daily lives despite suffering milder disease.

The position involved working on a large multi-centre prospective observational study of patients with early rheumatoid arthritis (ERAS). Although a large number of manuscripts utilising this cohort had been published describing the natural (but treated) course of this condition, no one had made any serious attempt at analysing the psychological well-being data collected by a number of centres. Furthermore, it became clear that the large volume of data collected over a number of years posed a serious analytic problem. The analytic skills I had developed during my first degree in psychology were not adequate for studying real-life longitudinal data. Furthermore, it was apparent from my reading of the scientific literature that few others possessed these skills either.

Examining the psychological well-being data collected in the ERAS cohort seemed like an excellent opportunity to gain greater insight into the factors impacting on psychological well-being in individuals with rheumatoid arthritis and at the same time develop my skills in longitudinal data analysis. Thankfully others felt the same, and with the support of my supervisors I was lucky enough to be awarded an ESRC-MRC interdisciplinary studentship to undertake an extended period of study to examine these issues.

1.2 Aims of the dissertation

The aims of the current dissertation are twofold. The first is to examine changes in psychological well-being in rheumatoid arthritis over an extended period of time. More specifically, changes from the early stages of the disease and their relation to the course of the disease as well as to demographic and psychological factors. In the early stages of the disease, prior to the use of disease modifying treatments, the individual is presented with a major life event: the onset of a chronic physical condition that at that time causes them considerable pain and functional limitation, potentially posing a serious threat to their future health and well-being. Little is known about changes in psychological well-being early in the course of the disease, or how changes at that time relate to psychological well-being several years later.

The second aim is to examine how latent variable modelling techniques can be applied to provide a more detailed examination of changes in psychological well-being than currently reported in the literature, making efficient use of the wealth of data available in the ERAS cohort. Few studies with large sample sizes have examined psychological well-being in rheumatoid arthritis over an extended period. It is the combination of these two aims in the programme of research that is presented in this dissertation that provides the opportunity to drive scientific understanding in this area forward.

1.3 Structure of this dissertation

The first three chapters of this dissertation provide an introduction to the topic and methods used in the empirical chapters. Chapter 2 provides an introduction to rheumatoid arthritis and the topic of psychological well-being in chronic physical illnesses in general. Chapter 3 systematically reviews the existing evidence base considering changes in psychological well-being in rheumatoid arthritis over the course of the disease and the association between demographic, clinical and psychosocial factors with changes in psychological well-being. At the end of the chapter the specific objectives of the dissertation are outlined. Chapter 4 introduces the topic of latent variable modelling with particular emphasis on the application of latent variable modelling techniques to longitudinal data, and an overview of a common problem in longitudinal studies, the presence of missing data.

The following four chapters present the main empirical work undertaken during the doctoral studies. Chapter 5 provides a detailed analysis of the psychometric properties of the measure of psychological well-being used in the ERAS cohort, the Hospital Anxiety and Depression Scale. The dimensionality of the measure is assessed and issues concerning possible item bias, for example due to the somatic symptoms of the condition, are addressed. Chapter 6 examines longitudinal changes in psychological

well-being in the ERAS cohort and explores the possibility of multiple groups of patients with distinct patterns of change in distress over time. Chapter 7 extends these findings to consider the association of changes in psychological well-being to changes in the somatic symptoms of RA. Chapter 8 examines how illness cognitions, specifically individuals beliefs about their condition, impact on changes in well-being using data from a separate prospective study of rheumatoid arthritis patients.

The final chapter, Chapter 9, provides a general discussion of the findings of the empirical chapters in the context of the objectives outlined in Chapter 3. In addition, a discussion of the utility of latent variable modelling and observational studies in general is presented, as well as recommendations for future research. It is also important to note that Appendix A provides details of the manuscripts published, or currently under review, in peer review journals that are directly or indirectly related to the research presented in this dissertation.

Chapter 2

General introduction

2.1 Rheumatoid arthritis

2.1.1 Background

RA is a chronic systemic autoimmune disease with a flaring-remitting pattern primarily affecting the joints. It is the most common form of inflammatory arthritis worldwide (Majithia & Geraci, 2007). Inflammation of the synovial membrane that lines the joints and tendon sheaths causes the joints to become swollen and painful and stiffness limits their movement (Figure 2.1). The joints most commonly involved are the small joints of the hands, feet and cervical spine, however larger joints, such as the shoulder or knee, may also be affected. Over time, erosions and destruction of the joint surface can lead to deformity and restrict the range of movement, impacting on the individuals ability to complete normal daily activities, such as dressing, bathing and walking.

Although RA primarily affects the joints, unlike osteoarthritis, extra-articular manifestations are common affecting around 15–20% of individuals with RA (Young & Koduri, 2007). The most common extra-articular manifestation is the rheumatoid nodule, probably the most characteristic feature of the disease. As well as the skin, extra-articular features may affect organs such as the glands (e.g. Sjogrens syndrome), blood vessels (e.g. vasculitis and Raynaud's disease) and lungs (e.g. pulmonary lesions and interstitial lung disease). Furthermore, several complications of the disease are common, such as anaemia, ischemic heart disease and osteoporosis.

RA has a wide clinical spectrum ranging from mild joint symptoms to severe inflammation and joint damage. The disease burden of RA is considerable. One third of people with the disease will have stopped working within two years of disease onset (Young et al., 2002). Psychological problems are common and impact on the relationship between disease variables and outcome (Dickens, McGowan,

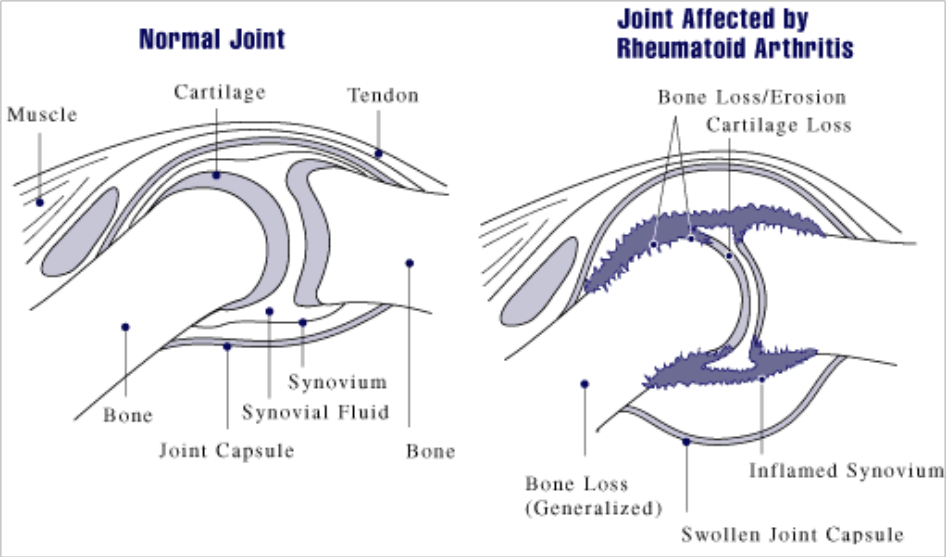

Figure 2.1: Rheumatoid arthritis joint

Table 2.1: American College of Rheumatology classification criteria for rheumatoid arthritis

Patients must have four of the following seven criteria:
• Morning stiffness lasting at least 1 hour*
• Arthritis (swelling) in three or more joints*
• Arthritis in hand joints*
• Symmetrical jont inflammation*
• Rheumatoid nodules
• Abnormal serum rheumatoid factor
• Radiographic changes (erosions or decalcification) of hand

* Present for at least six-weeks

Clark-Carter, & Creed, 2002).

Diagnosis of RA is made on clinical, serological and radiological grounds—typically using the American College of Rheumatology classification criteria (Arnett et al., 1988). The criteria are listed in Table 2.1. A Rheumatologist will make a diagnosis of RA if an individual fulfills four of the seven criteria for a period of at least six weeks. It is now recognised that these criteria do not accurately identify individuals with recent-onset RA (Harrison, Symmons, Barrett, & Silman, 1998). Resultantly there has been a drive to treat inflammatory arthritis, which may progress towards RA, with appropriate disease-modifying treatment as soon as possible after symptom onset (NICE, 2009b)

2.1.2 Epidemiology

RA is the most common type of inflammatory arthritis. Although RA can occur at any age, its incidence increases with age with a peak age of onset around 50 years. Furthermore, the overall occurrence of RA

is 2 to 4 times greater in women than men. A 2002 Norfolk based population study estimated the yearly incidence in the UK to be 1.5 males per 10,000 and 3.6 females per 10,000 (Symmons et al., 2002). This equates to approximately 12,000 new cases per year in the UK. A more recent estimate using 10 years of data from the General Practice Research Database (GPRD)—a database of medical records from over 600 UK primary care practices—suggests the figure is substantially higher at 26,000 new case per year (National Audit Office, 2009). Both estimates indicate that, due to the cumulative number of patients' surviving into old age, the prevalence of RA in the UK is not insignificant. It is estimated to be around 0.8% to 1% of the adult population, equating to in the region of 400,000 to 580,000 people with the condition (Symmons, Barrett, Bankhead, Scott, & Silman, 1994; National Audit Office, 2009).

A systemic review of the global incidence and prevalence of RA revealed some variation across countries (Alamanos, Voulgari, & Drosos, 2006). The review identified 28 studies reporting either prevalence or incidence figures for adults using the 1987 ACR diagnostic criteria. Southern European studies had a lower incidence (1.7 per 10,000) than northern European studies (2.9 per 10,000) and north American studies (3.8 per 10,000). A similar pattern was observed with regard to prevalence studies. Despite these variations, the prevalence rate is stable across countries, at approximately 0.5–1%. However, there are populations where particularly high or low prevalence has been observed, indicative of a genetic effect. For example, Native American Indians have the highest reported occurrence of RA (5.3%, Del Puente, Knowler, Pettitt, & Bennett, 1989; and 6.8%, Harvey, Lotze, Stevens, Lambert, & Jacobson, 1981). Whereas studies of rural African populations have failed to find a single case (Brighton, Harpe, Staden, Badenhorst, & Myers, 1988; Silman et al., 1993). Furthermore, migrant studies have shown that individuals of African (MacGregor, Riste, Hazes, & Silman, 1994) and Pakistani (Hameed & Gibson, 1997) origin living in the UK having lower prevalence rates, suggesting possible genetic protection.

2.1.3 Aetiology

RA is a form of autoimmunity, the failure of an organism to recognise its own constituent parts, which results in an immune response against its own cells or tissue. The causes of this autoimmunity remain unknown, but it seems that the interaction between genetic and environmental factors play an important role in the development of disease in susceptible individuals.

2.1.3.1 Genetic factors

Family and twin studies have shown an increased risk of the development of RA if a close relative has the disease. For example, MacGregor et al. (2000) in a study of UK and Finnish twins found a increased

concordance in monozygotic compared to dizygotic twins, with 50–60% of the occurrence explained by shared genetic effects.

Attempts to identify the genes involved in the predisposition to RA have indicated the major histocompatibility complex (MHC) a large genetic region on the short arm of chromosome 6. A large part of the MHC comprises human leukocyte antigen (HLA) genes. HLA class II genes, in particular HLA-DR4 and HLA-DRβ_1, have been strongly linked to RA (Silman & Pearson, 2002). The encoded proteins related to these genes are crucial in determining the individual's immune response to antigenic stimuli. Studies have found that susceptibility to RA is associated with several different HLA DRβ_1 alleles, with individuals with the so-called 'compound heterozygote' genotype carrying a substantially greater risk than individuals with a single allele (Thomson et al., 1999). However, there is some indication that the relationship between HLA and RA may be more related to disease severity, than to the development of RA (Meyer et al., 1999).

While HLA clearly plays an important role in the predisposition to RA only 50% of the genetic contribution to RA is thought to be associated with HLA (MacGregor et al., 2000). Other non-MHC genes must therefore also be involved. Genes encoding cytokines such as tumour necrosis factor α (TNFα) and several interleukins (ILs) have also been implicated in the aetiology of RA, although attempts to replicate these findings are often negative (Silman & Pearson, 2002).

It is not entirely surprising that research investigating genetic factors predisposing individuals to the development of RA is largely inconclusive. RA is a heterogeneous disease, it is likely to be polygenic and the causative role of different genes may vary between individuals, with different combinations of polymorphisms in a selection of different genes (the genotype) may predispose different clinical manifestations of the disorder (the phenotype) (Barton & Worthington, 2009; Klareskog, Padyukov, Rönnelid, & Alfredsson, 2006). In addition, non-inherited environmental factors are also likely to be of great importance.

2.1.3.2 Environmental factors

Population studies have shown that environmental factors play a major role in the aetiology of RA (Isaacs & Moreland, 2002). Environmental factors are considered as triggers rather than as being directly involved in the disease process. A complex interplay between genetic and environmental factors are probably important for the initiation of the disease process in susceptible individuals.

Certain viruses and bacterial agents contain identical peptide sequences to autoantigen, and infection with these microbial agents can induce an immune response that cross-reacts with the auto antigen,

termed 'antigen mimicry'. Epstein-Barr virus (EBV), Parvovirus B19, Mycobacterium Tuberculosis, Escherichia Coli and Proteus Mirabilis have all been implicated, although results are inconsistent (Silman & Hochberg, 2001).

Hormonal factors may also play a possible role in the aetiology of the disease, as suggested by the increased prevalence of RA in females (Silman & Hochberg, 2001). RA incidence has been observed to be higher in women with sub-fertility, and also during the pre-menopausal or post-partum period. Also use of the oral contraceptive pill has been found to be related to a reduced risk of developing RA and male sex hormones levels, including testosterone, have been observed to be lower in men with RA compared to controls.

There have been a number of studies investigating the role of other comorbidities, particularly other automimmune diseases, as risk factors for RA. Type 1 or insulin dependent diabetes and autoimmune thyroid disease have been found to be increased frequency in individuals' with RA and their families (Silman, Ollier, & Bubel, 1989). Furthermore, diet and stress have also been considered to play a possible role in the disease expression (Pattison, Harrison, & Symmons, 2004; Pattison, Symmons, & Young, 2004).

2.1.3.3 Other factors

Research investigating the causal perceptions of individuals' with RA has revealed various lay theories regarding the aetiology of the disease. Williams (1986) conducted in depth interviews with a small number of people diagnosed with RA for at least 5-years. The most frequently mentioned causal factors were stress and heredity. However, the study revealed a number of misconceptions regarding causal factors, such as old-age, 'wear-and-tear' damage to the joints, and the weather. These observations were confirmed by later quantitative research (Moss-Morris et al., 2002).

Old age is not a cause of RA. This belief is likely to have arisen from the cumulative increase in individuals' suffering with the condition with age, but as has already been noted RA can affect individuals of any age. This perception is likely to be linked to the belief that RA is a result of 'wear-and-tear' damage to the joints. Although this is true of osteoarthritis, and may exacerbate the symptoms of RA, 'wear-and-tear' damage has not been found to be associated with the development of RA (Hill, Bird, Hopkins, Lawton, & Wright, 1991). Finally, although cold and damp weather is often reported as being associated with symptom exacerbation, and the increased incidence of RA in northern compared to southern European countries, there is little evidence to suggest that weather is a causal factor in the development of RA (Gorin et al., 1999).

2.1.4 Physiology

RA is one of a number of autoimmune rheumatic diseases, which also includes systemic lupus erythomatosus, anti-phospholipid syndrome, polymyalgia rheumatica, and Sjögrens syndrome. Although the autoimmunity in RA involves both the innate and the adaptive arm of the immune system, its clinical features are directly related to dysregulation of the immune system whereby it attacks the joints causing inflammation and damage.

2.1.4.1 Autoimmunity

The immune system includes two types of white blood cell—B cells and T cells. B cells are involved in the humoral response and are an essential component of the adaptive arm of the immune system. Their principal function is to make antibodies (immunoglobulins; IgA, IgD, IgE, IgG and IgM) against foreign antigen (e.g. viruses and bacteria). B cells have unique receptors that will bind only to one particular antigen, which are produced randomly during their development in the thymus. Once a B cell encounters its associated antigen it will develop into either a plasma B cells or memory B cells. Plasma B cells secrete large amounts of antibodies that assist with the destruction of the antigen. They are short-lived. Apoptosis (self-destruction) is induced when the antigen that induced the immune response is removed. Memory B cells on the other hand live for a long time. They are specific to the antigen encountered during the primary immune response enabling a quick response following subsequent exposure to the same antigen.

T cells form part of the innate arm of the immune system and are involved in cell-mediated immunity. This involves the removal of virus-infected cells, as well as protecting against fungi, cancers and intracellular bacteria. This does not directly involve antibodies but instead involves the activation of macrophages, natural killer cells, cytotoxic T-lymphocytes (induce apoptosis) and various cytokines (influence function of other cells) in response to an antigen. Although T cells do not produce antibodies they are seen as directing antibody production.

Once an antigen is ingested by a B cell the pathogens proteins are digested to peptides and attached to class II MHC proteins that are unique to the type of B cell. This complex triggers the production of T helper cells (i.e. CD4+ T cells) which activate specific B cell. The T cell secretes cytokines that activate the B cell causing it to develop into a plasma B cell. In addition, further cytokines released induce the production of more T cells (Feldmann & Maini, 2008).

Since antibodies are produced randomly antibodies for 'self' molecules are commonly produced—

these are known as autoantibodies. Usually, useful antibodies to foreign antigen are positively selected whereas autoantibodies are negatively selected and therefore do not persist. However, in RA autoantibodies to immunoglobulin-G (IgG), known as rheumatoid factor (RF), are present (Isaacs & Moreland, 2002). Initially the RF antibodies are typically IgM antibodies to IgG (IgM-anti-IgG). IgM-RF forms large immune complexes with IgG that are rapidly cleared from circulation and are commonly found at low levels in normal individuals. More dangerous IgG-anti-IgG occur by chance genetic mutation (Isaacs & Moreland, 2002). These autoantibodies are antibodies against them self—resulting in a vicious cycle. The immune complexes formed by IgG-RF with IgG are small and not easily cleared from circulation. They can also cross the endothelium leaving the blood vessels. Once in the tissues they bind with FcRIIIa receptors on the surface of macropaghes present in only a few specific places including in the synovium, lung, serosa, bone marrow. Thus triggering the production of interleukins, such as as IL-6, TNF-α and IL-1β, resulting in the same inflammation as would occur from a real infection (Feldmann & Maini, 2008). The inflammation of the synovium (synovitis) is the dominant feature in RA. The situation is made worse in the joints since as a result of the inflammation anti-IgG antibodies enter the synovium and make autoantibodies inside the joint. Synovitis leads to replacement of cartilage by a layer of vascular soft tissue (pannus) and similar erosion of the bone by vascular tissue at the articular margin. It is this damage that leads to deformity and restricts the range of movement of the joint (Feldmann & Maini, 2008).

2.1.4.2 Inflammation & disease activity

Many serological markers of disease activity and severity have been identified. Disease activity in RA is routinely assessed by standard biological measures. Erythrocyte sedimentation rate (ESR) relates to the distance blood cells fall in one hour, which is an indirect measure of the proteins such as C-reactive protein (CRP), that are released during inflammation (Wolfe, 1997). CRP is a more specific, although still relatively general, measure of inflammatory activity. Normal levels are considered to be <10mm/per hour for ESR and <8mg/l for CRP, however it is important to remember that since both are measures of non-specific inflammatory activity they may be raised, for example, as a result of infectious illness. Despite this they still provide important markers of inflammation in RA. Both have been found to be related to mortality in the general population (Strandberg & Tilvis, 2000; Kaptoge et al., 2010), as well as in the RA population (Young et al., 2007; Wolfe, Michaud, Gefeller, & Choi, 2003; Wållberg-Jonsson, Johansson, Ohman, & Rantapaa-Dahlqvist, 1999). ESR and CRP are commonly used in composite measures of disease activity, such as the Disease Activity Score (Prevoo et al., 1995).

A variety of pro-inflammatory cytokines including IL-6, TNF-α, IL-1, and IL-8—responsible for the initiation of the acute phase response—are also frequently elevated and fluctuate with disease activity (McInnes & Schett, 2007). However these cytokines are expensive to measure in routine clinical practice and the prognostic value of some of these cytokines is still not clear.

Rheumatoid factor, IgM-RF rather than IgG-RF, are commonly measured, indeed abnormal levels form one of the seven ACR diagnostic criteria listed in Table 2.1. Recently however the importance of circulating anti-cyclic citrullinated peptide antibodies (anti-CCP) has been discovered. Although these antibodies are not expressed in the affected tissue, and therefore unlikely to be directly involved in the pathogenesis of RA, the presence of anti-CCP antibodies provides a useful diagnostic test for RA. Nishimura et al. (2007) found that sensitivity was only 65%—similar to that of rheumatoid factor—specificity was high at 95%. This indicates that when anti-CCP antibodies are not observed RA is unlikely, although presence did not necessarily mean that the individual had RA. Screening for anit-CCP is increasingly common in clinical practice using widely available assays.

2.1.5 Treatment

There are two specific aims of the drug management in RA. Symptom relief, in particular pain relief, is the first and usually the main priority for patients. Secondly, modification of the disease process to slow, or even stop, radiological progression, which is closely associated with progressive functional impairment. Ultimately the aim of drug management is to achieve disease remission through disease modification. Remission has been defined in a number of different ways, but is generally taken to mean scores below a certain threshold on a disease activity index (e.g. the EULAR criteria are DAS <2.6; Fransen, Creemers, & Van Riel, 2004). Until recently there was a tendency for rheumatologists to treat patients conservatively, generally due to the worry of adverse side effects of the drugs (Schoels et al., 2010). However, there is increasing understanding that management during the early stages of the disease (i.e. the first 2 years) are the most important for long-term outcome (Kiely et al., 2009; Smolen et al., 2010). As a result treatment is now far more aggressive, in the form of earlier use of disease modifying drugs and greater use of therapies in combination. Indeed this is reflected in the treatment guidelines developed by NICE (NICE, 2009b).

2.1.5.1 Symptom relief

Non-steroidal anti-inflammatory drugs (NSAIDs) are the traditional first-line treatment for RA, and arthritides in general, as they directly reduce joint swelling and thus pain. NSAIDS, including ibupro-

fen, diclofenac and selective COX-II inhibitors such as celecoxib. Their mode of action is to inhibit the enzyme cyclooxygenase, which catalyzes prostaglandins that act as messenger molecules in the process of inflammation (Young, 2008). The main problem with NSAIDs is that adverse reactions are common, including gastrointestinal and renal effects (Young, 2008). While newer selective COX-II inhibitors were hoped to reduce gastrointestinal adverse reactions they have been shown to increase the risk of cardiovascular disease, and in several recent cases have been withdrawn from the market (e.g. rofecoxib, brand name Vioxx; Couzin, 2004). Despite the risk of adverse reactions most people with RA will take NSAIDs for a significant amount of time (NICE, 2009b).

Pain is the principle sign of inflammation, although adequate disease control with NSAIDs or disease modifying drugs will often result in satisfactory pain relief for many people there will be times when further relief is needed, for example during disease flare. In such circumstances analgesics such as paracetamol and opiods (e.g. codeine and morphine) are often used to relieve pain (NICE, 2009b).

Glucocorticoids (steriods; e.g. prednisolone) are also used to reduce inflammation via the control of certain hormones, such as cortisone (Young, 2008). They may be given to reduce systemic inflammation via oral, intra-muscular, or intra-venously administration, or alternatively localised as intra-articular injections. However long-term use results in severe side effects, including hypertension, diabetes, osteoporosis and weight gain (Donihi, Raval, Saul, Korytkowski, & DeVita, 2006; Verhoeven & Boers, 1997; Nikiphorou & Young, 2010). The NICE guidelines recommend the use of steroids to alleviate symptoms in recent-onset RA whilst waiting for slow-acting disease modifying drugs to take effect and in established RA for the management of disease flares (NICE, 2009b).

Anti-depressants are also used for people with RA. Apart from the obvious benefit of anti-depressants when a person with RA is suffering from major depression low-doses of tricyclics such as amitriptyline have been shown to relieve articular pain and tenderness in patients with RA (Grace, Bellamy, Kassam, & Watson Buchanan, 1985; Frank et al., 1988) and help with muscle relaxation, especially if they have disrupted sleep (Moldofsky, 2001). However, the recent NICE guidance on RA found that evidence from randomized-controlled trials only supported the effectiveness in reducing joint swelling, and helping to lift a low mood and chronic fatigue at quite high doses, typically used to treat major depressive disorder (NICE, 2009b).

2.1.5.2 Disease modification

Disease modifying anti-rheumitic drugs (DMARDs) are used to slow down the damaging component of the disease process (Young, 2008). These include methotrexate, sulphasalazine, hyrdoxchloroquine,

leflunomide and gold injections. Traditionally, DMARDs were only prescribed after the diagnosis of RA was made, or when radiological progression was observed, however there is now evidence that there is a 'window of opportunity' and the sooner DMARDs are prescribed the better the response and long-term outcomes are improved. Resultantly, DMARDs are often prescribed for any persistent inflammatory arthritis, which may later develop into RA (NICE, 2009b). Furthermore, due to the improved benefit of early introduction there is a tendency to use stronger DMARDS, such as methotrexate that also have higher risks of more severe side effects, or using two or more DMARDs in combination (NICE, 2009b).

In the last ten years a major improvement has been seen with the development of agents designed specifically to block key protein messenger molecules, such as TNFα (etanercept) or IL-1 (anakinra), or cells, such as B-lymphocytes (rituximab), that play an important role in the disease process. This group of drugs are generally referred to as 'biologics'. Biologic therapies have been shown to have dramatic effects with clinical trials showing improvements in symptoms and measures of both function and radiological damage sustained over several years (Y. F. Chen et al., 2006). However, due to their cost, around £10,000 per year compared to £300 per year for DMARDs (National Audit Office, 2009), biologic therapies are only used for individuals with established active disease that have failed to respond adequately to conventional disease modifying drugs. Owing to their high cost several biologic therapies, such as abatacept (NICE, 2009b), fall outside the cost-effectiveness cut-off prescribed by NICE and hence are not available under the NHS.

2.1.5.3 Other treatment

As well as the various classes of drugs used to manage RA other treatments are widely used. Physical treatment, in the form of physiotherapy and occupational therapy is commonly offered (NICE, 2009b). Physiotherapy and occupational therapy, particularly aerobic exercise, have been shown to be particularly useful for people with RA without increased 'wear-and-tear' related joint degeneration (de Jong et al., 2004; Hammond, Young, & Kidao, 2004; Neuberger et al., 2007). Exercise is useful because it builds muscle strength to support the joints. Furthermore, assistive devices, such as tap turners and wrist splints have also been shown to be useful (Hammond, 2004).

There is some evidence to show that diet is important. Clinical trials have found evidence for symptom improvement associated with vegan gluten-free (Hafström et al., 2001), vegetarian (Müller, Wilhelmi de Toledo, & Resch, 2001) and the so-called Mediterranean diet (Sköldstam, Hagfors, & Johansson, 2003). Furthermore, diets high in omega-3 have also found support for individuals with inflammatory joint pain (Goldberg & Katz, 2007).

Some people also require professional psychological intervention. Pain management programmes involving cognitive behavioural therapy have been shown to be effective in the short- (Dixon, Keefe, Scipio, Perri, & Abernethy, 2007; Sharpe, Sensky, Timberlake, Ryan, & Allard, 2003; Knittle, Maes, & Gucht, 2010; Pradhan et al., 2007; Zautra et al., 2007) and long-term (Sharpe, Allard, & Sensky, 2008). Although psychological intervention is deemed important by many rheumatologists (e.g. Sheehy, Murphy, & Barry, 2006), access to psychological services is often absent for many individuals. The National Audit Office report found that access to psychological services was not available to RA patients in more than half of acute NHS Trusts in the UK (National Audit Office, 2009). However, the Department of Health initiative *Improving Access to Psychological Therapy* will widen the availability of psychological services to individuals with chronic illnesses including RA.

A substantial number of individuals with RA try complimentary or alternative therapies, including acupuncture, copper bracelets, aromatherapy, massage, reflexology and homeopathy. Despite their wide use, evidence for the effectiveness of complimentary or alternative therapies in RA is limited and probably no more than a placebo effect (Macfarlane et al., 2011; NICE, 2009b). Although, there is limited evidence that acupuncture may be effective in other rheumatological conditions (Ernst & Lee, 2010).

There is increasing recognition of the importance of education in the management of RA, and in particular structured education programmes (Hammond, 2004). Furthermore, there has been a drive for individuals with RA to take a more active role in the management and monitoring of their RA in the form of 'expert patients' (Chilton & Collett, 2008; Hewlett et al., 2005; Department of Health, 2001). A Cochrane meta-analytic review found evidence for short term beifit of patient education programmes, however no long-term benefit was observed (Riemsma, Kirwan, Taal, & Rasker, 2003). Nevertheless, education is likely to be an important component in achieving appropriate self management allowing individuals to make the cognitive, behavioral and emotional responses necessary (Barlow, 2001).

2.1.6 Disease course & prognosis

2.1.6.1 Early RA

At the initial onset of the disease, when antigens are presented to susceptible individuals, the disease is asymptomatic. Usually the onset of symptoms is gradual and insidious, however, for some symptom onset may be quite rapid, developing over the course of a few weeks (Young, 2005). Initially, pain swelling and stiffness are likely to affect the hands and wrists, but individuals may feel fatigue and general malaise (Carr et al., 2003). These early symptoms are not the result of RA but of inflammatory

polyarthritis a more generalised disorder that in some individuals will go on to develop into RA, in others symptoms may resolve or lead to the development of another form of chronic arthritis (e.g. seronegative spondarthritis).

There is no clear clinical distinction between inflammatory polyarthritis and RA. The ACR criteria do not provide help as many of the criteria may be only present in individuals with established disease that has been present for a number of years (e.g. erosions & nodules; Harrison et al., 1998).

The long-term course of RA is highly varied. Scott and Huskisson (1992) distinguish three different trajectories. The most common, observed in around two-thirds of individuals, is a progressive disease with periodic flares and remissions. Around a quarter experience a more intermittent disease course with longer periods of intermission and possibly remission. A third group consisting of around 5% experience an extremely severe form, where joint damage and destruction occurs quickly.

Several inception cohorts have provided information about the natural (treated) history of RA (e.g. Early RA Study, Early RA Network, Norfolk Arthritis Register, Yorkshire Early Arthritis Register; for details see: Young, 2005, 2004). These inception cohorts typically have a baseline visit when the individual is first seen by the specialist, typically prior to the initiation of disease-modifying treatment. Accumulated evidence from these studies suggests that the course of RA is established early, and that the most important phase for therapy is the first 1 to 2-years. (Smolen et al., 2010; Young, 2004).

For a number of individuals remission is achieved. A review indicated that for individuals with generalised inflammatory arthritis remission was common, achieved by 30% to 40%, but was lower for individuals whom had been diagnosed with RA at around 10-30% (Katchamart et al., 2010). A recent study using the ERAS cohort has indicated that the sustained clinical remission over a period of 5-years was acheived by 11% (Jayakumar et al., 2011, see Appendix A).

Early treatment Early treatment is imperative in RA with several studies showing that earlier treatment has a greatly improved benefit to the patient over the short-and longer term (NICE, 2009b). However the time between symptom onset and treatment initiation is typically quite long. The recent NAO report investigated just this (National Audit Office, 2009). The report identified five stages in the typical diagnosis and treatment pathway: (i) symptom onset; (ii) presentation to G.P.; (iii) referral to specialist; (iv) treatment (disease-modifying) initiation; and (v) ongoing care.

Optimal timing between symptom onset and initiation of disease-modifying has been suggested to be less than three months (NICE, 2009b). However the NAO report found that typically the time taken between the initial onset of symptoms and presentation to the GP was more than 3-months for over

half of individuals, and was over 1-year of around one-fifth of individuals. The reason for the delay in presenting to a G.P. were likely to be a lack of awareness of RA meaning that people do not distinguish it from osteoarthritis, or assuming that the G.P. can do nothing to help them. After visiting a G.P. the time to treatment initiation is usually fairly rapid (National Audit Office, 2009).

Time taken between stages 3 and 4 is typically fairly short. In 2005, the NHS implemented a target of a maximum of 18-weeks between referral and treatment initiation. The NAO report found that this target increased from 46% to 97% in the two years of their investigation (National Audit Office, 2009).

2.1.6.2 Prognosis in patients with persistent disease

Not only is the long-term course of RA varied but so, unsurprisingly, are the long-term outcomes. Overall, observational studies have revealed pattern of increasing functional disability (Young et al., 2000; Wolfe, 2000; Scott et al., 2000). Generally a 'j-shaped' curve is observed, with an initial improvement following initiation of disease-modifying treatment, followed by a gradual and insidious decline in function after around two years (Sokka, Kautiainen, Hannonen, & Pincus, 2006; Kobelt, Jönsson, Lindgren, Young, & Eberhardt, 2002).

Functional disability can fluctuate considerably over time, and when related to disease activity is amenable to drug therapies. Early in the course of the disease function is mainly impacted by pain and stiffness. However, over time joint damage makes an increasing contribution, it is this factor that drives the progressive decline in function (Scott et al., 2000).

The cumulative degree of joint damage in RA is typically assessed using x-rays of the hands, wrists and feet. Radiological damage is one of the diagnostic criteria for RA and is present at diagnosis in a considerable number of individuals (Dixey, Solymossy, & Young, 2004). The classic features observed are erosions and joint space narrowing, but in individuals who have had the disease for many years more serious features may be observed, including subluxation, misalignment and ankylosis.

This increasing functional limitation can have negative consequences for peoples lives. For example, one third of people with the disease will have stopped working within two years of onset and around half will be unable to work through disability within ten years (De Croon et al., 2004; Young, Norton, & Koduri, 2009, see Appendix A). Furthermore, in patients who do not respond to treatment, surgery may be required to relieve pain and improve joint function where the joint has been severely deformed. James et al. (2004) found that within 5-years 11% of individuals not taking biologic therapy had undergone orthopaedic surgery to a large or small joint. Furthermore, around 15% of people also required appliances or aids such as home alterations, splints and wheelchairs.

2.1.6.3 Morbidity & mortality

An increased risk of mortality has been observed in RA. Several studies have demonstrated an increased mortality risk, particularly with respect to cardiovascular disease, interstitial lung disease and lymphoma (e.g. Young et al., 2007, see Appendix A, Koduri et al., 2010, see Appendix A, Sokka, Abelson, & Pincus, 2008). The causes of these are only beginning to be understood. It is true that the risk is at least partially associated with drug toxicity. As has already been noted the drugs used to manage RA are related to increased risk of gastrointestinal complications, renal damage and heart disease. However, RA is known to be a systemic disease with the inflammatory processes also having extra-articular effects, including impacting on the lungs and vascular system (Young & Koduri, 2007). In particular, the link with cardiovascular disease has received a great deal of interest over the last decade (Gabriel, 2008).

2.1.6.4 Economic impact

RA can, and often does, result in a wide range of complications for the individual. Not only does RA have a personal impact to the individual and their family, but also there is a significant economic cost resulting from the direct cost to the NHS and associated health care support services, but also indirectly to the economy through lost productivity. The National Audit Office report highlights the importance of early referral to the economy. It was estimated that increasing the number of individuals treated within 3-months from the current level of 40% to 80% would cost £3.6m but would save around £5m through reduced G.P. visits and unecesary diagnostic tests (National Audit Office, 2009).

2.1.7 Summary

Clearly, RA represents a huge cost to the UK economy as well as the individual patient. It is a chronic inflammatory disease of unknown cause, for which there is currently no cure. Resultantly, the aim of drug management is to reduce symptoms and modify the disease process its impact on individuals varies, as does its course over time. Greater understanding of the psychosocial factors associated with RA are important, since they may act as moderators and mediators in the pathway between disease and psychological and physical well-being in RA. Furthermore, they may ultimately impact on health outcomes such as the need for orthopaedic surgery, work disability and mortality.

2.2 Well-being in RA

It is evident from the sections concerning disease progression and outcomes in RA that there are a variety of ways in which the condition impacts on the well-being of the individual. Most obviously, the pain, stiffness and joint damage associated with the condition limit functional ability, which gradually and insidiously increases over the course of the disease (Young et al., 2000). This impacts on individuals abilities to complete normal daily activities, including dressing, bathing, walking and eating, and may interfere with psychological well-being and the ability of the individual to complete their social roles (Kosinski et al., 2002). It is useful to consider the topic of well-being in RA within the broad concept of health related quality of life.

Health related quality of life is an amorphous concept, largely based on a multi-dimensional perspective of health as physical, psychological and social functioning. Health has been traditionally defined as 'complete physical, mental and social well-being and not merely the absence of disease or infirmity' (World Health Organisation, 1946) and assessed by indices that focus on disease and illness, including mortality, health service use, subjective indicators of morbidity, disability and health behaviour (e.g. smoking, alcohol use etc.). However, since the 1960's there has been an increasing interest concerning quality of life (Bowling, 1997). This research has focused on defining what exactly quality of life is. Drawing from the philosophical literature concerning happiness (eudaimonia) there has been an increased focus of attention away from negative aspects of health and well-being to positive ones such as life satisfaction (Seligman & Csikszentmihalyi, 2000).

Quality of life is an extremely broad term that encompasses all aspects of an individual's circumstances, including housing, work, environment, leisure activities, social network, social support. Health related quality of life however is more narrowly focused and concern aspects of physical and psychological well-being, such as functional ability, bodily pain, psychological distress, life-satisfaction, vitality and social role functioning. Contemporary measures of health related quality of life focus on summing across these domains (e.g. SF36, Euroqol).

It is important to bear in mind that physical and psychological well-being fall under the umbrella of quality of life, however, in practice it is often more meaningful to consider these domains separately. The following sections provide an overview of physical and psychological well-being in the wider context of chronic physical illness as well as more specifically concerning RA.

2.2.1 Physical well-being

The pain and damage caused to the joints by the inflammation associated with RA and the resultant loss of function clearly impact on physical well-being and can lead to physical disability. The mechanisms can be considered within the conceptual framework proposed by Verbrugge and Jette (1994) and adapted to RA by Escalante and del Rincon (2002). This models posits that the main disease–disability pathway is a causal chain. This causal chain reflects the natural series of events that occur as consequences of RA that may ultimately lead to disability.

Commonly referred to as the disablement process, the pathway from disease to disability is described as being characterised by four distinct stages (Verbrugge & Jette, 1994). The first of which, *pathology*, relates to the diagnosed disease (i.e. RA) and the pathophysiological mechanisms by which the disease manifests itself as physical symptoms (e.g. inflammation and joint damage). The second stage, *impairment*, reflects the deranged physiology at the level of the organ or the organ system (e.g. pain, swelling, stiffness). The third stage is functional *limitation*, the lack of ability to perform basic normal daily activities as a direct consequence of the impairment (body level). The fourth and final stage is physical *disability*, which reflects the individuals difficulty, limitation, or inability to perform activities of the person within a social or physical environment (societal level).[1]

Escalante and del Rincon (2002) expand this model in order to describe the disablement process in RA. They consider a dual processes model, with separate pathways for pain and joint damage. That is, inflammation causes joint pain and swelling which leads to limitation in terms of mobility, strength and dexterity. Whereas, joint damage causes deformity also leading to limited mobility, strength and dexterity. Outside of the main disease–disability pathway they consider the impact of demographic and psychosocial factors on each of the four stages, as well as the impact of comorbid physical conditions on disability.

2.2.2 Psychological well-being

2.2.2.1 Definition

As with the study of quality of life there has been an increase in the focus of positive aspects of psychological well-being (Seligman & Csikszentmihalyi, 2000). Despite this increased interest in positive

[1]The WHO International Classification of Impairments, Disabilities and Handicaps (ICIDH; World Health Organisation, 1980) further differentiates the disability category into *activity restriction*, a restriction in the ability to perform instrumental activities as a result of the functional limitation, and *handicap*, the inability to complete their normal social role. Due to confusion surrounding the conceptual framework of the ICIDH (Barbotte, Guillemin, & Chau, 2001), the differentiation of disability into these categories is not considered further.

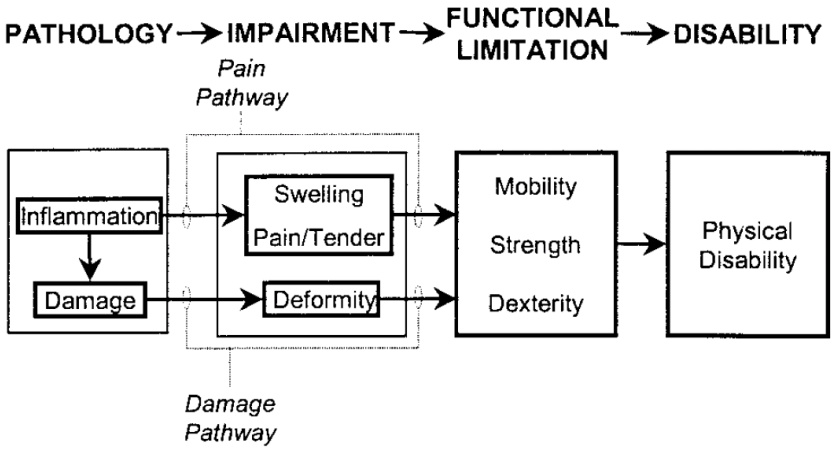

Figure 2.2: The disablement process (source: Escalante & del Rincon, 2002)

well-being, since the implications of RA have negative impacts on physical well-being, research has generally focused on negative aspects of psychological well-being. This is also generally true of research in other chronic physical conditions—although there are exceptions (e.g. Strand et al., 2006; Danoff-Burg & Revenson, 2005).

Negative aspects of psychological well-being, henceforth referred to as *psychological distress*, are typically assessed in terms of symptoms of anxiety and depression. Depression refers to a wide range of conditions characterised by persistently low mood (low *negative affect*) and a loss of interest or pleasure (low *positive affect*). Symptoms of depression typically include feeling sad, empty or tearful, having diminished interest or pleasure in life, weight loss or gain, sleep disturbance, feelings of restlessness or being slowed down, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate, and recurrent thoughts of death (American Psychiatric Association, 2000).

While anxiety disorder is also associated with low mood it is not particularly related to positive affect. There is a large overlap with symptoms of depression—including low mood, restlessness, fatigue and sleep disturbance—however, anxiety disorder is characterised by excessive anxiety or worry that the person finds difficult to control (American Psychiatric Association, 2000).

Two broadly similar diagnostic systems are used to diagnose depressive and anxiety disorders. The ICD-10 Classification of Mental and Behavioural Disorders (World Health Organization, 1992), commonly used in the UK, and the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV; American Psychiatric Association, 2000). Both systems recognise that depression and anxiety differ in severity across individuals, however they assume that depressive and anxiety disorders exist as real phenomena, and that therefore it is possible to objectively misdiagnose people as either depressed or non-depressed, and anxious or non-anxious. Borsboom (2008) points out

that the presence or absence of symptoms of anxiety or depression relate to the probability of membership of latent classes of individuals (i.e. groups that are unobserved) with depressive or anxiety disorder. He refers to this as the *diagnostic* perspective. Although these latent classes are not directly observable, they are nevertheless assumed real phenomena.

An alternative view is that depression and anxiety are *dimensional*, that is individuals fall somewhere along some latent continuum, relating to severity. From a psychometric perspective, these continua are real but the points along the continua used as diagnostic criteria that define disorders are arbitrary (Borsboom, 2008). Expanding on this position, researchers have proposed a multi-dimensional view of psychological distress, whereby anxiety and depressive disorders are lower-order factors in a hierarchical model with negative affect as the higher-order factor (Clark & Watson, 1991).[2] This 'tripartite' model was later extended to include positive affect and anxious arousal as further higher-order factors onto which depression and anxiety load, respectively (T. A. Brown, Chorpita, & Barlow, 1998; Krueger & Finger, 2001)

Krueger, Watson, and Barlow (2005), Watson (2005) and several years earlier Mineka, Watson, and Clark (1998) go further to suggest that all mood and anxiety disorders fall within a complex hierarchical model. Along with psychological distress, two other higher order factors relating to bipolar disorders and fear disorders (e.g. panic disorders, social phobia) are themselves subsumed within a further higher-order emotional disorders factor. It is this dimensional perspective of psychological distress that is applied in this dissertation. However, the majority of previous research has used the diagnostic perspective. It is this research that is reviewed now.

2.2.2.2 Psychological well-being in chronic physical illness

The prevalence and incidence of psychiatric disorder, and in particular depression, in RA and other chronic physical illnesses has received considerable attention. Population studies have revealed an increased prevalence of depression in individuals with a chronic physical illness (e.g. Egede, 2007; Kessler et al., 2003; Wilhelm, Mitchell, Slade, Brownhill, & Andrews, 2003; Fiest, Currie, Williams, & Wang, 2011; Moussavi et al., 2007). For example, Fiest et al. (2011) examined the prevalence of major depressive episodes, diagnosed using the World Mental Health-Composite Diagnostic Interview based on DSM-IV criteria, in a sample of 36,894 from the Canadian Community Health Survey. They found that, in those aged over 50-years, the prevalence of depression was 3.7% in those with at least one chronic physical illness, compared with 1.0% for those with no chronic physical illness. Other studies have also

[2]Hierarchical factor models are discussed further in Chapter 5.

reported marked differences in the rates of depressive disorder (Egede, 2007; Moussavi et al., 2007), presumably due to differences in methods of classifiying participants as depressed, as well as cultural and socio-economic differences betweeen the populations under study. Nevertheless, the pattern of findings is the same, rates of depressive disorder tend to be in the order of two to four times higher in individuals with chronic physical illness.

Rates of depression appear to increase with the seriousness of the consequences of the chronic physical condition. Population studies find that arthritis or rheumatism is associated with increased levels of depressive disorder that is similar to conditions such as diabetes, cardiovascular disease and multiple sclerosis (Kessler et al., 2003; Wilhelm et al., 2003; Fiest et al., 2011). A review of studies specifically concerning RA estimated the prevalence of psychological disorder in RA to be between 13 and 20% (Dickens & Creed, 2001). A later report by the same research team systematically reviewed 12 case-control studies comparing RA samples with healthy populations (Dickens et al., 2002). The study found a moderate increase in symptoms of depression, rather than diagnostic rates, in RA samples ($r = .21, p < .001$).

There is one major issue with regard to the diagnosis of depressive and anxiety disorder in chronic physical illness: there is considerable overlap in the symptomatology of most chronic physical illnesses with the somatic symptoms of depression and anxiety, including fatigue and sleep disturbance. Since it may be unclear whether these symptoms can be attributed to mood disorder or are actually sequelae of the physical illness. Indeed a recent meta-analysis of diagnostic studies indicated that commonly used tools to assess severity of symptoms of depression or more generally psychological distress[3] revealed that when applied to chronic physical illness populations suffered from reduced diagnostic accuracy (reduced sensitivity, specificity or both depending on the instrument; NICE, 2009a).

This suggests that at least some of the increased prevalence of depression in chronic physical illnesses is due to misdiagnosis as a result of individuals mis-attribution of symptoms of the physical condition. To counter this issue, a diagnostic interview method using only non-somatic criteria has been developed but is not widely used in research (Zimmerman, Chelminski, McGlinchey, & Young, 2006). Furthermore, the American Heart Association has recently released guidelines for depression screening in CHD patients (Lichtman et al., 2008)—though these guidelines have attracted criticism due to the apparent lack of research on which they are based (Holmes, 2011). Clearly caution needs to be taken when assessing levels of psychological distress in RA since levels may be artificially inflated as a function of disease

[3]Beck Depression Inventory, Patient Health Questionnaire (9 and 2-item versions), General Health Questionnaire, Centre of Epidemiology Studies-Depression, Geriatric Depression Scale, Hospital Anxiety and Depression Scale, Zung Self Rated Depression Scale

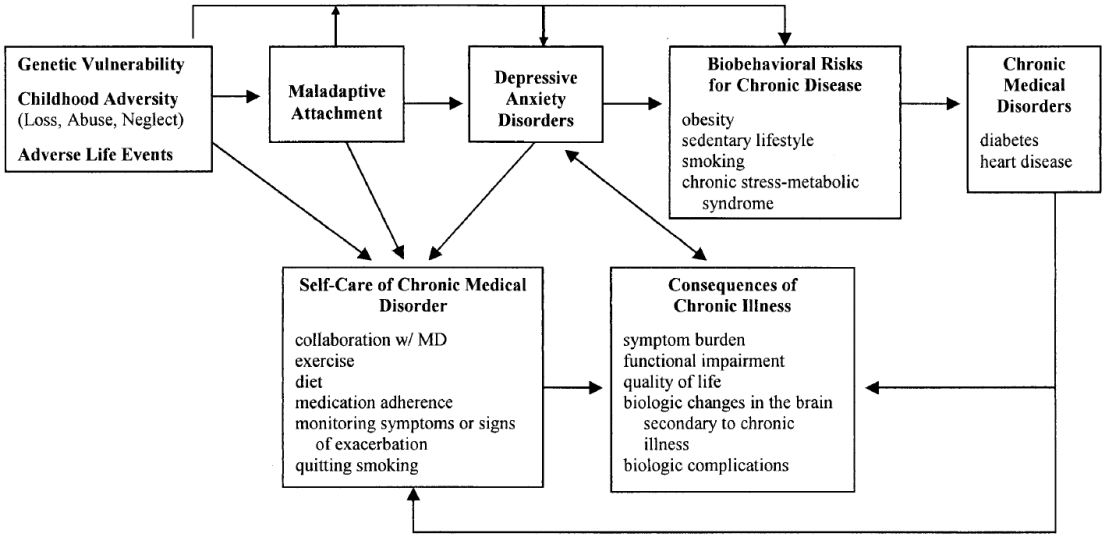

Figure 2.3: Conceptual model of the relationship between psychological distress and physical illness (source: Katon, 2003, p.218)

severity. Nevertheless, it is extremely unlikely that this issue accounts for the magnitude of the increased prevalence observed. The reasons for this increased prevalence are discussed in the following section.

2.2.2.3 The relationship between disease and psychological well-being

The relationship between chronic physical illness and distress is almost certainly reciprocal. That is, not only can the chronic physical illness increase levels of distress and cause the onset of, for example, a depressive episode but the reverse is also true. Higher levels of psychological distress and a history of depressive disorder may precede the onset of the physical condition. Katon (2003) presents a model that describes the ways in which distress and physical illness are related (Figure 2.3). This model suggests three main factors of genetic vulnerability, childhood adversity and adverse life events (including the onset of a chronic physical illness) as impacting on the risk for developing psychological disorder. These factors are also related to risk factors for developing chronic physical illness, such as obesity, sedentary lifestyle and smoking. In addition, symptoms of the chronic physical illnesses and related functional impairment as well as indirect pathophysiological effects on the brain, such as increased levels of cytokines and other inflammatory factors, may cause or exacerbate psychological disorder.

Disease → distress Prospective population based studies have shown that chronic physical illness is related to an increased risk of the later development of depressive disorder. For example, Patten (2001) observed that in a Canadian sample of 11,859 adults that were free of depressive disorder (assessed by

diagnostic interview) at the baseline assessment, the presence of one or more chronic physical illness was associated with an increased risk of depressive disorder two-years later (OR = 2.5, [95% CI: 1.3-4.6]). The associated risk increase was relatively stable across the chronic physical conditions considered, including arthritis and rheumatism.

Studies of clinical samples suggest a similar pattern. The incidence of depression increases after myocardial infarction, with most of the increased risk experienced in the first month (Strik, Lousberg, Cheriex, & Honig, 2004). Furthermore, a systematic review observed comorbid depression to be common in diabetic samples (Anderson, Freedland, Clouse, & Lustman, 2001).

Caution must be taken when interpreting these findings due to the likelihood of reverse causality. That is, although individuals at the earlier time point did not have clinical levels of depression it cannot be ruled out that they did not have sub-threshold levels of depression, or a history of depression that was related to the onset or exacerbation of the physical condition. Nevertheless, it does seem logical that physical disorder increases the risk later depressive disorder, despite some of the effect observed being due to reverse causality.

Distress → disease Population based studies highlight that depression is a risk factor for the development of future chronic physical illness, particularly cardiovascular disease. Systematic reviews of population studies report moderate to strong associations between depression and anxiety with incident coronary heart disease, in the order of a 60 to 100% increased risk (Hemingway & Marmot, 1999; Kuper, Marmot, & Hemingway, 2002; Rugulies, 2002; Nicholson, Kuper, & Hemingway, 2006). Almost identical findings are reported by systematic reviews of clinical samples (Barth, Schumacher, & Herrmann-Lingen, 2004; Nicholson et al., 2006; Van Melle et al., 2004). Furthermore, population based cohort studies have shown depression to be an independent risk factor for stoke (Jonas & Mussolino, 2000; Larson, Owens, Ford, & Eaton, 2001).

To my knowledge there is no published prospective data concerning earlier depression and the onset of RA. However, a recent study does provide some retrospective evidence. Looper, Mustafa, Zelkowitz, Purden, and Baron (2011) examined the association between a history of depressive disorder and illness severity in a sample of 104 inflammatory arthritis patients with symptoms of less than 1-year. Excluding patients experiencing a current depressive episode, they found that not only did the 28 patients with a history of depression have higher self-ratings of disease severity than those with no history of depression, in terms of functional limitation and disease activity, but physicians assessment of disease activity and the Disease Activity Score were also increased. Surprisingly, no difference in psychological distress levels

were observed between those with and without a history of depression.

2.2.2.4 The impact of distress on illness outcomes

Psychological well-being in chronic physical illness is not only essential in terms of health-related quality of life, but also with regard to disease progression and outcomes. Across a wide range of disorders increased levels of distress have been shown to be related to poor disease control, health outcomes and mortality (Prince et al., 2007; Katon, Lin, & Kroenke, 2007). A review of meta-analytic studies examining the association between psychological distress and mortality across clinical and community samples revealed that the evidence for an association was strongest for depression, compared to anxiety, and when considering mortality related to cardiovascular disease (Norton, 2008).

There are several plausible biobehavioural mechanisms by which depression may be linked with mortality. Considering first behavioural factors perhaps the most obvious mechanism is for an increased risk of suicide. While suicide rates are undoubtedly raised in individuals with depression, suicide can explain only a small part of the increased mortality since it is relatively uncommon (Cuijpers & Schoevers, 2004). For example, of the 31 studies of non-psychiatric samples identified by Wulsin, Vaillant, and Wells (1999) that reported suicide rates, suicides accounted for more than 1% of deaths in only 1 study. Other potential mediators are lifestyle factors, such as smoking, alcohol use, poor diet and obesity, less physical activity and hazardous behavior. All have been linked with depression and are associated with increased mortality (Cuijpers & Schoevers, 2004). Considering specifically individuals with chronic physical illness a meta-analysis has found depression to be related to non-adherence to prescribed therapies in a range of medical conditions (DiMatteo, Lepper, & Croghan, 2000).

Another possible explanation for the association between depression and excess mortality is biological, through dysregulation of the hypothalamic pituitary adrenal axis (Holsboer, 2000), the immune system (Kiecolt-Glaser & Glaser, 2002), and also the autonomic nervous system (Ridker, Buring, Shih, Matias, & Hennekens, 1998). Both of which have been linked to the development of various medical conditions, most notably cardiovascular disease, but also diabetes, osteoporosis, arthritis, and certain cancers (Kiecolt-Glaser & Glaser, 2002). Furthermore, considering coronary heart disease specifically, depression has been shown to be associated with decreased heart rate variability, which has been independently shown to be related to worse survival (Carney, Freedland, Miller, & Jaffe, 2002).

The evidence base in RA is not so developed, however, depression has been linked with adverse clinical and psycho-social outcomes including increased risk of mortality (Ang, Choi, Kroenke, & Wolfe, 2005), work disability (De Croon et al., 2004), and worse quality of life (Kosinski et al., 2002; Lempp et

al., 2011). Furthermore, the strong evidence for a link between depression and cardiovascular disease is especially pertinent in RA. As was previously noted, the incidence of cardiovascular disease in RA has been shown to be increased in comparison to the general population and accounts for a large proportion of the excess mortality attributed to RA (Gabriel, 2008).

2.2.3 Stress and coping

The relationship between psychological and physical well-being from a medical perspective was summarised by Katon (2003) (Figure 2.3). Expanding on the way in which a chronic physical illness impacts on psychological well-being it is useful to consider it as a stressful situation. A chronic physical illness can be defined as a stressful life-event that is characterised by recurrent stressful situations associated with the symptoms of the condition. Individuals with a chronic physical illness have to cope with the persistent stress caused by their condition, in an attempt to maintain health related quality of life (De Ridder, Schreurs, & Bensing, 1998; Moos & Schaeffer, 1984; Zautra, 1996).

2.2.3.1 The transactional model of stress and coping

A large body of research has considered the the role of coping and adjustment in chronic physical illness using the framework of the stress-coping model proposed by Lazarus and Folkman (1984). According to this framework, commonly referred to as the *transactional model*, stress is triggered by an external event (*stressor*) that the individual perceives to exceed their personal resources to effectively cope with the stressor. These coping resources include the psychological, social and physiological resources available. The central feature of the transactional model is that stress and coping are not single responses to isolated events but are a dynamic system involving continuous adjustments to the event. It is for this reason that this model is so applicable to the study of chronic physical illness.

The 'transactions' in the name of this model refer to changes in behaviour (coping response) that are directed by an individuals cognitive appraisal of the situation. This appraisal system consists of three components: (i) a *primary appraisal*, the initial assessment of the potential harm of the event; (ii) a *secondary appraisal*, an assessment of whether the coping resources available are sufficient to meet the demands of the event; and (iii) a *cognitive reappraisal* of the event as it develops over time.

Heijmans et al. (2004) compared the perceptions of potential disease-related stressors across a number of chronic conditions in a cross-sectional study of over 1300 patients. In comparison to other conditions, patients with RA were observed to experience high levels of pain, fatigue, functional disability, social disability, visible changes to their appearance and disease fluctuations. A cluster analysis was per-

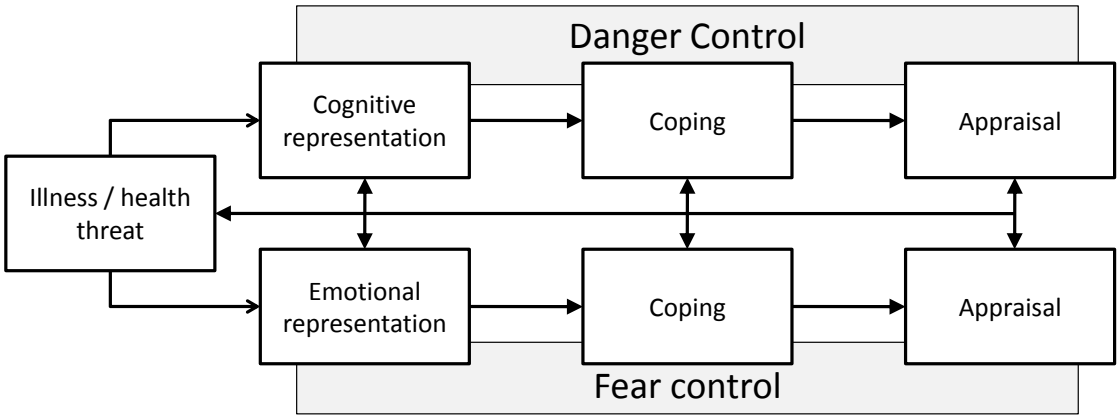

Figure 2.4: The self regulation model of illness cognitions

formed on the disease-related stressors. RA patients mainly fell into two clusters who reported moderate or high levels of disability and low to moderate levels of control over disease-related stressors.

A central feature in the transactional model is the individual's perception of control. This closely relates to the concepts in other models relating to health behaviour, including self-efficacy (Bandura, 1977), learned-helplessness (Abramson, Seligman, & Teasdale, 1978) and attribution theory (Weiner, 1986). These models along with other illness related cognitions and coping, can be described in terms of the Self Regulation Model (SRM) of illness cognitions which focuses on the individuals cognitive representation of the illness as informing coping responses (Leventhal, Meyer, & Nerenz, 1980; Leventhal, Nerenz, & Steele, 1984).

2.2.3.2 The self regulation model of illness cognitions

The SRM focuses on how individuals with a chronic physical illness use the information available to them to regulate their behaviour over time in order to achieve a goal, such as avoiding pain (Leventhal et al., 1984). The model posits an adaptive system wherein (i) the cognitive representation of the illness experience guides (ii) coping responses, which is followed by (iii) appraisal of the coping efforts. Illness representations are dynamic, and are updated with new information from external (e.g. social communication) and internal sources (e.g. personal appraisal of coping efforts). A novel feature of the SRM is that it distinguishes between cognitive and emotional processing. Cognitive, in terms of how people regulate their responses to *illness danger* ('What is this health threat, and what can I do about it?') and emotional in terms of their *emotional control* ('How do I feel about it, and what can I do to make myself feel better?'). The model is depicted in Figure 2.4.

The specific content of an illness representation is termed *illness perceptions*, which have been de-

scribed as 'an organized set of beliefs regarding how the illness affects our body, its likely impact on life activities and experiences, whether it can be cured and so on' (A. A. Kaptein & Weinman, 2004, p.85). Naturally, illness perceptions are markedly different across conditions but considerable variation between individuals with the same condition has also been observed (Moss-Morris et al., 2002). Perceptions inevitably vary in accuracy, detail and coherence. For example, one would expect that an individual with RA who has lived with the condition for many years would have perceptions of the condition that are rather more accurate, detailed and coherent than another who has only recently received a diagnosis of RA. Other than the amount of personal experience, personality and cultural factors have also been shown to be related to an individual's illness perceptions (Diefenbach & Leventhal, 1996). A considerable body of research has identified five key dimensions of illness perceptions—namely, identity, cause, time-line, consequences and control (Petrie, Weinman, Sharpe, & Buckley, 1996).

Important and related factors are emotional perceptions and illness-coherence. The former can be seen as a domain specific indicator of the distress associated with the illness whereas the latter relates to the extent to which the illness makes sense to the individual. Emotional perceptions are processed in parallel to the main cognitive illness perceptions. For example, illness perceptions may evoke a powerful emotional response that influences coping, and conversely the distress caused by the condition may impact on cognitive illness perceptions, such as the perception and interpretation of symptoms. These concepts will be introduced in the following chapter along with a discussion of the literature on the longitudinal association between psychological characteristics and psychological well-being in RA.

Chapter 3

Longitudinal studies of psychological well-being in rheumatoid arthritis

3.1 Introduction

The aim of this chapter is to systematically review the literature concerning depression in RA. Specifically, to examine (i) how psychological well-being changes over time and (ii) to determine the demographic, clinical and psychosocial characteristics that are longitudinally associated with changes in psychological well-being. Expanding on the first aim, the objective of the literature review is to identify how psychological well-being changes over the course of the disease, that is to examine the psychological response to the onset of the disease. Changes early in the course of the disease, soon after the onset of symptoms and diagnosis of the condition, will naturally be a central focus of this part of the review.

With regard to the second aim, the objective is to assess the ways in which demographic, clinical and psychosocial factors account for changes in psychological well-being. Particular emphasis will be given to studies assessing changes early in the course of the disease. That is, how factors close to the time of disease onset impact on adjustment to life with the disease. How changes in physical well-being relate to changes in psychological well-being will also be considered.

3.2 Methodology

3.2.1 Identification of relevant studies

Relevant studies examining psychological well-being longitudinally were identified from the Institute for Scientific Information's Web of Science and the U.S. National Institute of Health's National Library of

Medicine's PubMed databases. The key-words "arthritis" "rheumatoid arthritis" "inflammatory arthritis" "depress*" "psychol*" "longitudinal" "prospective" "change" were included in various combinations.[1] Details of the search terms and the number of papers identified are given in Table 3.1. The optimal combinations was observed to be "rheumatoid arthritis" AND "depress* OR psychol*" AND "prospective OR longitudinal OR change". Limits were also included, such as English language publications and journal articles, to ensure that further irrelevant papers and conference abstracts were excluded. The citations identified were merged and duplicate citations excluded, resulting in a total of 798 citations. A flow chart indicating the numbers of studies excluded based on screening of the title and abstract or after examination of the full text is given in Figure 3.1.

Titles and abstracts of all of the citations were screened. The majority ($n = 721, 78\%$) were excluded as they were not relevant (e.g. non-RA sample, did not assess psychological well-being; experimental design, qualitative, retrospective, review) or were cross-sectional in design (22%). The full texts of the remaining 77 articles were obtained and screened for inclusion. A further 25 were excluded either because a longitudinal analysis of changes in psychological well-being was not presented, they were prospective daily or weekly diary studies lasting less than 3-months, or they were based on previously published data with no additional data regarding longitudinal changes in psychological well-being was presented. An additional, two papers were identified by screening reference lists of included studies and review papers.

In total, 50 published papers describing 33 distinct cohorts were identified that assessed changes in psychological well-being (over a total follow-up period of at least 3-months) for individuals that were clearly diagnosed with RA (generally using the accepted ARA criteria; Arnett et al., 1988). Seven of the papers concerned data from the European Research in Incapacitating Diseases and Social Support network (EURIDISS). This includes patients recruited from rheumatology clinics in France, Holland, Norway, and Slovakia. Although the data collection procedure was similar in each of three countries several similar papers were published using the cohort using the samples of individual countries. It is assumed that this reflects researchers level of access to the data, rather than selective reporting.

Longitudinal studies that did not report changes in psychological well-being over the period of follow-up were excluded. Changes may have been reported descriptively as means at each time point, or change scores may have been calculated and used in further analysis, for example as the dependent variable in a regression model. Regression models where the outcome variable was psychological well-being at follow-up must have included the baseline psychological well-being score in the model (i.e. a

[1] In PubMed the key-words were included as exploded MESH headings.

residualised change score analysis). Where no baseline control was included it is not clear to what extent the results represent changes in psychological well-being and so were not included. Papers were also excluded if they only prospectively measured outcomes considered to be psychosocial factors, such as helplessness, without any psychological well-being outcome.

Table 3.1: Search terms and hits

Search	Term	PubMed	WoS
1	arthritis	191,611	>100,000
2	"rheumatoid arthritis"	85,861	83,739
3	"inflammatory arthritis"	1,811	22,344
4	depress*	302,479	>100,000
5	psychol*	868,650	>100,000
6	depress* OR psychol*	1,076,896	>100,000
7	longitudinal	118,467	>100,000
8	prospective	754,693	>100,000
9	change	558,940	>100,000
10	prospective OR longitudinal OR change	2,545,886	>100,000
11	#1 AND #6 AND #10	1,332	633
12	#2 AND #6 AND #10	642	446
13	#12 + limits	456[a]	406[b]

Note. [a] PubMed limits: Humans, English, Adults. [b] WoS limits: English, Excluding meeting abstracts and proceedings paper. * wild-card ending to allow for various forms or pluralisation's of words

3.2.2 Quality assessment

An assessment of the methodological quality of the studies included in the review was based on four domains: Sample, Design, Analysis, Reporting (Table 3.2). A maximum score of three was allowed for each domain, except for design since the robustness of the design is the most important factor in observational studies where the maximum score was four. It follows that the maximum quality score that could be achieved is 13. This quality rating system was devised by the author but is based on recommendations of the STROBE statement checklist for cohort studies (von Elm et al., 2007) and Egger, Smith, and Schneider (2001).

The quality of the sample was based on its representativeness as assessed by the male:female ratio, and the average age. The quality of the sample was also based on the average disease duration and the size of the sample used in the analysis.[2] An average disease duration of less than 2-years was given a higher quality rating since changes would more accurately reflect changes associated with adjustment to living with RA early in the course of the disease. Studies with such a sample are henceforth referred to

[2]Usually this was the sample size at the last follow-up since most studies employed a complete case analysis.

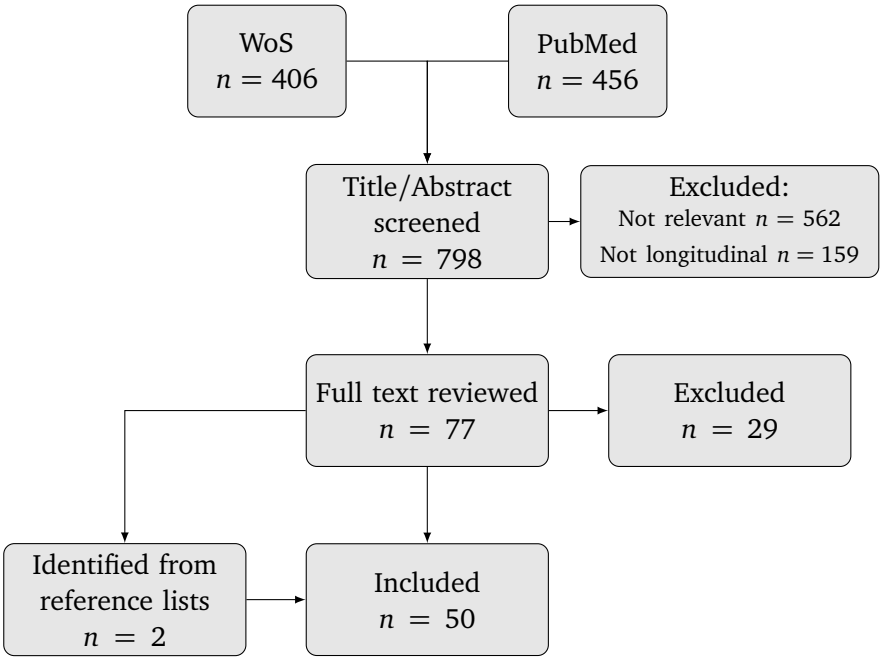

Figure 3.1: Flowchart of included studies

as 'early RA samples'.

The quality of the design was based on four factors. Firstly, the validity of the tool used to assess psychological well-being. Studies were given this score if a well-validated measure of psychological well-being measuring a distinct psychological dimension was employed (e.g. the Beck Depression Inventory [BDI] for depression, or the State-Trait Anxiety Inventory [STAI] for anxiety). Measures specifically designed for rheumatological populations were also included (e.g. the Arthritis impact measurement scale). Studies using single items (e.g. 'Have you had a problem with depression in the last 6-months?'; Wolfe & Michaud, 2009) or using tools that are not well validated (e.g. Quality of life status and change; Bendtsen & Hörnquist, 1996) were scored zero. Good quality designs were also indicated by follow-up on three or more occasions, a total period of follow-up greater than three-years, and dropout of less than 20% of the sample over the period of follow-up.

Regarding the statistical analysis, poor quality studies were those that had employed only descriptive analysis, bivariate correlations or t-tests (i.e. not adjusted for potential confounding variables). Analyses that employed regression or some related method of analysis that controlled for baseline psychological well-being and controlled for demographic, clinical and psychological variables were considered high quality. A further quality score was given if the study had used a statistical method that is appropriate to using data at multiple times (e.g. path analysis or multi-level growth curve model).

The quality of the reporting of the study was assessed with regard to the inclusion criteria being clearly defined, the demographic and clinical characteristics at baseline being reported, and differences

between the whole sample and those included in the analysis (e.g. those not dropping out of the sample in complete case analyses). It must also be noted that poor reporting may have resulted in lost points in other domains if the data were not available. An example is, if the number of participants retained at the end of the study was not reported (e.g. Eberhardt, Larsson, & Nived, 1993).

It must be noted that quality scoring is subjective and potentially unreliable. Since the quality scoring in this review was not validated elsewhere and was only based on the views of one individual, the quality scores only provide a rough indication of study quality. As a result of this limitation a conservative approach to interpreting quality scores is implemented. Rather than referring to studies as high versus low quality, studies falling above the quality criteria are simply assumed to have adequate methodological rigor for their findings to be included in this review. Studies that do not meet the basic quality criteria remain in the quality scoring table (Table 3.3) but are excluded from the textual discussion and the best evidence synthesis table (Table 3.4). The criterion were, studies scoring three or less overall ($\leq$ 23%), or scoring more than three but zero for any of the four domains. Based on these criteria two studies were exlcuded (Eberhardt et al., 1993; Parker et al., 1992). So 50 studies were initially included but 48 are discussed in the remainder of this chapter.

Table 3.2: Quality scoring criteria for the methodological and reporting characteristics of longitudinal studies of psychological well-being in RA

Study feature	Score
1. *Sample*	
Less than 70% male or female	0.5
Mean age less than 60-years	0.5
Mean disease duration less than 2-years	1
Final number of participants more than 300	1
2. *Design*	
Psychological well-being precisely measured	1
Number of follow-ups 3 or more	1
Total follow-up time more than 3 years	1
80% of participants retained	1
3. *Analysis*	
Adjustment for clinical and demographic covariates	0.5
Adjustment for psychosocial covariates	0.5
Control for baseline score	1
Appropriate statistical analysis*	1
4. *Reporting*	
Report drop out differences	1
Inclusion criteria clearly defined	1
Clinical and demographic characteristics reported	1

Note: * Use statistical methodology appropriate for longitudinal data collected at three or more time points

Table 3.3: Quality ratings for included studies

Citation	Country	N	Dropout	Follow-up (yrs)	Female	Age (yrs)	Dis. duration (yrs)	Quality
Barlow et al. (2002)	UK	82	27%	2	87%	59.0	11.4	35%
Bendtsen and Hörnquist (1996)	Sweden	222	53%	2	69%	63.1	17.8	46%
Bishop and Converse (1986)	Canada	39	na	8	67%	57.8	14.3	46%
Brekke et al. (2003)	Norway	659	54%	2	80%	53.3	11.0	62%
Brekke et al. (2001)	Norway	1024	20%	2	79%	61.4	12.8	54%
G. K. Brown (1990)	US	369	34%	7	75%	53.0	3.3	58%
G. K. Brown, Wallston, and Nicassio (1989)	US	387	40%	3	75%	50.9	3.3	65%
G. K. Brown, Nicassio, and Wallston (1989)	US	366	22%	2	75%	50.9	3.3	46%
Chaney et al. (2004)	US	58	28%	2	59%	53.0	9.0	62%
Crotty et al. (1994)	Australia	75	56%	12	100%	41.8	1.5	77%
Demange et al. (2004)	France, Holland, Norway	693	22%	3	69%	52.5	2.1	85%
DeVellis and Blalock (1992)	US	83	31%	2	70%	51.1	9.4	42%
Doeglas et al. (2004)	Holland	292	10%	4	65%	53.0	1.8	85%
Downe-Wamboldt and Melanson (1998)	Canada	78	18%	2	77%	74.6	>10	38%
Eberhardt et al. (1993) [*Excluded*]	Sweden	89	na	3	63%	53.0	11.5	23%
Evers et al. (1997)	Holland	95	4%	2	70%	57.0	0.3	58%
Hawley and Wolfe (1988)	US	400	23%	10	74%	54.8	9.5	54%
Hider et al. (2009)	UK	159	48%	4	72%	56.4	13.6	35%
Katz (1995)	US	554	42%	4	100%	56.5	16.6	50%
Lowe et al. (2008)	UK	148	14%	2	80%	56.2	4.5	42%
Margaretten et al. (2009)	US	172	na	5	89%	52.0	7.5	38%

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Table 3.3: . . . continued from previous page

Citation	Country	N	Dropout	Follow-up (yrs)	Female	Age (yrs)	Dis. duration (yrs)	Quality
McFarlane and Brooks (1988)	Australia	53	43%	2	72%	52.5	11.0	50%
Meenan et al. (1988)	US	410	27%	2	69%	52.0	14.0	50%
Morris et al. (2008)	US	1136	51%	8	80%	61.5	17.8	77%
Morris et al. (2011)	US	1115	53%	19	80%	55.4	>10	73%
Nagyova et al. (2005)	Slovakia	160	23%	4	84%	48.7	1.9	62%
Nicassio and Wallston (1992)	US	na	na	2	75%	52.0	3.3	19%
Ødegård et al. (2007)	Norway	238	37%	5	74%	52.0	2.3	69%
Palkonyai et al. (2007)	Austria, Hungary	118	na	7	72%	55.7	16.6	31%
Parker et al. (1992) [*Excluded*]	US	80	21%	3	0%	60.7	13.3	23%
Persson et al. (2005)	Sweden	165	4%	5	64%	51.4	0.8	62%
Raspe (1987)	Germany	100	25%	3	79%	49.0	0.7	35%
Rupp et al. (2006)	Holland	330	28%	2	71%	58.1	6.4	31%
Scharloo et al. (1999)	Holland	94	24%	2	56%	52.2	12.4	62%
Schiaffino and Revenson (1995)	US	na	na	2	75%	53.0	1.9	35%
Schiaffino et al. (1998)	US	na	na	2	90%	53.0	3.0	27%
Schiaffino et al. (1991)	US	101	36%	2	90%	52.8	<2	42%
Schieir et al. (2009)	Canada	320	44%	2	69%	57.1	0.6	58%
Sharpe et al. (2001)	UK	53	58%	6	70%	55.1	1.1	58%
Smedstad et al. (1997)	Norway	238	9%	3	73%	51.6	2.2	54%
C. A. Smith and Wallston (1992)	US	368	35%	5	76%	50.5	3.2	58%
T. W. Smith et al. (1994)	US	92	22%	2	60%	62.0	15.0	58%
Strating et al. (2006)	Holland	292	56%	5	71%	51.0	1.9	73%

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Table 3.3: . . . continued from previous page

Citation	Country	N	Dropout	Follow-up (yrs)	Female	Age (yrs)	Dis. duration (yrs)	Quality
Thyberg et al. (2009)	Sweden	320	8%	4	65%	58.0	<1	69%
Thyberg et al. (2005)	Sweden	320	7%	3	68%	56.0	<1	69%
Treharne et al. (2007)	UK	154	13%	3	75%	55.4	na	65%
Uhlig et al. (2000)	Norway	238	24%	4	74%	52.2	2.2	62%
Lankveld et al. (2000)	Holland	109	27%	2	59%	52.2	13.3	62%
West and Wållberg-Jonsson (2009)	Sweden	50	18%	4	67%	50.6	<1	69%
Wolfe and Michaud (2009)	US	22131	na	18	76%	61.6	12.2	38%

3.3 Changes in psychological well-being

Fourteen studies involving 10 different cohorts[3] examined psychological well-being trajectories in early RA samples (i.e. within 2-years of disease onset; Crotty et al. (1994); Persson et al. (2005); Schieir et al. (2009); Thyberg et al. (2009, 2005); West and Wållberg-Jonsson (2009); Sharpe et al. (2001); Doeglas et al. (2004); Evers et al. (1997); Nagyova et al. (2005); Raspe (1987); Schiaffino et al. (1991); Schiaffino and Revenson (1995); Strating et al. (2006)). Most of the studies reported on changes in psychological distress at the group level, rather than within-individual changes. Usually, this was by reporting mean scores on measures of psychological distress at each follow-up assessment. Only one study considered changes at the individual level. Crotty et al. (1994) calculated 44-month change scores as the slopes of separate regression models for each participant in their study of 75 Australian RA patients. No studies reported directly on changes in positive well-being.

Of the 14 studies of early RA samples, five reported observing significant improvements in psychological distress (Crotty et al., 1994; Persson et al., 2005; Schieir et al., 2009; Thyberg et al., 2005; West & Wållberg-Jonsson, 2009), whereas only one study has shown a significant worsening (Sharpe et al., 2001). However, a further eight studies reported that levels of distress were stable over time (Doeglas et al., 2004; Evers et al., 1997; Nagyova et al., 2005; Raspe, 1987; Schiaffino et al., 1991; Schiaffino & Revenson, 1995; Strating et al., 2006; Thyberg et al., 2009). More specifically, the latter eight studies did not find levels of psychological distress to be stable over time but rather it did not change significantly based on the particular statistical test employed.

As vote-counting procedures are notoriously unreliable (Egger, Davey Smith, & Altman, 2001) a more robust meta-analytic procedure was employed. Raw scores reported by each study were standardised and transformed to represent the average change at the group level from the baseline assessment. The pooled change from the baseline assessment was then calculated using variance weighted least squares (VWLS), whereby the conditional variance used in the estimation was the inverse of the standard error of the mean for each observation. Unlike ordinary least squares estimation this method does not assume homogeneity of the variance across studies. The conditional variance is specified resulting in more accurate estimates of the standard errors of the model parameters. A quadratic term for time allowing for non-linear change was included in the model.

It is worth highlighting that the procedure employed may itself be unreliable[4] and I know of no

[3] Three studies used data from the EURIDISS cohort, two from Schiaffino et al.'s New York cohort and two Thyberg et al.'s TIRA project

[4] Data are not adjusted for clustering within samples

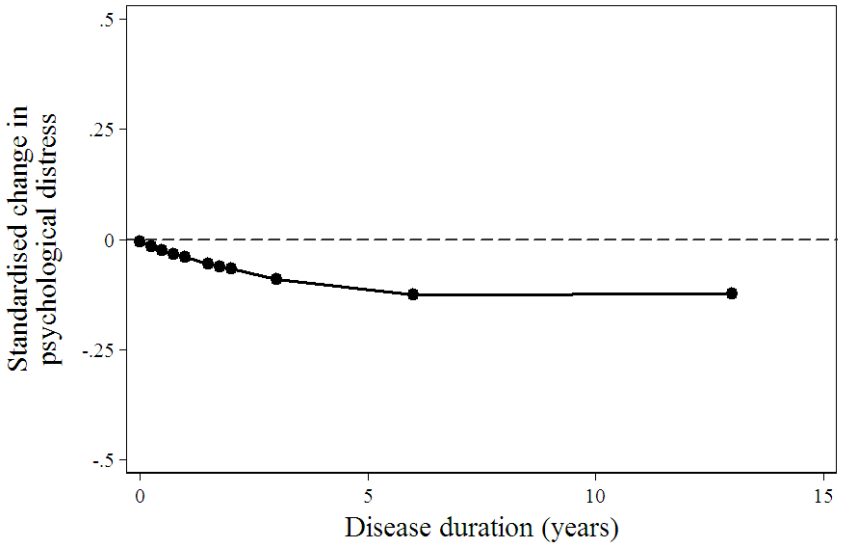


Figure 3.2: Pooled change (standard deviation units) in distress from entry into study of 14 studies reporting data where inclusion criteria is disease duration less than 2-years

other instance where this specific approach has been employed to pool changes over time from multiple studies. Therefore, the following observations should be treated with caution. However, it is almost certainly more reliable than a basic vote-counting procedure and so it may be argued provides some useful information.

Of the 14 studies, data from 11 were included in the analysis. Crotty et al. (1994) did not report mean scores for the sample at each assessment occasion. Schiaffino and Revenson (1995) and Thyberg et al. (2005) were excluded since they reported the same data as other studies involving the same cohorts. The data from three studies concerning the EURIDISS study were included as the data reported represented data from different sub-groups of the cohort (Strating et al., 2006; Doeglas et al., 2004; Nagyova et al., 2005).

The pooled trajectory, shown in Figure 3.2, indicates that overall there is a small decline in psychological distress that levels off over-time, equivalent to approximately 9% of a standard deviation over the first year. Confidence intervals are not shown, but encompass 0 (i.e. no change) at all intervals. This analysis would therefore provide limited support for a trend of (possibly non-linear) improvement in psychological distress at the group level over time early in the disease course.

3.3.1 Clusters of trajectories

Only one of the 14 studies concerning early RA samples specifically attempted to identify distinct patterns of psychological distress following the onset of RA. Persson et al. (2005) examined the heterogeneity in

changes in psychological distress over the 5-years following diagnosis of RA by first splitting their sample about the median baseline level of distress, and then further splitting them into groups based on whether distress had reduced over time, stayed the same, or increased. Using this rather arbitrary method, they found that the two groups below the median were relatively similar over time in terms of average distress scores (i.e. there was little change over time). In those above the median some did reduce over time, whereas others showed consistently high levels of distress. This final group, consisting of 12% of the sample, differed from the others in terms of perceived level of social support.

A further study is worth noting here, though it is not based on an early RA sample. Recently, Morris et al. (2011) used a more appropriate technique to identify distinct clusters of distress trajectories in a sample of 1115 participants with established disease in the UCSF RA Panel study (mean disease duration >10-years). K-means clustering was performed on aggregate data describing the over-time characteristics of the depression (Geriatric Depression Scale [GDS]) data—baseline scores, average scores, maximum and minimum scores, within-person standard deviations, and the proportion of assessments for which participants had a score of 7 or higher (indicating caseness). Three clusters were selected by the authors, and were labelled 'little/no depression' (66%), 'intermittent' (25%), and 'chronic' (9%). The study was limited in two main ways. Firstly, the timing of entry into the study (the baseline score) was arbitrary with the average disease duration at this time being greater than 10-years. Resultantly, inferences about changes early in the course of the disease, or even over the course of the disease, are not possible. Secondly, the aggregate data used in the analysis described average scores and the variability in scores for each person, but no data concerning actual trends over-time were included. It is perhaps not suprising then that levels of depression for the clusters identified were stable over-time. Other methods that based on clustering of observed individual trajectories are available and present an opportunity for the assessment for distinct groups following similar trends over-time.

3.4 Predictors of change in psychological well-being

This section covers the evidence from longitudinal studies for the association between various factors and future psychological well-being. It is split into three parts distinguishing between demographic, clinical and psychosocial factors. Although cross-sectional associations are not the focus of this review a brief discussion of the cross-sectional associations observed for each is provided for context and to highlight the differences between cross-sectional and longitudinal relationships. Table C.1 (in the appendix) provides a brief summary of the findings of each study with respect to predictors of the changes in psy-

chological well-being. Details concerning the proportion of studies observing significant associations for specific demographic, clinical and psychosocial factors are provided in the best evidence synthesis table (Table 3.4). Only studies meeting the specified quality criteria were included. The best evidence table summarizes the level of support for an association between the factor and psychological well-being as strong, moderate or weak—relating to >66%, >33% but <66%, and <33% of studies reporting significant association, respectively. Furthermore, for factors where few studies are published extra caution in interpreting the strength of the association must be taken due to the lack of evidence base. These are indicated by the term "lack" in the table when less than 5 studies consider the construct of interest.

Since the methods used in the studies are heterogeneous and typically only a small number of studies consider each of the different factors it is not appropriate to pool estimates using meta-analytic techniques. Instead a simple vote-counting procedure is used to assess the weight of evidence. Since statistical significance depends on sample size as well as effect size the following findings should be treated cautiously. To provide a more detailed narrative the findings of studies using this vote-counting procedure are complemented with discussion of the effect size and the quality of the studies.

Table 3.4: Best evidence synthesis table

Domain	Factor	Cross-sectional	Longitudinal
Demographic	Age	3/14 (21%) weak	4/16 (25%) weak
	Gender	2/8 (25%) weak	3/10 (30%) weak
	Ethnicity	0/1 (0%) weak [*lack*]	1/3 (33%) weak [*lack*]
	SES	5/14 (36%) moderate	6/11 (55%) moderate
Clinical	Disease duration	1/9 (11%) weak	2/12 (17%) weak
	Disease activity	7/15 (47%) moderate	8/16 (50%) moderate
	Joint damage	1/2 (50%) moderate [*lack*]	0/2 (0%) weak [*lack*]
	Somatic symptoms	16/19 (84%) strong	14/24 (58%) moderate
Psychosocial	Social support	6/6 (100%) strong	3/7 (43%) moderate
	Coping		
	Problem-focused	0/2 (0%) weak [*lack*]	1/2 (50%) moderate [*lack*]
	Emotion-focused	3/3 (100%) strong [*lack*]	0/3 (0%) weak [*lack*]
	Active	2/5 (40%) moderate	4/6 (66%) moderate
	Passive	1/2 (50%) moderate [*lack*]	3/3 (100%) strong [*lack*]
	Cognitions		
	Identity	1/1 (100%) strong [*lack*]	1/2 (50%) moderate [*lack*]
	Cause (+ internal attribution)	0/2 (0%) weak [*lack*]	2/3 (66%) moderate [*lack*]
	Chronicity (+ stable attribution)	1/2 (50%) moderate [*lack*]	2/3 (66%) moderate [*lack*]
	Cyclical	0/1 (0%) weak [*lack*]	1/1 (100%) strong [*lack*]
	Control (+ self-efficacy, helplessness, hopelessness)	5/7 (71%) strong	4/8 (50%) moderate
	Consequences	0/2 (0%) weak [*lack*]	3/3 (100%) strong [*lack*]
	Coherence	lack	lack

Note: Level of evidence considered strong if >66% of studies report significant association, moderate if >33% but <66% of studies report significant association, and weak if <33% of studies report significant association. Extra caution must be taken when considering studies with a "lack" of evidence base, considered to be <5 studies.

3.4.1 Demographic characteristics

Considering first the association between demographic characteristics and changes in psychological well-being in RA, it is important to note that in most studies demographic characteristics were not the focus but were included as control variables in studies examining the association between clinical and psychosocial factors and changes in psychological well-being. Nevertheless, it is important to consider how demographic characteristics relate to psychological well-being since controlling for the effects of demographic factors in future analysis is essential to ruling out confounding relationships.

3.4.1.1 Age

An important characteristic in relation to RA is age. Logically, the greater number of elderly people with RA is due to the cumulative incidence of RA with age—since RA cannot be cured. Age is widely known to be positively related to biological markers of disease activity (Wolfe, 1997) and is also related to an increased likelihood of co-morbid conditions (Hyrich et al., 2006; Young & Koduri, 2007). Resultantly one would perhaps expect distress to be positively related with age also. However, the evidence for such an effect was at best weak.

Three of the 14 studies reporting cross-sectional comparisons found significant correlations between age and psychological well-being (Hawley & Wolfe, 1988; Treharne et al., 2007; Uhlig et al., 2000). Furthermore, rather than observing a positive association between age and psychological well-being, significant negative associations were observed in two studies (Hawley & Wolfe, 1988; Treharne et al., 2007). That is, the impact of disease on psychological well-being being was greater for those of a younger age.

Hawley and Wolfe (1988) found that controlling for pain, functional disability, number of active joints and family income, increasing age was related to a reduction in symptoms of both anxiety ($\beta = -.22, p < .001$) and depression ($\beta = -.19, p < .001$). Similarly, Treharne et al. (2007) found age to be related to a reduction in the symptoms of depression ($\beta = -.23, p < .05$) but not anxiety ($\beta = -.13, p < .001$), but also found an increase in reported life satisfaction ($\beta = .30, p < .05$), after controlling for a wide range of demographic, clinical and psychological variables. Although, Uhlig et al. (2000) found that cross-sectionally mean age was higher in individuals with high versus low levels of psychological distress they did not control for other variables.

Moving on to consider the relationship between age and change in psychological well-being, the evidence for an effect is equally weak. Sixteen studies included in the review assessed the effect of age

on changes in well-being, of which only four reported a significant association (Schiaffino et al., 1998; Ødegård et al., 2007; Meenan et al., 1988; Hawley & Wolfe, 1988).

Hawley and Wolfe (1988) was the only study reporting a significant longitudinal association between age and psychological well-being to also report a significant cross-sectional association. They observed that the 69 (22.5%) individuals whom they classified as having a moderate to large worsening of depressive symptoms were on average 5-years older than those experiencing no change in symptoms. Similarly, Meenan et al. (1988) observed a small but significant effect relating to an increase in depression equivalent to around 20% of a standard deviation in the depression change score for each decade increase in age ($\beta = .02, p < .05$). However, Ødegård et al. (2007) found conflicting results for the effect of age on psychological distress. In relation to symptoms of depression the authors also reported that— controlling for gender and various clinical factors—age was related to increased levels of depression assessed by the Arthritis Impact Measurement Scale (AIMS; $\beta = .01, p < .001$) and also by the General Health Questionnaire (GHQ; $\beta = .04, p < .001$) but decreased levels of anxiety assessed by the GHQ ($\beta = -.05, p < .001$). Furthermore, Schiaffino et al. (1998) observed a moderate negative association between age and depression in a residualised change score analysis of 63 RA patients over a period of 4-months, controlling for education, income, disease severity and illness perceptions ($\beta = -.32, p < .05$).

In summary, the evidence for an association between age with psychological well-being is indicative of only a weak association if indeed one does exist. The majority of studies observed no significant association either cross-sectionally or longitudinally. It is worth noting that positive studies tended to consist of larger sample sizes than negative ones, perhaps suggesting an issue with power. Nevertheless, age is likely to have an important relationship with psychological well-being in RA since it is related to physical well-being (Young et al., 2000). Gender differences are also important, and it is to this topic that we now move.

3.4.1.2 Gender

There was only very limited support for an association between gender and psychological well-being in the longitudinal studies included in this review. Only one of eight studies reported observing a significant cross-sectional association (Evers et al., 1997) and three of 13 studies a significant longitudinal association (Hawley & Wolfe, 1988; Ødegård et al., 2007; West & Wållberg-Jonsson, 2009).

In a study of psychological well-being in 91 Dutch RA patients (70% female) recruited within 1-year of disease onset, Evers et al. (1997) found that women tended to report significantly higher levels

of anxiety at baseline. This was true even after controlling for age, education, clinical status, social support and coping styles. The trend was also for higher reported levels of depression in females, but the magnitude of the difference was non-significant. The same study also reported that gender was associated with higher anxiety (but again not depression) over a period of 12-months using a residualised change score analysis ($\beta = .11, p < .05$). Contrastingly however, Ødegård et al. (2007) reported that, controlling for gender and clinical status, females were significantly more likely to experience a reduction in symptoms of anxiety ($\beta = -.29, p = .01$)—again no significant effect on depressive symptoms was observed.

In a study of patients with established RA, Hawley and Wolfe (1988) found that in patients with worsening levels of anxiety there was a greater proportion of males than in those experiencing no change. This observation is inconsistent with the previous studies, although differences in the samples and methodologies used possibly account for the ambiguity in the findings. It is unlikely that this can be accounted for by regression to the mean due to lower initial levels of anxiety in men, since the study reported no difference in levels between the sexes at the baseline assessment.

The only study to report a significant association between gender and psychological well-being that did not directly relate to symptoms of anxiety was West and Wållberg-Jonsson (2009). They observed a significant improvement in SF36 mental component score (MCS) score in both sexes over a period of 72-months in 51 Swedish RA patients (34 female) with recent onset RA. However the magnitude of the change was significantly larger for men the women. Since this assessment relates to general psychological distress, which includes anxiety, it may be that the effect was accounted for by symptoms of anxiety.

Although several studies have reported a significant association between gender and psychological well-being in RA the vast majority do not. Furthermore, those that do, provide rather ambiguous findings. Together this suggests that gender is probably not not an important factor in psychological well-being in RA. This is surprising since population studies generally indicate that women have an increased lifetime risk of depressive disorder compared to men and also report higher levels of psychological distress (e.g. Hyde, Mezulis, & Abramson, 2008). It is not clear whether this difference in symptom reporting reflects actual levels or simply that women are more likely to report symptoms than men (Tousignant, Brosseau, & Tremblay, 1987). Furthermore, it is widely accepted that not only is RA more prevalent in women but that generally the severity of the disease is worse too (Kvien, Uhlig, Ødegård, & Heiberg, 2006). It appears that the association of gender with psychological well-being in RA is complicated, and may be confounded by disease severity.

3.4.1.3 Ethnicity

Few studies examined the relationship between ethnicity and psychological distress. This is most likely because of the over representation of people of 'white' (American/European) ethnic origin in rheumatological samples. Only one study examined cross-sectional differences in distress across ethnic groups finding no associations (Hawley & Wolfe, 1988). Furthermore, only one of the three studies that included an assessment of the longitudinal effects of ethnicity found an association with change in psychological distress. Margaretten et al. (2009) examined severity of depressive symptoms of 172 patients attending San Francisco General Hospital, finding that symptoms tended to be lower in Asians compared to other groups—namely White, Hispanic, and African American. Conversely Morris et al. (2011) found non-white ethnicity to be associated with increased likelihood of membership in the 'chronic' cluster in their longitudinal analysis of the UCSF RA Panel study.

From the literature available there is little available evidence linking ethnicity to depression in RA. However, this is an area that needs further examination, particularly due to the association of ethnicity to socio-economic status.

3.4.1.4 Socio-economic status

A far larger number of studies has considered the impact of socio-economic status on psychological distress in RA. Across these studies, socio-economic status (SES) was operationalised in a number of different ways. The largest group of studies ($n = 9$) considered education, with smaller number considering marital status ($n = 3$), income ($n = 2$), and social class ($n = 1$) as the indicator of SES. Overall, there was rather stronger evidence for an effect of socio-economic status on psychological well-being than other demographic characteristics, at least cross-sectionally. Seven out of 11 studies observed a cross-sectional association, although only 5 out of the 13 studies observing a significant longitudinal effect.

For education, 4 out of 9 studies observed a significant cross-sectional association with psychological distress (G. K. Brown, Wallston, & Nicassio, 1989; Doeglas et al., 2004; Schiaffino et al., 1991, 1998) and 4 out of 10 observed a longitudinal association (Schiaffino et al., 1998; Nicassio & Wallston, 1992; Hawley & Wolfe, 1988). For example, Schiaffino et al. (1998) observed a moderate negative association between education, dichotmised as either graduating from high school or not, and depression. The magnitude of the effect was similar for both concurrent depression ($\beta = -.26, p < .05$) and residualised change over a period of 4-months ($\beta = -.27, p < .05$). However, Doeglas et al. (2004) reported a

similar cross-sectional effect ($r = -.19$) in 263 patients from the Dutch arm of the EURIDISS study but found that longitudinally when controlling for initial depression the effect was reduced to non-significant ($b = -.09$, $p > .05$). Similarly, a moderate cross-sectional effect attenuated to a weak non-significant longitudinal effect was observed by Schiaffino and Revenson (1995). In contrast, Nicassio and Wallston (1992) reported the opposite, a non-significant cross-sectional association but significant negative one longitudinally.

Of the two studies examining the effect of income, both found a cross-sectional association between higher income and lower psychological distress (Hawley & Wolfe, 1988; Schiaffino et al., 1998), though only one observed an association between income and changes in psychological distress (Hawley & Wolfe, 1988).

Three studies considered the cross-sectional association between marital status and distress, finding no significant association (Hawley & Wolfe, 1988; Sharpe et al., 2001; Treharne et al., 2007). Both (Hawley & Wolfe, 1988; Treharne et al., 2007) also considered longitudinal associations. The former found that unmarried patients were more likely to experience a worsening of symptoms of depression but not anxiety. The latter study found no association with residualised changes in depression, anxiety or life satisfaction at 6-month or 12-month follow-ups. Morris et al. (2008) used a latent curve model[5] and found marital status to be related to future mood in a large sample of patients with established disease. Specifically, unmarried patients were at an increased risk of persistently increased levels of depressive symptoms ($b = -.81$, $p < .01$)

Only one study considered social class. In this study, Chaney et al. (2004) examined the longitudinal relationship between causal attributions and depressive symptoms in 42 American RA patients. At the baseline assessment the correlation between social class and depression was small and non-significant ($r < .19$, $p > .05$). As this association was non-significant it was excluded from the longitudinal analysis.

These studies highlight that the magnitude of the effect with regard to socio-economic status and psychological well-being is at most weak to moderate. This is perhaps not surprising since it is likely that there are several intermediate factors that mediate the impact of socio-economic status on psychological well-being. Nevertheless, they indicate that controlling for socio-economic factors in analyses examining the relationship between clinical and psychological factors and well-being is essential, since the latter effect must be greater than those of socio-economic status and other demographic factors to rule out confounding relationships.

[5] See section 4.3 for details

3.4.2 Clinical characteristics

A large number of studies have considered the role of clinical characteristics on the impact of psychological well-being. For the purposes of this review it is useful to consider clinical characteristics split across several categorizations. Initially disease duration, which was shown earlier in this chapter to be related to levels of psychological distress at the group level, is considered. Followed by the consideration of characteristics relating to disease activity, such as serological markers of inflammation and joint counts. The longitudinal association between psychological distress with somatic symptoms, including pain, functional limitation and joint stiffness, is then discussed. Finally, the link between the progressive joint damage associated with RA and distress is considered.

3.4.2.1 Disease duration

Directly relating to the analysis in section 3.3, a large number of studies included disease duration as a control variable in their analysis (G. K. Brown, Nicassio, & Wallston, 1989; G. K. Brown, Wallston, & Nicassio, 1989; Chaney et al., 2004; Lowe et al., 2008; McFarlane & Brooks, 1988; Nicassio & Wallston, 1992; Rupp et al., 2006; Treharne et al., 2007; Uhlig et al., 2000; Hawley & Wolfe, 1988; Brekke et al., 2003; Meenan et al., 1988; Morris et al., 2008; Scharloo et al., 1999; Margaretten et al., 2009). Most considered samples with established disease and observed no association between disease duration and psychological well-being, with the exception of two studies (G. K. Brown, Nicassio, & Wallston, 1989; Treharne et al., 2007). G. K. Brown, Nicassio, and Wallston (1989) found a significant association between disease duration and distress [effect size not reported], although this was not reported in later studies using this cohort (G. K. Brown, 1990; G. K. Brown, Wallston, & Nicassio, 1989; Nicassio & Wallston, 1992). Additionally, Treharne et al. (2007) compared groups with early, intermediate and long-standing disease and found that individuals in the latter two groups had lower levels of anxiety ($\beta = -.19$, $p < .05$) but not depression ($\beta = -.09$, $p > .05$) or life satisfaction ($\beta = -.04$, $p > .05$).

It is important to note that none of these studies, with the exclusion of Treharne et al. (2007), considered whether changes in distress were non-linear over the course of the disease. The finding of most studies perhaps suggests that for patients with long disease duration levels of distress are relatively stable. Taken together with the earlier findings this perhaps suggests an average pattern of distress reducing in the few years following diagnosis and then remaining stable over time.

3.4.2.2 Inflammation

Several studies examined the association of serological markers of inflammation with psychological distress. There was no indication that a specific marker of inflammation was particularly predictive of psychological distress and overall the results were rather ambiguous.

Eryrthocyte sedimentation rate (ESR) was the most commonly assessed marker of inflammation, but there was only very weak evidence for an association between ESR and distress. Cross-sectionally, only one of the seven studies observed a significant association with concurrent levels of distress ($r = -.22$; West & Wållberg-Jonsson, 2009). The evidence for a longitudinal association was slightly better, three of the six studies observed a significant relationship (Ødegård et al., 2007; West & Wållberg-Jonsson, 2009; Treharne et al., 2007). Treharne et al. (2007) found that in a multivariable linear regression analysis, ESR was not associated with anxiety, depression or life satisfaction at baseline ($\beta = -.05$ to .11, $p > .05$), but was associated with future levels of anxiety ($\beta = -.28$, $p < .01$) and life satisfaction ($\beta = .18$, $p < .05$) but not depression ($\beta = -.11$, $p > .05$).

Similarly, West and Wållberg-Jonsson (2009) also observed a significant longitudinal association for ESR with distress, in terms of the SF36 MCS ($r = -.33$). In their study of 51 Swedish RA patients, they also found similar effect sizes for CRP with emotional role functioning ($r = -.28$) but not the MCS. However, neither of the two other studies considering c-reactive protein (CRP) reported a significant effect (Sharpe et al., 2001; Uhlig et al., 2000). For Uhlig et al. (2000) the trend was in the expected direction but the magnitude of the effect smaller and non-significant despite the larger sample size.

Three further studies considered rheumatoid factor. As with CRP, Uhlig et al. (2000) found no cross-sectional association, although the trend was in the expected direction. Evers et al. (1997); Ødegård et al. (2007) did, however, provide some support for a longitudinal association. (Evers et al., 1997) found evidence for an association with anxiety ($\beta = -.14$, $p < .05$) but not depression ($\beta = .08$, $p > .05$), and Ødegård et al. (2007) found the opposite, an association with depression ($\beta = .75$, $p = .001$ for RF+ vs. RF-) but not anxiety (β not reported).

Overall, there was only relatively weak support for a longitudinal association between inflammation and distress. It is not surprising that small effects are observed. Inflammation, as indicated by serological markers, is likely to be mediated through the joint swelling and tenderness caused by the inflammation. This is supported by the observation that studies not controlling for these variables tended to be more likely to observe significant effects (Ødegård et al., 2007; Evers et al., 1997; West & Wållberg-Jonsson, 2009).

3.4.2.3 Joint counts

Ten studies considered the association between simple counts of the number of tender or swollen joints and psychological well-being (Nagyova et al., 2005; Schieir et al., 2009; Sharpe et al., 2001; Evers et al., 1997; McFarlane & Brooks, 1988; Smedstad et al., 1997; Uhlig et al., 2000; Hawley & Wolfe, 1988; Persson et al., 2005; Morris et al., 2008). Of these four out of the eight examining cross-sectional associations reported a significant association (Hawley & Wolfe, 1988; Nagyova et al., 2005; Schieir et al., 2009; Sharpe et al., 2001), and two out of six that considered the longitudinal relationship found a significant effect (Morris et al., 2008; Persson et al., 2005).

An early study of the impact of disease activity on psychological well-being in a small sample of 30 patients followed up over 3-years, McFarlane and Brooks (1988) observed moderate correlations between psychological distress and a count of the number of swollen joints ($r = .28$). However, correlation between the swollen joint score and depression 3-years later was weak, after partialling out initial depression ($r = .12$). This finding was echoed by later studies with larger sample sizes over the following decade (Evers et al., 1997; Smedstad et al., 1997; Uhlig et al., 2000). More recent studies, however, have provided more positive support for an association. In a study of 124 patients from the Slovakian arm of the EURIDISS study, (Nagyova et al., 2005) found swollen joints to be related to concurrent levels of distress assessed by the GHQ at all four assessment points, however linear regression indicated no cross-lagged effect of joint count when controlling for earlier distress. This was echoed by another study involving 216 patients in the Norwegian arm of the EURIDISS study (Smedstad et al., 1997) and 180 Canadian RA patients (Schieir et al., 2009).

Morris et al. (2008) using a latent growth curve analysis reported an association between swollen joint count and distress in their sample of 561 patients from the UCSF RA Panel study. Although significant, the size of the effect was negligible ($b = .09$, $p < .01$). Furthermore, Persson et al. (2005), in their study of distinct distress trajectories, observed that, despite the overall correlation between swollen joint count and distress being small ($r = .14$), swollen joint count was increased in the group with high and increasing levels of distress. The differences in findings with respect to these studies is likely to be due to the larger sample sizes in more recent studies. It appears that swollen and tender joint counts are only moderately to weakly associated with distress, most likely because of the stronger relationship of both factors with pain. That is, pain mediates the impact of joint count on distress.

3.4.2.4 Disease activity

Inflammatory markers and joint counts form the basis of the Disease Activity Score. This is a composite variable formed by a linear combination of the count of the number of tender joints, the number of swollen joints and either ESR or CRP, and recently a patient report of the disease activity on a visual analogue scale (Prevoo et al., 1995). This widely used measure was included in the analysis of eight studies included in this review (West & Wållberg-Jonsson, 2009; Scharloo et al., 1999; Bishop & Converse, 1986; Rupp et al., 2006; Lankveld et al., 2000; Margaretten et al., 2009). As with the inflammatory markers and joint counts there was limited evidence for an association with distress both cross-sectionally and longitudinally. Two of four studies considering the cross-sectional relationship reported a significant effect (Thyberg et al., 2009; Schiaffino et al., 1998), and two of six studies considering a longitudinal association reported a longitudinal effect (West & Wållberg-Jonsson, 2009; Scharloo et al., 1999).

Inflammation and the swelling and tenderness of joint counts would not be expected to have a direct effect on psychological well-being. But instead would be expected to be mediated by somatic symptoms in a causal chain. It is to somatic symptoms that we now turn.

3.4.2.5 Joint damage

Over-time persistent inflammation of the joints ultimately leads to destruction of the joints, leading to functional disability. Relatively few studies considered the impact of joint damage on future psychological well-being, perhaps because of the considerable overlap with functional disability. Rupp et al. (2006) and Uhlig et al. (2000) examined the relationship between Sharpe score—an assessment of the extent of erosions and joint space narrowing of joints in the hands, wrists and feet—on both concurrent and future well-being.

In their study of 227 Dutch RA patients Rupp et al. (2006) observed a significant cross-sectional relationship between Sharpe score and SF36 mental component score ($\beta = .19, p < .05$) even after controlling for demographic and other clinical characteristics—including pain but not functional disability. Uhlig et al. (2000) however did not observe any association between Sharpe score and psychological well-being, with the trend small and in the opposite direction. Neither study observed an association between joint damage and change in psychological well-being.

Although joint damage is an important clinical outcome in RA. It seems that its association with psychological well-being is not strong. It is more appropriate to consider the relationship between functional disability, which is in part determined by joint damage, and psychological well-being. The

lack of an association corroborates the finding of only very limited support for an effect of disease duration. If the effect was strong an increase in distress with increasing disease duration would be expected.

3.4.3 Somatic symptoms

A large number of studies considered the association between somatic symptoms and psychological well-being. Most focused on pain and functional limitation, although a limited number considered stiffness, fatigue and sleep disturbance.

3.4.3.1 Pain

Pain was found to be strongly associated with psychological well-being both cross-sectionally and also to some extent longitudinally. A total of 18 studies considered the cross-sectional association with pain. Of these, 11 reported significant effects (G. K. Brown, Nicassio, & Wallston, 1989; G. K. Brown, Wallston, & Nicassio, 1989; G. K. Brown, 1990; Evers et al., 1997; Hawley & Wolfe, 1988; Lowe et al., 2008; Schiaffino et al., 1991; Schiaffino & Revenson, 1995; Sharpe et al., 2001; Smedstad et al., 1997; Thyberg et al., 2009). The evidence for a longitudinal relationship was weaker, eight out of 18 studies reported a significant effect (G. K. Brown, Wallston, & Nicassio, 1989; G. K. Brown, 1990; McFarlane & Brooks, 1988; Nicassio & Wallston, 1992; Sharpe et al., 2001; Lankveld et al., 2000; Lowe et al., 2008; Ødegård et al., 2007). Across these studies pain was most commonly assessed using a visual analogue scale anchored with phrases such as “no pain at all” and “worst pain ever”.

In a series of studies using the same large sample of patients Brown, Nicassio and Wallston (1989; 1989; 1990; 1992) found evidence for a weak effect of pain on future depression. Moderate effects were observed in the first study, but were attenuated in later analyses that controlled for the effects of concurrent pain and depression. Nevertheless, cross-lagged path analysis supported the impact of pain on depression but not the reverse. In the final study to use this cohort, Nicassio and Wallston (1992) provided evidence to support their hypothesis that one of the ways in which pain was related to increased future depression was through sleep disturbance. Controlling for age, education, disease duration and functional disability the interaction between pain and sleep disturbance explained an additional 2% of the variance ($F = 8.22, p < .001$).

Smedstad et al. (1997) reported similar effects. They studied 236 Norwegian RA patients on three occasions over 2-years. Controlling for joint count, ESR and HAQ disability, pain was not significantly related to future distress by either the AIMS anxiety or depression scores. It is possible that controlling

for disability was unwise, since the influence of pain on distress is, at least, partially mediated by the impact of pain on an individuals ability to complete normal physical tasks. Pain and disability were indeed highly correlated, and theoretically it is certain that we would expect disability to be strongly influenced by pain.

Only one study considered the association between pain and life-satisfaction. Across two time-points 6-months apart, Treharne et al. (2007) observed no association between pain and life-satisfaction, cross-sectionally or longitudinally after controlling for demographic and other clinical characteristics. However, it should be noted that no association was observed between pain with anxiety or depression either in this study. Since the analysis controlled for disability the point made in the preceding paragraph holds true here as well—the influence of pain on depression may be (fully) mediated by its impact on disability.

3.4.3.2 Functional limitation

Functional limitation is a major outcome in RA, and is typically the secondary outcome that is assessed after disease activity. By far the most widely used tool for assessing limitation in RA is the Health Assessment Questionnaire (HAQ) disability index (Fries, Spitz, Kraines, & Holman, 1980). This was true in this review, although recently the use of the SF36 physical function (PF) scale and physical physical component score (PCS) are becoming more prominent.

Similar to pain, functional limitation showed a strong cross-sectional association with psychological well-being. Ten of the 11 studies including such a comparison observed a significant effect (G. K. Brown, Wallston, & Nicassio, 1989; G. K. Brown, Nicassio, & Wallston, 1989; Chaney et al., 2004; Demange et al., 2004; Evers et al., 1997; Hawley & Wolfe, 1988; Nicassio & Wallston, 1992; Schiaffino et al., 1991; Sharpe et al., 2001; Smedstad et al., 1997; Thyberg et al., 2009; Treharne et al., 2007). This was true whether psychological well-being was assessed by measures of general distress, depression, anxiety or even life-satisfaction.

Bivariate correlations were in the order of $r = .44$ to .50. Even after controlling for demographic and other clinical factors the effect tended not to be dramatically reduced. For example, Treharne et al. (2007) observed that controlling for age, sex, employment status, marital status, disease duration, pain, fatigue and comorbidity the standardised regression coefficient for depression, anxiety and life-satisfaction were large ($\beta_D = .48, \beta_A = .30, \beta_{LS} = -.50$).

Longitudinally, however, reported effect sizes where considerably attenuated when controlling for initial distress. Only six of the 15 studies that examined for a longitudinal association observed a sig-

nificant effect (DeVellis & Blalock, 1992; Doeglas et al., 2004; Persson et al., 2005; Sharpe et al., 2001; Margaretten et al., 2009; Treharne et al., 2007). Notably, none of the 4 studies examining anxiety longitudinally observed a significant association with prior functional limitation (Treharne et al., 2007; Smedstad et al., 1997; Evers et al., 1997; Hawley & Wolfe, 1988). Therefore, it would appear that the there is something specific to depression rather than psychological distress in general. Although not specifically the focus of this review, it is noted that studies using cross-lagged models found no evidence for depression predicting future functional limitation, indicating that causally prior limitation impacted on the change in future psychological well-being, such that individuals with worse functional limitation were at risk of experiencing greater deterioration in depression over time. However, it may be more important to consider how longitudinal changes in depression are associated with concurrent changes in disease severity and functional limitation.

Only two studies examined the relationship between changes in functional limitation and psychological well-being. Both observed strong effects. In their classic study, Hawley and Wolfe (1988) found that for the 308 patients included in the analysis changes in distress over the 4.5-years of follow-up were moderately associated with changes in disability. This was true for both depression and anxiety—$r = .30$ and .26, respectively. Furthermore, Katz (1995) observed an increased odds of having experienced an worsening of functional disability in the preceding period (OR $= 3.96, p < .05$) in 319 patients from the UCSF RA Panel with high rates of depression . Further analysis, revealed that a change in disability impacted on distress when there was a concomitant loss of valued life activities.

The complex association between changes in functional limitation and changes in psychological distress will be returned to in further detail later in this chapter.

3.4.3.3 Stiffness

Only two studies considered the impact of stiffness on changes in psychological distress (McFarlane & Brooks, 1988; Morris et al., 2008). Both assessed stiffness by asking participants to state how long they experienced early morning stiffness. Early morning stiffness is a characteristic feature of RA. Although not specific to RA, stiffness for more than one-hour after waking does form part of the diagnostic criteria (Arnett et al., 1988).

In their study of 30 RA patients with established disease, McFarlane and Brooks (1988) observed no cross-sectional or longitudinal association between the duration of early morning stiffness and psychological distress. However, the better quality study of Morris et al. (2008) involving a sample of over 500 patients from the UCSF RA Panel followed for 8-years did observe a longitudinal association, controlling

for several clinical variables. However, morning stiffness is highly related to functional disability, this was not controlled for in the study, and it seems likely that the mode of effect is the same—that is by impacting on valued life activities.

3.4.3.4 Fatigue

Three studies considered the effects of fatigue. All three studies reported a significant positive cross-sectional association between levels of fatigue and levels of psychological distress (Treharne et al., 2007; Brekke et al., 2003; Thyberg et al., 2009). Correlations were in the order of $r = .4$. It is important to note that, as well as being a common symptom of RA, fatigue is also a symptom of depression so it is perhaps not surprising that strong and consistent associations were observed. Only Treharne et al. (2007) examined for a longitudinal relationship, finding no evidence for a role in fatigue predicting residualised change in distress over 6- or 12-months. Furthermore, the same study observed no association of fatigue with life satisfaction—cross-sectionally or longitudinally. This perhaps points to its overlap with the symptomatology of depression in RA.

3.4.4 Psychosocial factors

Stronger associations were observed between psychological well-being with clinical rather than demographic characteristics, particularly those that are assessed using self report measures (e.g. pain, fatigue and functional disability). However, much of the variance in residualised change is unaccounted for. I now turn to consider whether psychosocial factors play an important role in the relationship between disease and psychological well-being in RA.

3.4.4.1 Social support

Social support relates to the different aspects of how supported an individual feels by the members of their social network. In individuals with a chronic illness that is painful and disabling, such as RA, social support is likely to provide an important coping resource. This section reviews the findings of studies examining the influence of various different aspects of social support on changes in psychological well-being in RA.

Social support was a commonly examined psychosocial factor that was assessed in a total of 8 studies. However, social support consists of several related concepts and was assessed rather differently across these studies, including general social support, emotional support, satisfaction with social support, social network size, marital status, spousal support, and companionship. Cross-sectionally there

was strong evidence for a relationship between social support and psychological well-being. All of the studies included in this review observed a significant cross-sectional association for some form of social support (Emotional: G. K. Brown, Wallston, and Nicassio (1989); Demange et al. (2004); Doeglas et al. (2004); Treharne et al. (2007); Satisfaction/Perceived: Doeglas et al. (2004); Evers et al. (1997); Network: G. K. Brown, Wallston, and Nicassio (1989); Evers et al. (1997); Demange et al. (2004); Companionship/Spousal: Schiaffino and Revenson (1995); Demange et al. (2004)). The picture was rather different when considering longitudinal associations where only 3 out of 7 studies observed a significant longitudinal association with changes in psychological distress (Evers et al., 1997; G. K. Brown, Wallston, & Nicassio, 1989; Persson et al., 2005).

In a sample of 95 patients followed for 1-year, Evers et al. (1997) identified social network size ($\beta = -.18, p < .05$) but not perceived social support as predictive of residualised change in depression one year later. G. K. Brown, Wallston, and Nicassio (1989), however, reported that the level of emotional support but not social network size as being significantly related to change in depression, an effect that was observed to be consistent over two 6-month periods in 233 individuals ($\beta_{t_1} = -.28, \beta_{t_2} = -.24$). A more recent study of 158 RA patients identified individuals with low perceived social support as predictive of increased levels of distress 5-years later (Persson et al., 2005).

Social support is usually only considered as a positive coping resource. However, there is evidence that social support can have negative effects on well-being. Only one study examined such an effect. Schiaffino and Revenson (1995) examined whether problematic social support was related to worse future psychological distress in 64 RA patients, finding no evidence for a link either cross-sectionally or longitudinally.

The main thesis regarding the link between social support and psychological distress is that it acts as a buffer between a stressor (e.g. pain) and psychological well-being. Few studies actually examined such an effect, and interestingly there was relatively little evidence to support it. G. K. Brown, Wallston, and Nicassio (1989) found no evidence for a moderating effect of social support (either network size or emotional support) on the relationship between pain and depression measured 1-year later. Similarly, Schiaffino and Revenson (1995) found no moderating effect for positive or problematic social support on the association between threat appraisals and future psychological distress, although they did observe a weak but significant association moderating effect for positive social support with regards the link between challenge appraisals and psychological distress.

The studies reviewed in this section indicate social support is beneficial for psychological well-being in RA, at least cross-sectionally. Further research is needed to examine the causal role of social support

as a potential moderator of pain on social-role functioning and psychological well-being in RA.

3.4.5 Coping with RA

Symptoms of RA, particularly pain and fatigue, can result in functional disability and impact on an individual's ability to complete normal activities—activities that healthy individuals typically take for granted—causing stress to the individual (Heijmans et al., 2004). Studies of coping in RA have tended to focus on the ways in which individuals cope with their pain, since this is the central symptom of RA.

Although a relatively large number of studies have examined the role of coping on psychological well-being in RA the findings are mixed. Overall, the evidence that coping plays some role in the pathway between the symptoms of RA and psychological well-being is relatively strong cross-sectionally but somewhat weaker longitudinally.

For the sake of simplicity, studies included in this review that examine coping have been broadly categorised as applying two different approaches to the study of coping strategies. Namely, problem/emotion-focused coping and engagement/disengagement coping. Both of these can be considered within the Transactional Model of Stress and Coping (Lazarus & Folkman, 1984). It is important to note that there is a large amount of overlap between these approaches and both view coping strategies in terms of a dynamic process, rather than a disposition (A. A. Kaptein & Weinman, 2004). None of the studies included in the review applied a dispositional approach to coping.

3.4.5.1 Problem/emotion-focused coping

Problem-focused coping relates to attempts to alter the relationship between demands and resources. For example, an individual with RA trying to cope with joint pain may take analgesic medications and may seek social support. Emotion focused coping is used when it is perceived that the problem has no solution and there is little scope for control so the aim of the coping strategy is to protect psychological well-being (A. A. Kaptein & Weinman, 2004). An example is, thinking soothing or distracting thoughts.

Four studies examine coping strategies in RA that fit within this framework (Lankveld et al., 2000; Evers et al., 1997; Lowe et al., 2008; Scharloo et al., 1999). Together these studies provide evidence that emotion focused coping (strategies such as avoidance and denial) are cross-sectionally associated with better psychological well-being (Lankveld et al., 2000; Evers et al., 1997; Lowe et al., 2008). However, none of the studies observed an impact of of emotion focused coping on longitudinal changes in distress (Lankveld et al., 2000; Evers et al., 1997; Scharloo et al., 1999). The opposite was observed for problem focused coping. Cross-sectionally, coping strategies such as decreasing activity were not observed to

be related to psychological well-being (Lankveld et al., 2000; Evers et al., 1997) but there was some evidence for a longitudinal association. For example, Lankveld et al. (2000) examined the impact of coping on changes in psychological distress in a Dutch sample of 80 RA patients. They found that over a three-year period decreasing activity as a means of coping with pain was related to worse psychological distress although there was no cross-sectional association. The effect persisted after controlling for prior distress, and prior and current disease activity and symptoms ($\beta = .17$). However, emotion focused coping strategies of self-comforting and diverting attention were related to better psychological well-being cross-sectionally but not longitudinally.

3.4.5.2 Engagement/disengagement coping

The remaining studies fit broadly within a framework where coping strategies are either seen as engagement or disengagement coping (Lowe et al., 2008; G. K. Brown, Nicassio, & Wallston, 1989; Sharpe et al., 2001; Schiaffino et al., 1991; Treharne et al., 2007; Evers et al., 1997). Although similar to the above framework, engagement coping strategies may be emotion or problem-focused (e.g. confrontation, acceptance, seeking support), whereas disengagement coping strategies are invariably emotion-focused (e.g. avoidance and denial). Using this taxonomy there was evidence for disengagement coping impacting on future psychological distress. Specifically, Scharloo et al. (1999), Lowe et al. (2008) and G. K. Brown, Nicassio, and Wallston (1989) all found evidence for passive coping or avoidance relating to increased levels of distress over periods of between 2-months and 2-years.

3.4.5.3 Moderating effects

Central to the conception of coping is that it moderates the effect of the stressor (e.g. pain) on psychological well-being (Lazarus & Folkman, 1984). Evidence that coping moderates the impact on pain on change in psychological well-being is rather weak. Notably, many studies did not report any moderation effect. It is not clear whether they simply did not test for it, or whether they did but no effect was reported because it was non-significant (and therefore deemed unimportant). Only one study reported a significant moderating effect. G. K. Brown, Nicassio, and Wallston (1989) found disengagement coping rather than engagement coping moderated the effect of pain on depression over a period of 6-months.

3.4.5.4 Appraisals

The Transactional Model posits that coping involves a primary appraisal—that is an appraisal that the situation is threatening. Most studies in this review assume that the pain and limitation experienced by

an individual are in themselves stressful, failing to account for the individuals' appraisal of the situation. Schiaffino and Revenson (1995) did however investigate this effect. In a study of 64 RA patients, threat appraisal and challenge appraisal were not observed to have a direct effect on changes in distress and, furthermore, no moderating effect on the impact of pain was observed.

In summary, there is some evidence for the role of coping strategies, particularly those related to disengagement, being longitudinally related to changes in psychological well-being. However, few studies have considered the potential stress buffering or elevating effects of particular coping strategies.

A recent systematic review, published after this review was conducted, focused on the longitudinal association between coping and psychological distress in RA (Vriezekolk, Lankveld, Geenen, & Ende, 2011). The review included all of the studies discussed in the present review but also several others that did not control for baseline levels of psychological distress. Categorising all studies using a hierarchical variant of the engagement/disengagement taxonomy, they reported unadjusted bivariate associations between various coping strategies were moderate (engagement: $r = .007$ to .46; disengagement: $r = .29$ to .64), however evidence for a longitudinal association adjusting for baseline distress was weak, confirming the findings of this review. In addition, in line with this review they also found that the strongest evidence was for a moderate association between disengagement coping and changes in distress over time. The authors suggest that the 'flexible use of a variety of coping strategies across situations that may be beneficial for adjustment to a chronic disease, perhaps especially in RA with its fluctuating and often unpredictable disease course' (p.6 Vriezekolk et al., 2011). Coping flexibility is likely to be an important area for future research. Currently there is no research focusing on coping flexibility in RA, and to my knowledge, no studies have assessed whether coping flexibility is longitudinally related to distress in any population.

3.4.6 Illness cognitions

This section covers evidence for illness related cognitions that have been implicated in the adjustment to physical illness. A plethora of social and health psychological models have been developed to explain cognitive processes in illness. Rather than discussing each in turn a general model of illness cognitions, the Self-Regulatory Model of illness representations (SRM; Leventhal et al., 1984) is used as a framework within which evidence from studies applying other (related) theories is discussed. These related theories include studies of self-efficacy (Bandura, 1977), attribution theory (Weiner, 1986), learned helplessness (Abramson et al., 1978) and hopelessness depression (DeVellis & Blalock, 1992).

The SRM posits that individuals form a 'common-sense' representation of their illness that informs

coping procedures undertaken to tackle the illness threat (Leventhal et al., 1984). The specific content of illness representations are termed *illness perceptions*, which have been described as 'an organized set of beliefs regarding how the illness affects our body, it's likely impact on life activities and experiences, whether it can be cured and so on' (p.85 A. A. Kaptein & Weinman, 2004). Five key dimensions of illness perceptions have been identified—namely, identity, cause, time-line, consequences and control (Petrie et al., 1996)—which are introduced along with the discussion of the literature in the following sections.

3.4.6.1 Identity

Identity refers to the individual's mental schema for an illness. Their beliefs concerning the signs and symptoms—such as joint swelling and pain—that they attribute to an illness (Bishop & Converse, 1986). Two studies considered the role of illness identity. Unsurprisingly, both found identity to be related to self-reported somatic symptoms (Scharloo et al., 1999; Sharpe et al., 2001) as well as being related cross-sectionally with distress (Sharpe et al., 2001). Scharloo et al. (1999) observed a significant longitudinal association with depression ($\beta = .35, p < .001$). However, Sharpe et al. (2001) reported that identity was not selected in a stepwise regression model for depression assessed by the Hospital Anxiety and Depression Scale (HADS), although power was limited as a result of the small sample size in their analysis ($n = 22$).

3.4.6.2 Cause

Causal beliefs concern the factors believed to have resulted in the development of the illness and are typically multidimensional. Common causes ascribed to many conditions, including RA, are heredity, environment, stress, behaviour, fate or chance (Moss-Morris et al., 2002).

Three studies included in this review considered the role of causal perceptions on changes in distress. Perceptions concerning the causes of their RA held in the early stages of the disease were observed to impact on subsequent psychological well-being in one study (Scharloo et al., 1999). Specifically, individuals who perceived themselves to be responsible for their RA experienced significantly increased levels of distress 4-months later. However, two further studies observed no longitudinal association (Schiaffino et al., 1998; Sharpe et al., 2001).

The notion of causal perception in the SRM model has considerable overlap with Attribution Theory (Weiner, 1986), a topic that was the focus of two studies (DeVellis & Blalock, 1992; Chaney et al., 2004). Causal attribution theory posits that causal beliefs comprise of three dimensions: *locus of causality* (internal/external), *stability*, and *controllability* (Weiner, 1986). Interpreting the findings of (Schiaffino

et al., 1998) using this framework suggests that individuals with an internal locus of causality and high perceptions of the controllability of the condition [6] was related to increasing distress. This was partially confirmed by the two studies explicitly concerning causal attribution theory. Chaney et al. (2004) found individuals who tended to make internal attributions were more likely to experience increased depressive symptoms over a period of one-year ($r = .40, p < .05$), as well as a general disposition towards negative attributions ($r = .39, p < .05$).

Attributions relating to stability and controllability are discussed in the following sections.

3.4.6.3 Timeline

The expected duration of the illness is referred to as its *timeline*, relating to whether the condition is considered acute, cyclical or chronic (Leventhal et al., 1984). In practice perceptions of illness timeline are typically assessed in terms of the conditions perceived chronicity and cyclicality (Moss-Morris et al., 2002). It is assumed that individuals with beliefs that their condition is acute fall at the low-end of the chronicity continuum.

Only one study considered the relationship between individuals' perceptions of the chronicity of their RA and changes in psychological well-being (Scharloo et al., 1999), finding that increased perceptions of the chronicity of the condition were related to increased anxiety but not depression 1-year later ($\beta = .16, p < .001$). A separate study considered the role of perceptions of the cyclicality of RA, but did not consider chronicity (Schiaffino et al., 1998). This study observed no association between perceptions of the cyclicality of the condition and depression 4-months later.

Returning to the two studies concerning attribution theory, it is expected that individuals with a stable attribution style are likely to perceive their condition as more chronic. Only one study observed a significant effect. In their study of 57 RA patients over a period of 4-months, DeVellis and Blalock (1992) reported that individuals with a stable attribution style experienced greater increases in distress 4-months later ($\beta = .19, p < .05$).

3.4.6.4 Control

The role of control in the relationship between stress an illness has been extensively studies and forms a central component of a variety of psychological theories pertinent to this review. As well as the SRM, control forms part of Social Learning Theory (Bandura, 1977), Learned Helplessness (Seligman, 1972) and the Hopelessness Theory of Depression (Abramson, Metalsky, & Alloy, 1989) to name a few.

[6] assuming that perceptions of curability relate to controllability

The SRM splits control into two related dimensions—personal control and treatment control. These dimensions, deliberately, have some overlap with Social Learning Theory (Bandura, 1977). Bandura's concept of *self-efficacy* refers to an individual's perception of their ability to carry out a certain task, (personal) control is implicit within this. Furthermore, treatment control relates to Bandura's concept of *outcome-efficacy*, the belief that a certain behaviour (i.e. in this context taking medication) will lead to a certain outcome.

Three studies specifically, considered the longitudinal association of control with distress in the context of the SRM in RA patients. None of the studies however distinguished between personal and treatment control. Instead using a general measure of control included in the first version of the Illness Perception Questionnaire (Weinman, Petrie, Moss-Morris, & Horne, 1996). Of these studies only Schiaffino et al. (1998) observed a significant association between control, in terms of the curability of the condition, and distress, such that patients who saw RA as curable experienced increased levels of distress 4-months later. Both Sharpe et al. (2001); Scharloo et al. (1999) observed no longitudinal association after controlling for baseline levels of distress.

Four studies of three cohorts considered self-efficacy (Brekke et al., 2001, 2003; Lowe et al., 2008; Schiaffino et al., 1991). All observed significant bivariate correlations between self-efficacy and distress. In two studies of the same cohort of patients with established disease followed-up after 2- and 5-years self-efficacy for pain was found to be related to distress, such that individuals with greater perceptions of their ability to control their pain experienced lower distress (and pain) at both follow-ups ($b_{\text{2-years}} = .05, p < .05$; $b_{\text{5-years}} = .13, p = .04$). Lowe et al. (2008) also observed a significant association between self-efficacy and distress, but over a much shorter period of 2-months. They also reported an interaction between self-efficacy with acceptance, such that individuals with greater increases in acceptance and self-efficacy over the period of follow-up experienced the greatest improvement in distress. Schiaffino et al. (1991) however did not report the significance of any longitudinal association and perhaps it is appropriate to infer that none was observed.

Furthermore, Treharne et al. (2007) did not observe self-efficacy to be associated with future psychological distress or positive well-being. Further tests for moderation with either psychological distress or psychological well-being were also negative.

T. W. Smith et al. (1994) addressed helplessness, observing a non-significant relationship between helplessness and later depression, and no interaction between feelings of helplessness and cognitive distortion, which would have been expected. Although, DeVellis and Blalock (1992) did observe a significant longitudinal association between the related construct of hopelessness and changes in distress.

Although one must caution that the periods of follow up were very different, 4-years in the former and 4-months in the latter. [7]

3.4.6.5 Consequences

Consequences refers to beliefs concerning the effects of the illness on physical and psychological well-being, as well as wider social and economic consequences. Symptoms are commonly related to perceptions of consequences, a finding which has been observed for RA as well as a number of other chronic conditions (Moss-Morris et al., 2002).

Perceptions of the seriousness of the consequences of the condition predicted worse psychological distress one-year later (Schiaffino et al., 1998). Furthermore, an interaction was observed such that individuals who saw their disease as more serious experienced greater levels of distress at follow-up if they also had higher levels of functional disability. In a separate study of the same cohort, Schiaffino and Revenson (1995) reported that for individuals with greater perceptions of the consequences of the condition, having lower initial depression predicted higher depression at follow-up. In a separate study of 71 Dutch RA patients, Scharloo et al. (1999) observed perceptions concerning consequences as predictive of worse psychological distress one-year later ($\beta = .35, p < .001$). Perceptions of consequences also predicted increased levels of fatigue at follow-up. The finding with regard to the association between perceptions of consequences and psychological distress was further supported by a small study of just 22 RA patients recruited within 2-years of disease onset assessed 6 times over a 21-month period (Sharpe et al., 2001). Controlling for initial levels of distress, disability, pain and pain coping, higher perceptions of consequences were associated with higher levels of distress at later assessments.

Treharne et al. (2007) considered consequences in an analysis of baseline predictors of residualised change in psychological and physical well-being over a period of 6 and 12-months. Controlling for baseline well-being and sociodemographic characteristics, perceptions of consequences were not found to be associated with changes in psychological well-being (assessed by depression, anxiety or life satisfaction).

3.4.6.6 Coherence

Coherence is related to other illness perceptions, representing and individuals' perceived level of understanding of their conditions. Currently, no studies have considered the longitudinal association of illness coherence and psychological well-being.

[7] It may not be too much of a theoretical leap to suggest that helplessness relates to personal control, the perception that one can do something about one's situation, and hopelessness to treatment control, the perception that something can be done about the situation.

3.4.6.7 Summary

Together these findings provide evidence for the importance of illness perceptions in the dynamic relationship between disease and psychological well-being. Perceptions relating to causality, consequences and control[8] appear to be particularly important. Currently only the doctoral dissertation of Treharne (2004) considered the longitudinal association between illness perceptions and positive well-being. This study only considered consequences observing no impact on life satisfaction over 6-months.

3.5 Conclusions and justification for the current study

This chapter has systematically reviewed the evidence for the impact of demographic, clinical and psychosocial factors on changes in distress over time in RA. Although a total of 50 studies were identified, those focusing on a particular factor or topic, particularly for psychosocial, were usually small in number and resultantly the weight with which conclusions can be made is limited (see Table 3.4).

Evidence for the influence of demographic factors was in general weak. It seems unlikely that demographic factors have a direct influence on well-being, their effects mediated by clinical and psychosocial factors.

Most studies including disease duration as a covariate observed little association with psychological well-being. However, a crude meta-analysis of the average levels of distress reported by studies including only individuals with early RA indicated a potential reduction in distress over time. This first appears somewhat in contrast with the expectation that distress would be related to somatic symptoms such as functional limitation, which increase with time due to the progressive nature of the disease. Furthermore, population based studies report a deterioration in psychological well-being and quality of life in elderly groups (Netuveli, Wiggins, Hildon, Montgomery, & Blane, 2006; Zaninotto, Falaschetti, & Sacker, 2009). There are two potential explanations for this finding. Firstly, it may be that the diagnosis of RA is in itself a stressful experience that causes distress early in the disease course, which gradually over time normalises. A further explanation lies with disease control. It is notable that in studies of early RA patients that report reductions in distress, reductions in somatic symptoms, particularly pain, are also observed (e.g. Schieir et al., 2009; Thyberg et al., 2005). This points to reductions in distress early in the course of the disease being related to increased control of symptoms through the initiation of pharmacological treatments.

Longitudinally, although the evidence base was limited, there was little evidence to suggest that

[8] Personal control measured as self-efficacy

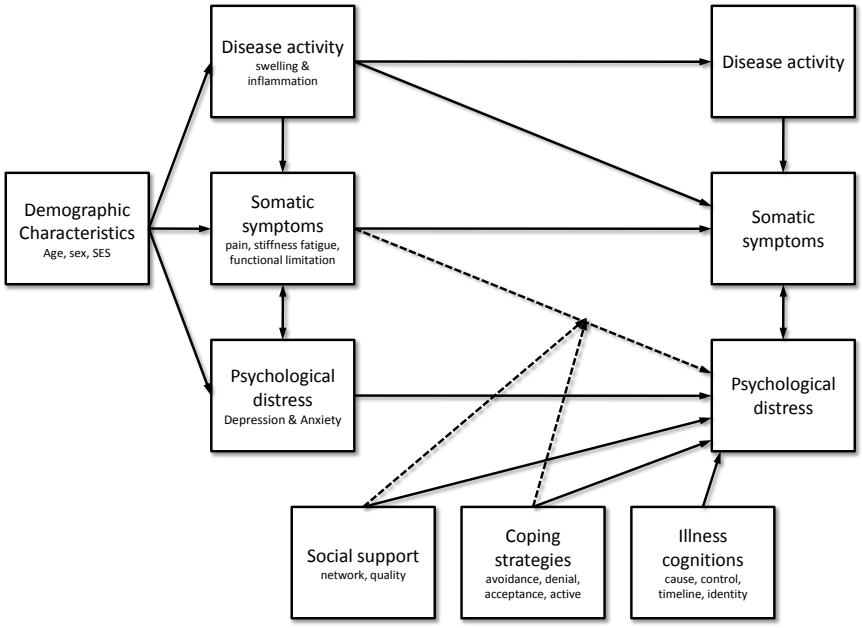


Figure 3.3: Simplified model of reviewed findings

changes in psychological well-being were related to levels of inflammation or joint damage. Although, since inflammation and joint damage undoubtedly influence symptoms of pain and functional limitation they are important distal antecedents to psychological well-being.

The overlap in the symptomatology of psychological disorder with somatic symptoms such as fatigue and pain perception is an issue. Furthermore, since somatic symptoms and distress are both typically assessed by self-report measures it is likely that the observed relationship is over-estimated due to the presence of common methods bias. Nevertheless, it is striking that as well as strong cross-sectional evidence for a link between somatic symptoms with distress, there is also moderate to strong evidence for somatic symptoms being related to increases in psychological distress even controlling for baseline levels of distress.

3.5.1 Theoretical model

The findings of the review are summarized graphically in 3.3. Solid lines indicate that evidence for a link between two factors is moderate or strong. Dashed lines represent association where an association is indicated by the literature but is supported by very few studies or where evidence is weak but still theoretically plausible. Lines between psychosocial factors with disease activity, symptoms and distress at the first time-point are not included for clarity, but are expected if measured concurrently.

Double headed arrows between concurrent symptoms and distress indicate that a bidirectional causal

association is expected. It is likely that psychosocial factors moderate these effects, again lines are not shown.

The dashed lines from social support and coping that intersect the path from somatic symptoms to future distress, indicates an expected moderating effect. Specifically, a buffering effect of social support on the effect of somatic symptoms on distress is expected. Furthermore, an escalation effect for disengagement coping on the same path is expected.

This model, which fits within the biopsychosocial framework (Engel, 1980), is adapted from the models of Katon (2003), Verbrugge and Jette (1994), Escalante and del Rincon (2002) and Leventhal et al. (1984).

3.5.2 Methodological quality

There were some major limitations concerning the methodologies applied by the studies included in this review. There were few studies with long follow-up, or with multiple assessment occasions, and, furthermore, when multiple assessment occasions were available typically statistical methods that could make use of the richness of such data were not applied. For example, the majority of studies used some form of residualised change analysis, examining changes between two time points. Only two studies employed techniques appropriate for the assessment of change over time. Morris et al. (2008) used latent trajectory models (described in Chapter 4) and Margaretten et al. (2009) employed a related population averaged technique referred to as *generalised estimating equation*.

3.5.3 Aims and objectives

To recap, the overarching aim of this dissertation is to examine how psychological well-being in RA changes over the course of the disease; and to identify demographic, clinical and psychosocial factors that influence how the disease impacts on psychological well-being. Outlined below are the detailed objectives of this study and some preliminary hypotheses with regard to the expected findings as each of the objectives is assessed. The first two objectives will be addressed by secondary analysis of data collected as part of an ongoing RA inception cohort, the Early RA Study (ERAS), that recruited all newly diagnosed patients attending nine rheumatology clinics at hospitals in England in the late 1980's and early 1990's. Due to the large size of the cohort and the detailed data with regard to psychological distress collected over a period of many years advanced quantitative methods will need to be used. The use of advanced quantitative methods for the analysis of longitudinal data will enable this study to

resolve some of the ambiguity created by the lack of methodologically appropriate techniques employed by many of the studies in this review. The three main objectives are now described.

Objective 1: To describe patterns of change in psychological well-being during the RA disease course Evidence from the systematic review suggests that early in the course of the disease there is potentially a reduction in psychological distress. Further evidence suggests that in patients with established disease levels of distress are relatively stable. Resultantly, it is hypothesised psychological distress will improve during the first years of the disease gradually stabilising with time. Furthermore, there is limited evidence from an early RA sample that there are distinct psychological distress trajectories following the onset of the condition (Persson et al., 2005). Combined with the reported level of heterogeneity in distress trajectories from other studies in this review (e.g. Hawley & Wolfe, 1988; Lowe et al., 2008; Morris et al., 2008) it is expected that heterogeneous distress trajectories will be observed, and that they will be more parsimoniously described by distinct trajectory characteristics, rather than a single overall pattern of change.

Objective 2: To quantify the association between psychological well-being and somatic symptoms The evidence for a cross-sectional association between psychological well-being and somatic symptoms of RA is strong. However, as evidenced by the systematic review, whether a longitudinal association exists is somewhat weaker, despite the strong theoretical position outlined in the previous chapter (see section 2.2.2.3). The second objective of the dissertation is to examine using appropriate statistical methods the strength of the longitudinal association between distress and somatic symptoms, such as pain and functional limitation. This will take into account the synchronicity of changes in both domains to provide greater insight into the causal mechanisms.

Objective 3: To investigate the impact of illness cognitions and coping on psychological well-being The systematic review provided evidence for a role of illness perceptions—particularly identity, cause and consequences—and coping strategies on the pathway between disease and psychological well-being. However, the examination of the role of illness perceptions and coping, and the causal mechanisms between the two, have not been thoroughly considered in RA samples, particularly in individuals soon after disease onset. The framework outlined by the Self Regulation Model of illness cognitions (Leventhal et al., 1984) will be used to guide the study of this objective and will consider whether illness perceptions and coping impact on psychological well-being. Since illness perceptions and coping were not assessed in the ERAS study, a separate prospective observational study was undertaken to address this objective.

Each of these three objectives is addressed in an empirical chapter—Chapters 6, 7, and 8. A further empirical chapter (Chapter 5) considers the construct validity of the measure of psychological well-being used in the ERAS study, the Hospital Anxiety and Depression scale (HADS; Zigmond & Snaith, 1983). This tool, although widely used, has generated much discussion in the literature with respect to the number of dimensions of distress that it taps into. Given the likelihood of bias due to the overlap in symptoms of RA and psychological disorder (Pincus, Griffith, Pearce, & Isenberg, 1996), the suitability of the HADS will need to be considered in detail since the accurate assessment of distress in RA is necessary for the interpretation of the findings from the longitudinal analyses presented. Due to the high level of statistical analysis used in the empirical chapters the following chapter provides a detailed description of the methods used.

Chapter 4

Latent variable modelling

4.1 Introduction

Due to the richness of the longitudinal data collected as part of the ERAS cohort it is necessary to use appropriately advanced analytical techniques. This chapter provides an overview of the methodological framework used in this thesis. This framework, which here is referred to as latent variable modelling (LVM), is essentially a generalisation of the general linear model to incorporate unobserved (i.e. latent) as well as observed variables. Also referred to as structural equation modelling (SEM), the term latent variable modelling is preferred as the models considered in this chapter include extensions of traditional SEM to incorporate multi-level data structures and mixture distributions. Numerous texts discuss these approaches in detail (e.g. Bollen, 1989; Raudenbush & Bryk, 2002; Skrondal & Rabe-Hesketh, 2004; Mulaik, 2009).

This chapter focuses on introducing the the concepts of latent variable modelling pertinent to the analyses conducted in the empirical chapters. It is split into three main sections. The first introduces latent variable modelling, describing its main principles, the assessment of model fit and estimation issues with categorical data (Section 4.2). The second section provides an overview of the application of latent variable modelling to longitudinal data (Section 4.3). The relationship to the multi-level model for change is discussed and the further generalisation of the latent variable model to include mixture distributions to explain heterogeneity in change is also discussed. The final section provides an overview of a common problem with longitudinal studies, the presence of missing data. The main issues concerning missing data are discussed, including the assumptions concerning the missing data mechanism made by conventional analytic methods and the ability of latent variable modelling to relax some of these assumptions and therefore provide more robust results.

4.2 Latent variable modelling

4.2.1 Overview

The latent variable modelling framework is rooted in the tradition of path analysis (Wright, 1934). As noted by Bollen (1989), the core features of latent variable modelling that can be traced back to its path analytic origins are: (i) the use of path diagrams to graphically represent (causal) relations between variables; (ii) equations relating covariances or correlation to the parameters represented in the path diagram; (iii) the decomposition of effects in influences that are considered 'direct' or 'indirect'. A latent variable model typically, although not necessarily, consists of two components: a *structural model* and a *measurement model*. These are described in the following sections.

4.2.1.1 Structural model

The path analytic component of a latent variable model is referred to as the *structural model*. This structural model describes the hypothesized relationships between theoretical constructs. Figure 4.1 presents a path diagram that may represent the hypothesized relationship between pain, joint stiffness and functional impairment in RA (the disablement process as described by Escalante & del Rincon, 2002). The square boxes indicate that the variables are observed from the data. It is important to note that this model is simply a pictorial representation of a regression equation. As such the model presented in Figure 4.1 can be written as

$$y = \gamma_0 + \gamma_1 x_1 + \gamma_2 x_2 + \zeta \tag{4.1}$$

where y is the dependent, or endogenous, variable relating to functional limitation and x_1 and x_2 are the predictor, or exogenous, variables relating to pain and joint damage, respectively. The γ terms represent the regression parameters for the model.[1] For example, γ_1 is the expected change in y for a one unit change in x_1 holding the value of x_2 constant. The error term ζ represents the residuals for the model. The key feature of path analysis is that it extends to the multivariate situation (i.e. where there are multiple regression equations, a simultaneous system of equations). These models are usually expressed using matrix notation, which is not discussed here.

[1] Traditionally, latent variable models were estimated with respect to the covariance matrix of the observed variables only. The means of the observed variables were not used. Resultantly, although it is now common to include the mean structure in the latent variable model, typically the constant term γ_0 is suppressed from the path diagram, as it is in Figure 4.1. Where included it would be represented as a regression on a constant, defined by a triangle.

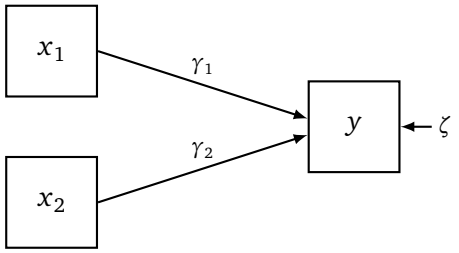


Figure 4.1: Path model

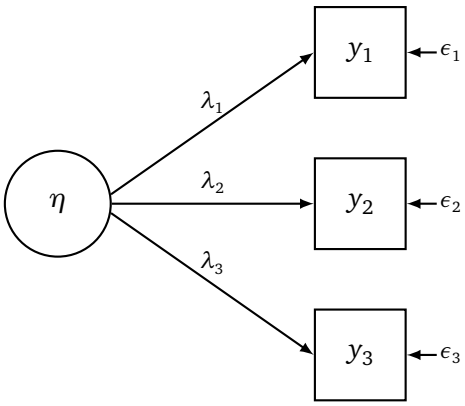


Figure 4.2: Confirmatory factor analysis

4.2.1.2 Measurement model

Latent variable modelling generalises the path analytic model to include latent variables. A latent variable represents a hypothetical concept that cannot be observed or measured directly but must be inferred from a set of observed indicator variables. For example, an individuals' level of functional impairment cannot be observed directly but may be inferred from their ability to complete various functional tasks. Within latent variable modelling a *measurement model* relates the latent variables to the indicator variables.

A latent variable model consisting of only a measurement model is typically referred to as a *confirmatory factor analytic* (CFA) model[2]. Models that include both structural and measurement models are commonly referred to as multiple-indicator multiple-cause (MIMC) models. Indicator variables are typically from self-report measures but may consist of other types of data. For example, indicator variables for a latent functional impairment variable may be an individuals rating of their ability to complete basic activities of daily living (walking, dressing etc.) on a continuous scale but could also include objective measures such as grip strength, a shuttle walk test, or a chair-stand test. Such a model is graphically

[2]CFA is historically grounded in the tradition of (common) factor analysis (Spearman, 1904, 1927) and is based on Thurstone (1947) concept of the *common factor model*. It is a theory-driven alternative to the data-driven method known as *exploratory factor analysis*.

depicted as a path diagram in Figure 4.2, which can be presented as a system of simultaneous equations

$$\begin{aligned} y_1 &= \lambda_1 \eta + \epsilon_1 \\ y_2 &= \lambda_2 \eta + \epsilon_2 \\ y_3 &= \lambda_3 \eta + \epsilon_3 \end{aligned} \tag{4.2}$$

The η within a circle in Figure 4.2 indicates a latent variable. Also of note is the direction of the arrows that go from the latent functional limitation variable η to the indicator variables y_1, y_2 and y_3, which might represent self-reported ability to complete basic activities of daily living, such as walking, dressing and bathing. This underlying assumption of factor analysis is that the observed relation between the indicator variables are a result of the responses being caused by the latent variable. Furthermore, the λ terms representing the regression weights, are also referred to as the factor *loadings* of the observed items on the latent variable. Commonly standardised factor loadings are presented, which can be interpreted as the correlation between the latent variable and the indicator. The residual terms ϵ represents the variance in the indicator variables unexplained by the latent variable.

4.2.2 Model fit

The fit of structural equation models is assessed by comparing the covariance matrix predicted by the model to the observed covariance matrix from the raw data. The χ^2 test of exact fit is a test of the equivalence of these two matrices, calculated as

$$\chi^2 = F_{\text{ML}}(N-1) \tag{4.3}$$

where F_{ML} is the minimised value of the maximum likelihood (ML) criterion. If the test is significant then the predicted covariance matrix does not sufficiently reproduce the observed covariance matrix. That is, the model does not fit the data well. However, several issues regarding the χ^2 test of exact fit have been noted (Mulaik, 2009). Most notably, with the large sample sizes typical of structural equation models the test is over-powered since the χ^2 value is a function of the sample size. That is, with large sample sizes solutions based on large samples may be rejected when the differences between the predicted and observed matrices are negligible.

As a result of the problems with the χ^2 test of exact fit a number of other indices have been proposed.

The number of "goodness-of-fit" indices developed is large, but only three popular indices that have been observed to perform favorably in simulation studies are discussed here. The *Root Mean Square Error of Approximation* (RMSEA; Steiger & Lind, 1980), so named because it assesses the extent to which a model fits *reasonably* well in the population. The RMSEA is calculated using the non-centrality parameter corresponding to the non-central χ^2 distribution of the test of exact fit. A value of the RMSEA of zero indicates perfect fit and values close to zero indicate close fit. Models with an RMSEA of less than .08 have been suggested to provide *acceptable* fit to the observed covariance matrix (Bentler, 2007).

A further index is the *Comparative Fit Index* (CFI; Bentler, 1990). This index evaluates the fit of the model to the null model (i.e. a model with the covariances between all variables fixed to 0 but the variance freely estimated). Values range between zero and one with those approaching one indicating good fit. A related method is the Tucker-Lewis Index (TLI; Tucker & Lewis, 1973), which additionally adjusts for the complexity of the model (i.e. less complex models with the same χ^2 as more complicated models are preferred). For both the CFI and TLI values above .95 are suggestive of *good* fit.

Information criterion are commonly used in the comparison of non-nested models.[3] Such indices allow for the comparison of fit by adjusting for the complexity of the model. Two indices are commonly reported for latent variable models and are discussed here, although more do exist. The Akaike Information Criterion (AIC; Akaike, 1974) is based on the χ^2, which is adjusted for model complexity by a penalty function that is added to the χ^2 value based on the number of parameters estimated by the model. A further index, the Bayesian Information Criterion (BIC; Schwarz, 1978), additionally adjusts for sample size such that the penalty increases with increasing sample size. Smaller values of both information criterion indicate better fit, no criteria have been defined with respect to the interpretation of the magnitude of difference in information criterion across models.

4.2.3 Non-normal and categorical data

The standard ML method for estimating structural equation models (Jöreskog, 1967) assumes that the data are multivariate normal. However, this assumption is often compromised in the presence of non-normal or categorical data (Bollen, 1989, p.p.131–134). Continuous variables that contribute to the violation of this assumption due to non-normal univariate distribution may be normalised by monotonic transformation—including square-root, logarithmic and inverse transformation. However, ordinal and nominal level variables are common for which transformation will not typically resolve the issue. The use of dummy variables for exogenous binary data and sets of dummy variables for ordinal and multinomial

[3] Nested models can be compared using a standard χ^2 difference test

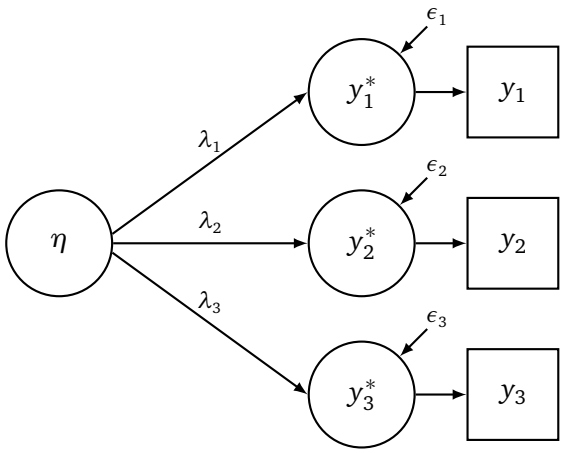


Figure 4.3: Confirmatory factor analysis with ordinal indicator variables

exogenous data is often satisfactory, resulting in biases to the assumption of multivariate normality that will not adversely effect model parameters (Bentler & Chou, 1995). However, ordinal or multinomial endogenous variables are more of a concern.

This issue is particularly salient for confirmatory factor analysis where ordinal variables, for example with a Likert type response format, are commonly used as measures of a theoretically continuous construct. Specifically, when the response format is skewed or there is a restricted number of response categories the variance may be under estimated, resulting in estimates of correlations and covariances (by the Pearson method) that are attenuated (Bollen, 1989). This has ramifications for the measurement model, causing (i) biased parameter estimates, (ii) biased fit statistics, and (iii) underestimation of the standard errors for model parameters (T. A. Brown, 2006).

Alternative estimation methods have been proposed for latent variable modelling that relax the assumption of multivariate normality. A detailed review and simulation study in the context of confirmatory factor analysis is provided by Flora and Curran (2004). A brief summary of these methods and the recommendations from this simulation are now given.

These alternative estimation methods are all based on the use of polychoric correlations.[4] The polychoric correlation, originally devised by Pearson (1900), estimates the linear relation between two unobserved continuous variables given only ordinal level data. The assumption is that the observed values of the ordinal variables are due to some unobserved underlying continuous *latent response distribution* (B. Muthén, 1983). This model is graphically depicted in Figure 4.3, the y^* variables indicate the unobserved continuous variables.

[4]Polychoric correlations are applied to ordinal variables. For binary variables tetrachoric correlations are used, and for mixtures of ordinal and continuous variables polyserial correlations are used. The same assumption that the categorical variables manifestly assess unobserved continuous variables holds.

Differences between the estimators are typically due to the weight matrix applied in conjunction with the polychoric correlation matrix and are extensions of the weighted least squares method (WLS; T. A. Brown, 2006)—sometimes referred to as the asymptotic distribution free method (ADF). The WLS estimator uses a weight matrix that adjusts for violations in multivariate normality by weighting the asymptotic variances and covariances and kurtosis. However, this method requires large samples for accurate estimation of kurtosis and, furthermore, may result in non-positive definite matrix in the presence of high levels of skewness in small samples (Flora & Curran, 2004).[5]

To counter these issues, B. Muthén, du Toit, and Sipsic (1997) developed a robust WLS method (WLSMV) that uses a diagonal weight matrix that is not inverted, and therefore does not require the matrix to be positive definite, along with robust standard errors. Furthermore, this method produces a mean and variance-adjusted χ^2 test statistic. The results of the simulation study conducted by Flora and Curran (2004) indicated that the WLSMV estimator was superior to WLS in samples ranging from 100 to 1000 with varying degrees of non-normality and model complexity. Furthermore, the WLSMV estimator performed well with sample sizes of 200 with high levels of skewness and kurtosis.

Another alternative is the unweighted least squares (ULS) estimator. This method, analogous to ordinary least squares, uses an identity matrix rather than a weight matrix avoiding assumption of multivariate normality. As a result, this estimator does not lead to estimates of standard errors or a χ^2 test statistic.

In addition to the WLS and related methods, robust ML is also commonly used in the presence of non-normal or categorical data (Bentler & Chou, 1995). As with the previously described methods, robust ML uses a weight matrix that adjusts the parameter estimates and fit statistics for non-normality. However, since the standard errors of the parameters rather than parameters themselves are adjusted, in the presence of categorical data, biased parameter estimates remain a potential problem.

It is important to note that the methods above apply not only to confirmatory factor analysis, the measurement part of latent variable modelling, but also to the structural model as well. That is, latent variable modelling allows for the multivariate generalisation of the generalised linear model.

4.2.4 Latent variable mixture modelling

Traditionally, latent variable models allowed for only the use of continuous observed and latent variables. As has been noted the development of more flexible estimation techniques in the 1980's and

[5] A non-positive definite matrix refers to a matrix with zero or negative eigenvalues. WLS estimation requires the weight matrix to be inverted, which is not possible if the matrix is non-positive definite.

1990's allowed for the inclusion of ordinal and nominal observed exogenous variables. However, recent extensions of the latent variable modelling framework have allowed for the inclusion of categorical latent variables, also referred to as mixture modelling (B. Muthén & Muthén, 2000; B. Muthén, 2001; B. Muthén & Asparouhov, 2009). This increased flexibility has lead to the development of newer and more complex models that are particularly useful in the analysis of the longitudinal data (Pickles & Croudace, 2010). However, before these models are discussed in detail a brief overview of latent variable mixture modelling is provided.

The CFA model incorporates continuous latent variables, the corresponding model incorporating a categorical latent variable is widely known as the *latent class model* (B. Muthén, 2001). Latent class analysis[6] can be viewed as a model based form of cluster analysis, which in particular relates to the k-means clustering approach. Although these models are not new (c.f. Lazarsfeld & Henry, 1968; McDonald, 1967), the ability to fit such models within a latent variable modelling framework allows for the use of the other features that increase the flexibility of situations where these model may be applied. For example, building on the earlier work of McDonald (1967, 2003), Lubke and Muthén (2005) applied a hybrid model incorporating both continuous and categorical latent variables, a *factor mixture analysis*. In addition, B. Muthén (1992) presents an interesting approach to the study of alcohol dependency that provides both a continuous and dimensional account for this disorder (section 2.2.2.1 provided a discussion of the categorical and dimensional accounts for depression).

These models are interesting and are beginning to be used more widely in the applied literature. However, the application of latent variable mixture models provides a host of interesting new possibilities. Prior to the discussion of latent variable mixture modelling in the context of longitudinal data continuous latent variable models are introduced.

4.3 Latent variable models for longitudinal data

Latent curve models (LCM) are an extension of (ordinary least squares) linear regression that accounts for the hierarchical structure of the data. Different parameterizations of this model have been ascribed different names (e.g. multi-level modelling, hierarchical linear modelling, mixed-effects models). Models fitted using the SEM approach are also commonly referred to as *latent growth models* or *latent growth curve models*. These are avoided in this dissertation as the term *growth* is misleading since models with

[6]Typically the term *latent class analysis* is applied when the indicator variables are categorical. For continuous indicator variables the term *latent profile analysis* is widely used. The term latent class analysis is used here to refer to both types of mixture model with continuous and/or categorical data.

decreasing as well as increasing trajectories are allowed.

The LCM is a special case of CFA (Meredith & Tisak, 1984; McArdle & Epstein, 1987; Meredith & Tisak, 1990). Although equivalent to hierarchical linear models (Raudenbush & Bryk, 2002) it is important to recognise that the different parameterizations give the models slightly different features. For example, the CFA approach allows for greater control over the residual correlation structure, whereas the multilevel approach can incorporate time values more flexibly (c.f Bollen & Curran, 2006). The LCM is introduced from a multi-level modelling perspective as it provide a more intuitive explanation of the model as a direct extension of the general linear model.

Linear regression is not appropriate for longitudinal data since the nested structure of the data violates several assumptions. Referring to the outcome at each time point y_t, the intercept term α, the time trend variable λ_t, the slope β and the disturbance for each time point ϵ_t we have a model describing the trajectory of the outcome over t time periods.

$$y_t = \alpha + \lambda_t \beta + \epsilon_t \tag{4.4}$$

Linear regression assumes that the disturbances have a mean of 0, is uncorrelated with the time trend variable λ_t, is homescadastic, and is non autocorrelated (Table 4.1). Fitting the model described in 4.4 violates these assumptions. For example, we would expect the disturbances of each individual to be associated with other observations for that individual. Also, for longitudinal trajectories, for example joint damage in RA, we would expect that the variance increases with time, resulting in heteroscadasticity. Furthermore, we would often expect disturbances to be autocorrelated, that is, for disturbances to be more highly associated at more proximal time points.

To deal with these violations we can extend the above model by indexing several of the parameters in the equation for each individual i, leading to the trajectory equation

$$y_{it} = \alpha_i + \lambda_t \beta_i + \epsilon_{it} \tag{4.5}$$

where y_{it} is the value of the outcome variable y for the ith individual at time t, α_i is the random intercept for individual i, and β_i is the random slope for individual i. This allows each individual i to have a distinct intercept and slope to describe the trajectory of the outcome variable y over time t. The value of λ_t is constant over all individuals (and hence is not indexed by i). For example, for three time points $t_1 = 0$, $t_2 = 1$, and $t_3 = 2$ for all individuals.[7]

[7]Typically the time variable λ_t is coded as $\lambda_t = t - 1$, allowing the interpretation of the intercept factor α_i as the starting

Table 4.1: Assumption of simple linear regression compared to latent curve model

Assumption	Linear regression	latent curve model
Disturbance has mean of 0	$E(\epsilon_t) = 0$ for $t = 1, 2, \ldots, T$	$E(\epsilon_{it}) = 0$ for $i = 1, 2, \ldots, N$ and $t = 1, 2, \ldots, T$ $E(\zeta_{\alpha i}) = 0$ for $i = 1, 2, \ldots, N$ $E(\zeta_{\beta i}) = 0$ for $i = 1, 2, \ldots, N$
Disturbance uncorrelated with covariates (and other disturbances)	$COV(\lambda_t, \epsilon_t) = 0$	$COV(\lambda_t, \epsilon_t) = 0$ for $i \neq j$ $COV(\epsilon_{it}, \zeta_{\alpha i}) = 0$ $COV(\epsilon_{it}, \zeta_{\beta i}) = 0$ $COV(\zeta_{\alpha i}, \zeta_{\alpha i}) = 0$ for $i \neq j$ $COV(\zeta_{\beta i}, \zeta_{\beta i}) = 0$ for $i \neq j$ $COV(\zeta_{\alpha i}, \zeta_{\beta i}) = 0$ for $i \neq j$
Homoscedasticity	$E({\epsilon_t}^2) = \sigma_{\epsilon\epsilon}$ for $t = 1, 2, \ldots, T$	$E({\epsilon_t}^2) = \sigma_{\epsilon\epsilon}$ for $i \neq j$
Nonautocorrelation	$COV(\epsilon_t, \epsilon_{t+1}) = 0$	$COV(\epsilon_t, \epsilon_{t+1}) = 0$ for $i \neq j$

Adapted from Bollen and Curran (2006).

The mean intercepts and slopes for individuals i are of interest and lead to the intercept and slope equations

$$\alpha_i = \mu_\alpha + \zeta_{\alpha i} \tag{4.6}$$

$$\beta_i = \mu_\beta + \zeta_{\beta i} \tag{4.7}$$

where μ_α and μ_β are the mean intercept and mean slope across all individuals i, respectively. Equation (4.6) represents the individual intercept α_i as a function of the mean of the intercept μ_α for all cases and a disturbance $\zeta_{\alpha i}$. Where $\zeta_{\alpha i}$ is the difference between the individuals score on outcome y and the grand mean where $\lambda_t = 0$. Similarly, equation (4.5) represents the individual slope β_i as a function of the mean of the slopes for all cases μ_β and a disturbance $\zeta_{\beta i}$.

Using multi-level terminology the trajectory equation (4.5) is commonly referred to as the level-1 equation, since it refers to the first level of assessment (observations), and the intercept and slope equations (4.6) and (4.7) as the level-2 equations, since they refer to the second level of assessment (individuals).

We can combine the trajectory, intercept and slope equations into a single model that is often referred to as the reduced form model,

$$y_{it} = (\mu_\alpha + \lambda_t \mu_\beta) + (\zeta_{\alpha_i} + \lambda_t \zeta_{\beta i} + \epsilon_{it}) \tag{4.8}$$

point of the trajectory since $\lambda_1 = 0$.

The first term in parenthesis is referred to as the fixed component and the second term the random component. The fixed components reflects the mean structure and the random component the sources of individual variability. It shows that the trajectory of y_{it} is a function of the mean intercept, the trend variable times the mean slope and a composite disturbance term. This formalization leads to familiar but less restrictive assumptions (Table 4.1).

4.3.1 Latent variable modelling approach

Meredith and Tisak (1984) demonstrated that the latent curve model could be fitted using confirmatory factor analysis, with the random intercepts and slopes as latent variables (McArdle & Epstein, 1987; Meredith & Tisak, 1990). Using the linear latent curve model as an example this model can be fitted using a two-factor multiple indicator confirmatory factor analysis. Figure 4.4 provides a path diagrammatic representation of the equations of the latent curve model.

The multiple indicators are repeated measures of y for each individual i over time points t. The first latent factor α represents the random intercept component of the trajectory. The loadings for this factor are all fixed to one. The loadings of the second factor β define the shape of the trajectory and also at which time point the intercept is. In the figure the time units are equally spaced, $t_1 = 0$, $t_2 = 1$, $t_3 = 2$, reflecting equal time passage between assessment such that the shape of the trajectory is linear. Note that any equally spaced values for λ_t could be used and the model would be equivalent—although the slope parameter would differ the model implied trajectory would remain the same.

The two factors are commonly referred to as the trajectory or growth factors, with α referred to as the intercept factor and β the slope factor. These are unobserved variables that are estimated from the data. Although it is typical to represent continuous latent factors using the Greek latter η, the Greek

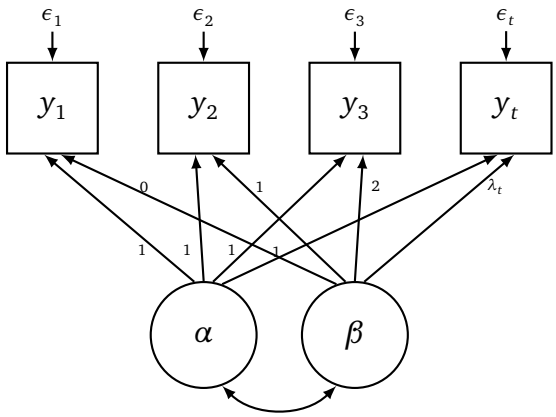


Figure 4.4: Linear latent growth curve model

letters α and β are used here, in line with the multi-level literature, since they make it more explicit that they measure different characteristics of the trajectory curve.

Unlike many CFAs the LCM explicitly models both the means and the covariance's among the observed variables, rather than just the covariances. However, a restrictive mean structure is applied, with the intercepts of the repeated measures set to 0 and the means of the factors estimated. Resultantly the model-implied mean structure is entirely dependent on the means of the latent factors (Bollen & Curran, 2006).

In addition the CFA approach estimates all the parameters of the latent curve model: residual variances of the repeated measures (the variance in the repeated measure not explained by the underlying growth process); the means of the latent growth factors representing the mean starting point the the mean rate of change; the variances of the growth factors reflecting the variability in the random intercept and slope factors around their mean; and also the covariance between the random intercepts and slopes.

4.3.2 Nonlinear time trajectories

In the previous section the linear latent curve model was described. For this model the values of the time variable λ_t must be equally spaced. In the example given $t_1 = 0, t_2 = 1, t_3 = 2$, however as noted equivalent results would be given by any other equally spaced values (e.g. $t_1 = 0, t_2 = 2, t_3 = 4$, or $t_1 = 0, t_2 = 10, t_3 = 20$ etc.). Furthermore, where the repeated measurements are not equally spaced the time variable loadings can reflect this. For example, in a study with three repeated measurements where assessments are made at baseline, 1-year and 5-years the loadings for the linear trajectory model could have the loadings $t_1 = 0, t_2 = 1, t_3 = 5$.

Nonlinear functions of time are easily estimated via two different methods. Firstly, further latent variables may be included in a manner akin to including polynomials in a linear regression model, or non-linear transformations of the λ_t loadings may be used.

Considering first the polynomial approach. Quadratic trajectories can be modelled by including a third latent variable in the model, where the loadings of the of the time variable λ_t are squared. The level-1 trajectory equation becomes

$$y_{it} = \alpha_i + \lambda_t \beta_{1i} + \lambda_t^2 \beta_{2i} + \epsilon_{it} \tag{4.9}$$

where λ_t^2 is the squared value of time at assessment t, and β_{2i} is the individually varying value of the

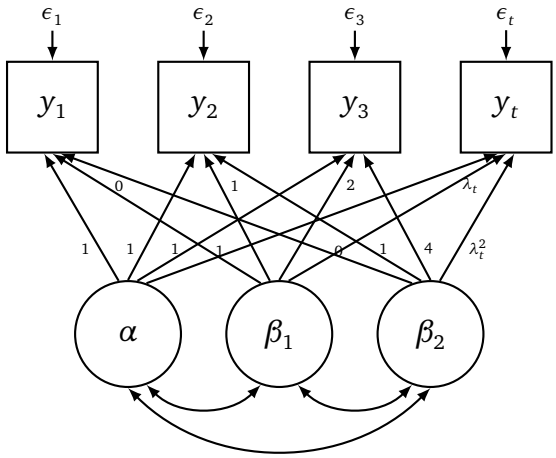


Figure 4.5: Quadratic latent growth curve model

quadratic component of the curve. That is, β_{2i} represents the curvature of the line. α_i still defines the intercept and β_{1i} the linear slope. Along with the intercept and slope parameters α_i and β_{1i} the curvature parameter β_{2i} is treated as a random variable and the level-2 equations are

$$\begin{aligned} \alpha_i &= \mu_\alpha + \zeta_{\alpha i} \\ \beta_{1i} &= \mu_{\beta_1} + \zeta_{\beta_{1i}} \\ \beta_{2i} &= \mu_{\beta_2} + \zeta_{\beta_{2i}} \end{aligned} \tag{4.10}$$

Equation (4.10) can be expressed as a path diagram (Figure 4.5). As with the random effects in the linear model β_{2i} is assumed to be uncorrelated with disturbance, $COV(\epsilon_{it}, \zeta_{\beta_{2i}}) = 0$ for all i and $t = 1, 2, \ldots, T$.

This method can be extended to cubic trajectories by including a third-order polynomial or, in principle, any number of polynomial terms. For identification of the quadratic latent curve model a minimum of four time points is required, and for each additional polynomial term included a an additional measurement i.e. 5 time points for cubic, 6 for quartic and so on. A proof of the identification of the quadratic model is provided by Bollen and Curran (2006).

In practice, Bollen and Curran (2006) recommend against the use of higher order models above the quadratic due to the increasing complexity of the interpretation. Since the linear model implies a constant change over time, the quadratic model a change in the rate of change over time, and the cubic model a change in the change in the rate of change over time.

An alternative approach is to incorporate non-linear transformations of the time loadings λ_t into the model. These unequally spaced loadings allow for the assessment of different nonlinear trajectories. This approach is described in detail by Browne and Du Toit (1991) and Toit and Cudeck (2001). Four common parametric forms are briefly discussed: exponential, logarithmic, square-root and reciprocal trajectories. For clarity, we can represent the LCM with a non-linear transformation of the time loadings as

$$y_{it} = \alpha_i + \lambda_t^{\dagger}\beta_i + \epsilon_{it} \tag{4.11}$$

where $\lambda_t^{\dagger}$ represents the transformed time loadings. For the exponential model $\lambda_t^{\dagger}$ corresponds to the transformation $1 - e^{1-\lambda_t}$. Exponential functions are common in the assessment of growth or decay since the exponential trajectory is monotonic tending to an asymptote without changing direction. This offers an advantage over polynomial models that may increase or decrease without limits. Under the exponential model β_i represents the model implied expected total change in y_{it} as time tends to infinity. An alternative specification of the exponential model described by Grimm and Ram (2009) uses the transformation $\lambda_t^{\dagger} = 1 - e^{\gamma}\lambda_t$. Again β_i is interpreted as the model implied expected total change in y_{it} as time tends to infinity. However, later change is directly proportional to earlier change with $e^{-\gamma}$. In the model γ is a fixed factor representing the rate of acceleration or deceleration over time. This implies that individual variability is allowed in the individual staring point and the total amount of change over time, but that the rate of change is fixed for all individuals.

Another useful nonlinear function is the natural logarithm of time. The logarithmic trajectory represents diminishing increments of change over time—as opposed to equal increments for the linear model. The logarithmic trajectory may be defined where $\lambda_t^{\dagger} = f(\lambda_t)$. For the logarithmic function of time $\lambda_t^{\dagger} = ln(\lambda_t)$, where $\lambda_t = 1, 2, 3, \ldots, T$ corresponds to $ln(\lambda_t) = 0, 0.693, 1.099, \ldots$ which corresponds to changes of 0.693 between time 1 and 2, 0.496 between time 2 and 3, 0.287 between time 3 and 4, and so on.

The square root trajectory may be defined where $\lambda_t^{\dagger} = \sqrt{\lambda_t} - 1$ and the reciprocal $\lambda_t^{\dagger} = 1 - \frac{1}{\lambda_t}$. Both also involve a diminishing rate of change. All transformations are coded such that the intercept relates to t_1—that is, where $\lambda_1^{\dagger} = 0$. The proportionate change for the four transformations discussed is displayed in Figure 4.6.

Meredith and Tisak (1990) provide a useful alternative method for modelling curvilinear trajectories by freeing one or more of the loading on the random slope factor. They propose that the first loading be

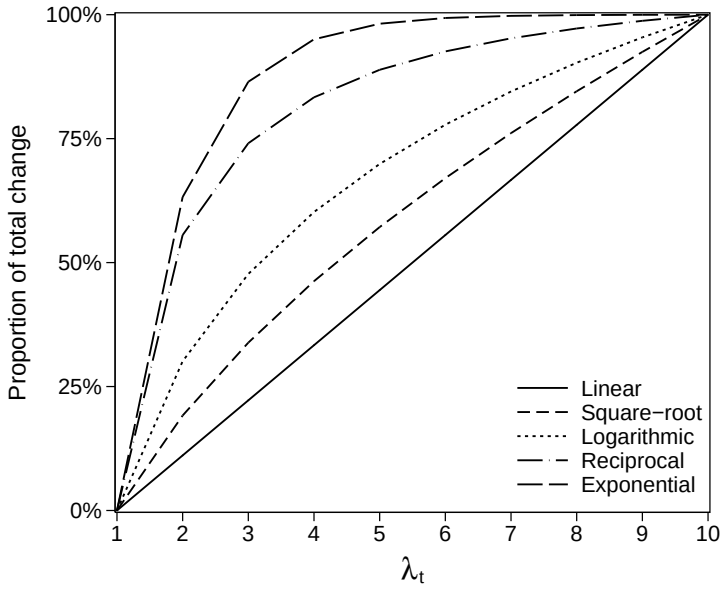


Figure 4.6: Proportional change over 10 repeated measures using non-linear transformations of time

set to zero ($\lambda_1 = 0$) and the second to one ($\lambda_2 = 1$) but freely estimating the λ_t for $t = 3, 4, \ldots, T$. The free loadings are a type of nonlinear spline that best fits the data between two time points. Models using this method with four or more time points are identified[8] Interpretation of the estimated factor loadings is straightforward. Since $\lambda_1 = 0$ and $\lambda_2 = 1$ the estimated factor loadings represent change in relation to the change observed between the first two time points (ratio). For example, if λ_3 were estimated to be 2 the change between time 1 and 3 would be interpreted as double that of the change between time 1 and 2 (i.e. linear change). However, if λ_3 were estimated to be 1.5 this would indicate that the change between time 1 and 3 was only 1.5 times the change between times 1 and 2—indicating a deceleration in the rate of change. A variation on this method is to fix the first loading to zero ($\lambda_1 = 0$) and the last to one ($\lambda_t = 1$) while freely estimating λ_t for $t = 2, 3, \ldots, T - 1$. In this case the interpretation is the proportion of the total change.

Other non-linear models, including cyclic patterns and piecewise growth are also possible but are not considered here. It is worth noting that the implementation of polynomial factors and non-linear transformations of the time λ_t loading simultaneously possible and may be considered an *ad hoc* approach to the fractional polynomial method (Sauerbrei & Royston, 1999; Long & Ryoo, 2010).

[8] Three or more if $\mu_{\alpha 1} \neq \mu_{\alpha 2}$ (Bollen & Curran, 2006).

4.3.3 Latent variable mixture models for longitudinal data

The previous sections have describe the latent variable modelling approach to the analysis of longitudinal data, through the use of continuous latent variables.[9] Latent variable mixture modelling approaches to longitudinal data that use categorical latent variables are also available, commonly referred to as *latent class growth analysis* (LCGA) or *group-based trajectory modelling* (e.g. B. Muthén, 2006a; Nagin & Odgers, 2010; Pickles & Croudace, 2010). Rather than considering individual trajectories and assuming that a single trajectory adequately approximates change over time for the entire population, LCGA provides a typological representation of change. That is, a categorical latent variable represents a mixture of subpopulations (*latent classes*) with distinct patterns of change where membership is unknown and is inferred from the data. Notably, LCGA assumes that there is no within class heterogeneity in either intercept or slope.

A further latent variable mixture modelling approach that incorporates both continuous and categorical latent variables provides a more flexible approach than the LCGA framework that naturally extends the LCM. This approach is commonly known as Growth Mixture Modelling (GMM; B. Muthén, 2001; B. Muthén et al., 2002). To the linear LCM (Equation 4.5) we add a categorical latent variable c representing the unobserved subpopulation group, with k levels ($k = 1, 2, \ldots, K$) and each individual i having a probability of membership in each of the k levels. Thus, a GMM can be expressed as

$$
\begin{aligned}
y_{it} &= \sum_{k=1}^{K} \Pr(c = k)[\alpha_{ki} + \lambda_{kt}\beta_{ki} + \epsilon_{kit}] \\
\alpha_{ki} &= \mu_{\alpha k} + \zeta_{\alpha ki} \\
\beta_{ki} &= \mu_{\beta k} + \zeta_{\beta ki}
\end{aligned} \tag{4.12}
$$

where the subscript k indicates that parameters are allowed to vary across latent classes. Thus, each latent class can be considered as being defined by its own linear growth model.[10] Figure 4.7 provides a graphical representation of equation (4.12) to show that, as with the LCM, the GMM can be can be considered a special case of a confirmatory factor analytic model. As such it is possible regress the categorical latent variable c onto a set of predictor variables to examine their association with class membership.

Since GMMs are susceptible to converging on local rather than global solutions it is typical to com-

[9] Other methods are in use, in particular autoregressive models. These are discussed in Chapter 7

[10] LCGA assumes that the values of $\zeta_{\alpha ki}$ and $\zeta_{\beta ki}$ are zero for all individuals i.

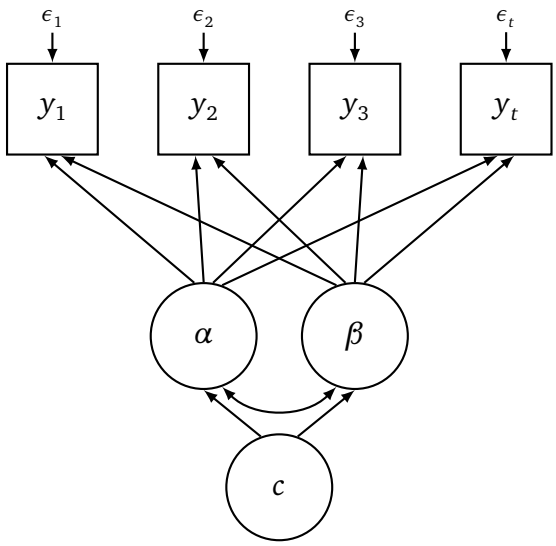


Figure 4.7: Growth mixture model

pare the convergence of models drawn from multiple random sets of starting values. Observing the same log-likelihood obtained from multiple sets of random starting values indicates that the solution is not at a local maximum. A two-stage process is used. Initially a large number of random sets of starting values are generated and optimized using maximum-likelihood for a fixed maximum number of iterations. Then a smaller number of sets with the highest log-likelihood values from the initial stage are optimized until convergence is achieved. For more complex models, such as those with a categorical latent variable with many levels or with more than one categorical latent variable, the number of random sets of starting values required to achieve convergence may be large (e.g. 1000 or more)—and there is the very real issue that there may be no global maximum.

For most analyses involving categorical latent variables, models with up to 6 latent classes are usually considered. The extraction of more than six latent classes may not be advisable for two reasons. Firstly, having a very large number of latent classes would result in a rather unparsimonious solution. Also, the likelihood of models converging on a global maximum is increasing unlikely.

Model fit cannot be assessed using standard goodness-of-fit indices used in structural equation modelling (i.e. RMSEA, CFI & TLI). Instead the best fitting model is identified using the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT), a variation of the χ^2 difference test applicable to mixture models, the Bayesian Information Criterion (BIC), and the consistent Akaike Information Criterion (CAIC) since the standard AIC is well known to over select the number of classes. All have been shown to perform well in simulation studies that consider their use in latent variable mixture models (Nylund, Asparouhov, & Muthén, 2007; Tofighi & Enders, 2006).

4.3.3.1 Summary

The first part of this chapter has introduced the topic of latent variable modelling, and has discussed the application of latent variable models to longitudinal data, in particular the LCM and its mixture modelling generalistion the GMM. The second part of this chapter turns to the issue of missing data that is a major concern in longitudinal studies. Again this issue is viewed from the perspective of latent variable modelling.

4.4 Missing data

Missing data is a pervasive problem in longitudinal studies, especially those with long periods of follow up. Missing data may arise for several reasons. A participant may not complete a particular assessment during one of the waves of follow up, for example, they may forget or refuse to complete a specific item of a questionnaire (*item missingness*). Alternatively the participant may miss an entire wave of data collection (*intermittent missingness*), or they may drop out of the study entirely (*drop out missingness*). Not only does missing data reduce the statistical power of the the analysis but it may result in biased parameter estimates if there are systematic differences between those with and without missing data.

Rubin (1976) defined different assumptions concerning missing data mechanisms. The most restrictive assumption, and the one made using most traditional analytical methods, is *missing completely at random* (MCAR). The assumption of MCAR holds when the probability that missing values on an outcome variable y are independent of the value of y or any other observed variables x. If m_y is a binary variable indicating that the value of y is missing this can be expressed as

$$\Pr(m_y|y,x) = \Pr(m_y) \tag{4.13}$$

That is, the conditional probability that y is missing, given y and x, is equal to the unconditional probability that y is missing. The implication is that the observed values of y are simply a random subsample of the complete data. The classic example is of a laboratory scientist accidentally dropping a tray of test tubes.

A less restrictive assumption is that data are *missing at random* (MAR). Under this assumption the probability that an observation is missing on variable y may depend on another observed variable x, but

not on the values of y itself.

$$\Pr(m_y|y,x) = \Pr(m_y|x) \tag{4.14}$$

In words, this expression means that the conditional probability that y is missing, given y and x, is equal to the conditional probability that y is missing, given x alone. That is, missingness is independent of the unobserved values of y.

The distinction between these two conditions is important because most conventional methods for handling missing-data (e.g. list-wise and pair-wise deletion) yield unbiased parameter estimates only under the assumption of MCAR. However, frequently this assumption is not met in practice. (Carpenter & Kenward, 2007) provides a detailed discussion of the limitations of conventional methods for handling missing data, including various forms of imputation such as mean substitution and regression imputation.

It is impossible to test whether the MAR condition is satisfied. Since the values of the missing data are unknown it is not possible to examine whether there are systematic differences on the outcome variable between those with or without missing data.

The missing data mechanism is referred to as *ignorable* when the MAR condition holds and the parameters governing the missing data process are independent of the parameters to be estimated. This is because there is no need to model the missing data mechanism as part of the estimation model. Allison (2002) suggests that MAR and ignorability can be treated as equivalent conditions, as even when the parameters governing the missing data process are not independent of the parameters to be estimated methods assuming ignorability perform adequately.

When the probability that an observation is missing on an outcome variable y is related to the actual value of y, even after conditioning on other observed variables x, the data is said to be not missing at random (NMAR).

$$\Pr(m_y|y,x) \neq \Pr(m_y|x) \tag{4.15}$$

Situations where the missing data mechanism is NMAR are typically referred to as *non-ignorable* since the missing-data mechanism must be modelled as part of the analysis to provide unbiased results.

4.4.1 Ignorable missing data

There are currently several methods that handle missing data in a principled way that is generally efficient and produces unbiased results under the assumption of MAR. The two most applicable in the context of longitudinal models, particularly LCM, are *full-information maximum likelihood* (FIML) and *multiple imputation* (MI). Alternative approaches, such as *inverse probability weighting*, are available but are not discussed as they are not employed in this dissertation.

4.4.1.1 Full information maximum likelihood

FIML, also sometimes referred to as direct ML (Enders, 2001), is similar to pair-wise deletion since the likelihood function is computed for each individual using all of their observed data. The total likelihood is the sum of the values of the likelihood for each individual. FIML differs from the usual ML fitting function for latent variable models since the saturated model is not included, however both methods produce identical log-likelihoods when there is no missing data (Bollen & Curran, 2006). FIML enables the calculation of the standard chi-square test statistic, and as an ML estimator maintains the desirable features of ML estimators, such as consistency, asymptotic unbiasedness, asymptotic normality, and asymptotic efficiency, providing asymptotic estimates of standard errors for significance testing. However, FIML conditions on the missing data of the independent variables, which means that list-wise deletion is applied to cases with missing values of the covariates.[11] It has the advantage over several other methods that additional covariates can be included in the model indirectly, even where there is no particular rational for including them in the model of interest—maximizing the likelihood that the underlying assumption that the data is MAR.

4.4.1.2 Multiple imputation

The use of MI has grown considerably in recent years, and has been incorporated into several statistical packages (e.g. Stata, SPSS, SAS, S-Plus/R). MI is a likelihood based method that has been shown to produce results that are consistent, asymptotically efficient and asymptotically normal when the MAR condition holds. As with FIML, MI allows for additional covariates can be included in the imputation model.

Deterministic imputation methods (e.g. regression imputation) are flawed since the imputed data are analyzed as if they were complete data, which produces downwardly biased variances for variables with

[11] Explicitly estimating the mean and variance of covariates with missing data brings them into the estimation model as dependent variables ensuring that all cases are included.

missing data, underestimates of the standard errors, and thus test statistics are overestimated inflating the chances of *Type-I* errors. MI solves this problem by adjusting for the fact that there is uncertainty about the missing values.

MI consists of 4 stages which are succinctly described by van Buuren, Boshuizen, and Knook (1999) as:

1. Specify the posterior predictive density $\Pr(m_y|y,x)$, where x is a set of predictor variables given the non-response mechanism and the complete data model
2. Draw random imputations from this density to produce M complete data sets
3. Perform M complete-data analyses on each completed data set
4. Pool the M analyses results into final point and variance estimates

To solve the problem of underestimating the variances of variables with missing data random variation is introduced into the predicted values of y. This is done by making random draws from the residual distribution of each imputed variable, which are added to the imputed variables. Moreover, repeating the imputation process multiple times to produce M imputed data sets provides a distribution of likely values for each missing data point. Performing the analysis multiple times and pooling the resultant estimates (using Rubin's rule) ensures that standard errors are not underestimated (Carpenter & Kenward, 2007).

The most widely implemented method is the multivariate normal model. This approach assumes variables are normally distributed and are a linear function of all other variables with a normal, homoscedastic error term, it performs well when normality assumption is violated (Schafer, 1999). An alternative method using chained equations has also been developed that is applicable to a wider variety of distributions, since it allows for imputation under generalized linear models (i.e. binary logistic regression, multinomial logistic regression, and Poisson regression; van Buuren et al., 1999).

The major drawback with MI is that for longitudinal data appropriate MI currently requires a fully Bayesian framework using Markov Chain Monte Carlo implemented in specialized software programmes, such as WinBUGS. However, imputing data using repeated cross-sections of the dataset and combining them for the final analysis has been shown to be relatively robust (Carpenter & Kenward, 2007). Recent developments in this area are likely to result in more robust methods being implemented in mainstream statistical programmes (Kenward & Carpenter, 2007).

4.4.2 Non-ignorable missing data

The basic approach to analyses using methods that assume ignorability of the missing data mechanism is the same as for standard regression models: adjust for all observable differences for observed and missing cases and assume that any unobserved differences are unsystematic. However, when the missing data mechanism is non-ignorable due to NMAR arising from unobserved variables predicting missingness the missing data mechanism must be modelled as part of the estimation process (Allison, 2002).

Both the FIML and the MI approaches described above can be adapted to deal with non-ignorable missing data. Adapting these approaches, however, is non-trivial and there is little software available to implement them (Allison, 2002). The generalised latent variable modelling framework is extremely flexible and allows for fitting several such models by FIML. Note that implicit in fitting these models is numerical integration over the missing data, to obtain a likelihood in terms of the observed data which can then be maximized (see Diggle & Kenward, 1994). In practice, this usually requires Monte-Carlo integration.

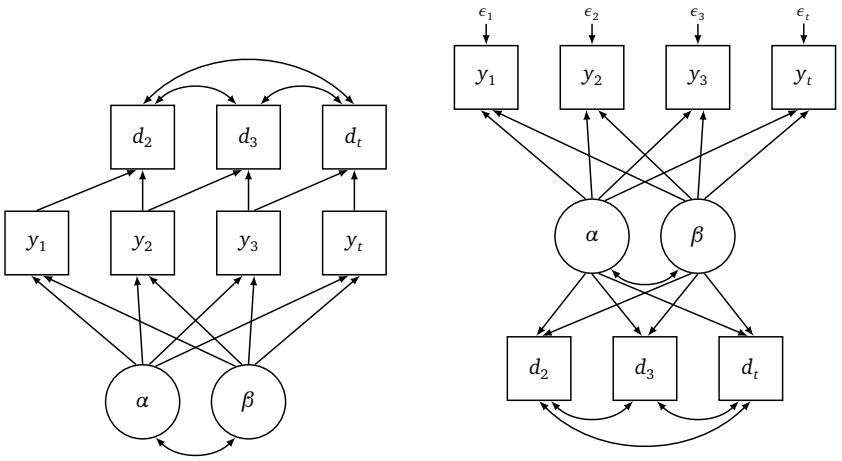
In general, two approaches to NMAR analysis have been developed and are beginning to be applied in the literature (B. Muthén, Asparouhov, Hunter, & Leuchter, 2011). Selection models, which developed out of the econometric literature as a means to deal with survey non-response (e.g. the Heckman selection model), have been applied in longitudinal analysis to jointly model the dropout process (e.g. Diggle & Kenward, 1994). The alternative approach is the pattern-mixture approach which averages data over missing data patterns (e.g. Little, 1995). These two approaches are now discussed.

4.4.2.1 Selection models

The first type of NMAR model considered is the selection model. Ignoring covariates, selection models consider missingness conditional on the observed data using the factorization

$$f(y, m_y) = \Pr(m_y|y) f(y) \tag{4.16}$$

where y represents the observed data and m_y is a set of missing data indicators. Essentially, y is first modelled as if there was no missing data then, given a value of y, we model whether the data is missing or not. The most widely used selection model concerning dropout from longitudinal studies is the model proposed by (Diggle & Kenward, 1994). For this model the missing data indicators are a set of survival indicators, which will be referred to as d_t, that are coded 0 prior to dropout, 1 at the time of dropout, and missing thereafter. This includes the survival indicators as dependent variables in a logistic regression



(a) Diggle-Kenward model **(b)** Wu-Carroll model

Figure 4.8: NMAR selection models

model with the observed y value at t and $t-1$ included in the model as predictors. According to this model, the assumption of MAR holds if dropout is not observed to be significantly related to the last observed value of the data, y_t.

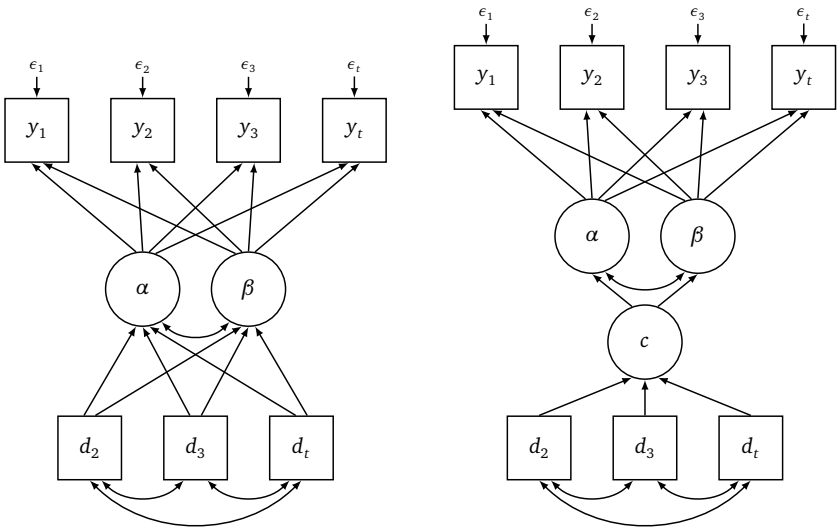
An alternative model is the Wu and Carroll (1988) selection model. This model rather than conditioning on the observed data conditions on the growth parameters of a LCM (i.e. the random intercept and slope factors). Figure 4.8 a depicts both the Diggle and Kenward (1994) and Wu and Carroll (1988) models diagrammatically.

4.4.2.2 Pattern-mixture models

An alternative approach that reverses the factorization applied in selection models are pattern-mixture models

$$f(m_y, y) = f(y|m_y)Pr(m_y) \tag{4.17}$$

where the observed data y is conditional on the missing data m_y. That is, pattern mixture models allow missingness to affect the distribution of the variable of interest. For conventional pattern-mixture models that assume intermittent missing values are MAR the d_t variables are a set of dummy variables indicating dropout occasion (i.e. coded as 1 at the time of dropout and 0 otherwise). This allows the means of the random intercept and slope factors to vary as a function of the dropout dummy variables, with a different growth trajectory for individuals that dropout at each occasion (pattern), plus an additional trajectory for those that do not dropout. In order for the model to be identified the random slope means for



(a) Conventional model **(b)** Roy latent dropout model

Figure 4.9: NMAR pattern-mixture models

individuals who dropout after the first observation is conventionally fixed to be equal that of individuals who dropout one time point later.

To calculate the overall growth parameters the mean of each of the random growth parameter estimates are mixed over the patterns, which essentially means the weighted average of the growth parameter across each pattern is calculated. This mixture can then be compared to the conventional single-class model estimated under MAR which assumes that the growth trajectory is equivalent across each dropout pattern.

Roy (2003) criticized the pattern-mixture approach proposing a latent dropout pattern-mixture model. The conventional model assumes every subject with the same dropout time shares a common distribution, which seems unlikely particularly when, as in this instance, dropout may be for a number of alternate reasons. The Roy (2003) model uses a latent class variable that is influenced by dropout time, and influences the random effect means for the outcome. Latent class membership is specified as a multinomial logistic regression with the dropout indicators as covariates. This model, which allows cases with the same dropout time to come from different distributions, can be considered a *shared-parameter* model and implies a growth mixture model (B. Muthén et al., 2011). The conventional pattern-mixture model and the Roy latent dropout pattern-mixture model are depicted as path diagrams in Figure 4.9.

Recent overviews of NMAR modelling for longitudinal data are given in Fitzmaurice, Davidian, Verbeke, and G. (2009) and B. Muthén et al. (2011). Since the assumption of NMAR is untestable. That is, it is not possible to ever rule out the biasing effects of unobserved variables, analyses are usually under-

taken as a sensitivity analysis to confirm results under the MAR assumption are robust to the most likely causes of non-ignorable missingness. In longitudinal studies the non-ignorability concern is typically focused on missing data due to dropout rather than intermittent missingness. Resultantly, it is only the likelihood that drop-out is non-ignorable that is considered in this dissertation .

4.5 Summary

This chapter has given a brief overview of the latent variable modelling framework, with particular reference to the analysis of longitudinal data. Also discussed has been the issues resulting from missing data that is common in longitudinal studies, the assumptions made by traditional analytic methods, and the use of latent variable modelling approaches as sensitivty analyses against possible non-ignorable missing data mechanisms. The techniques introduced within this chapter are used throughout the remainder of this dissertation. Applications and extensions of the methods introduced here are discussed in the following chapters.

The following chapter presents an assessment of the construct validity of the Hospital Anxiety and Depression scale using latent variable modelling methods.

Chapter 5

Psychometric analysis of the Hospital Anxiety and Depression Scale

5.1 Introduction

Prior to addressing the main aims of the dissertation it is necessary to examine the psychometric properties of the tool used to assess psychological distress in the following two chapters, the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Section 2.2.2.1 noted that in chronic physical illnesses the assessment of distress is complicated by the overlap of the symptomatology with the physical disorder. A detailed assessment of the validity of the HADS as a measure of the severity of psychological distress will ensure the conclusions of the following chapters can be made with confidence, with a robust understanding of the risk of bias due to conflating elements of psychological and physical well-being.

The HADS is a commonly used measure of psychological distress designed for use in patient populations. Numerous studies examining its construct validity using exploratory (EFA) and confirmatory (CFA) factor analytic and item response theory (IRT) techniques in various clinical and non-clinical populations have been published. Furthermore, several reviews of these psychometric studies have been undertaken (Bjelland, Dahl, Haug, & Neckelmann, 2002; Herrmann, 1997; Martin, 2005). However, disagreement concerning the underlying dimensionality of the HADS remains (c.f. Bjelland et al., 2002; Martin, 2005).

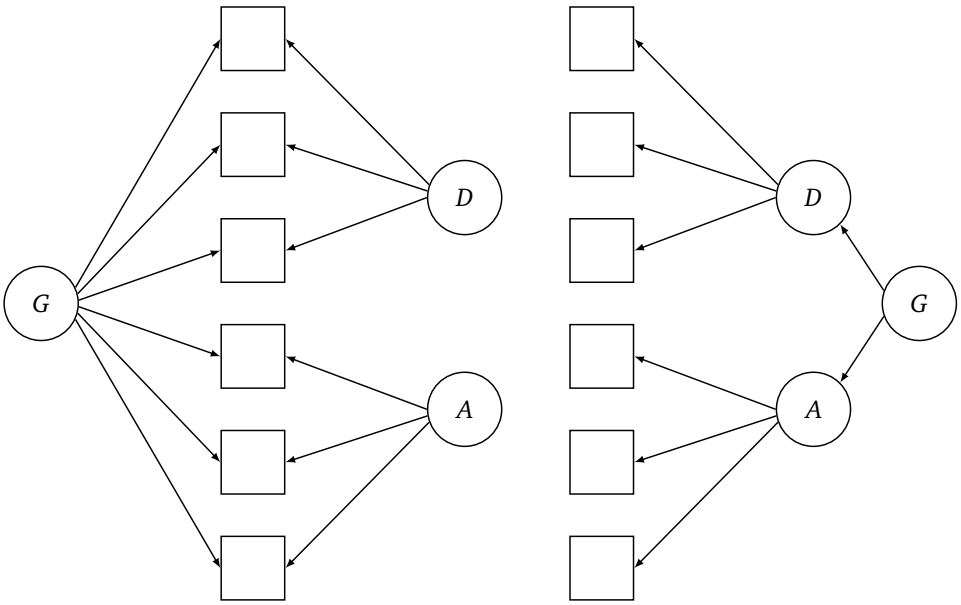
EFA studies generally support an obliquely rotated two-factor anxiety-depression model underlying the HADS (e.g. Bjelland et al., 2002; Moorey et al., 1991; Pallant & Bailey, 2005). However, CFA studies

find that such a model fits poorly to the data, generally finding superior fit for a three-factor solution with the anxiety sub-scale split into two separate, but highly correlated, factors (Caci et al., 2003; Desmond & MacLachlan, 2005; Dunbar, Ford, Hunt, & Der, 2000; Friedman, Samuelian, Lancrenon, Even, & Chiarelli, 2001; Johnston, Pollard, & Hennessey, 2000; Martin, 2005; Martin, Lewin, & Thompson, 2003; McCue, Buchanan, & Martin, 2006; Rodgers, Martin, Morse, Kendell, & Verrill, 2005). These have been labelled anxiety and negative affectivity (NA), as per the tripartite theory of depression (Clark & Watson, 1991).

The tripartite theory posits that the association observed between anxiety and depression is accounted for by a higher-order NA factor. NA has been described as a 'general trait of somatopsychic distress' (Watson & Pennebaker, 1989, p.248) that subsumes a wide range of negative emotions, which as well as anxiety and depression, includes anger, disgust, and guilt (Watson & Clark, 1984). Furthermore, the Tripartite theory stipulates that the specific component of anxiety is autonomic arousal marked by somatic symptoms, and that the prevailing component of depression is anhedonia characterized by low positive affectivity-a loss of pleasure and interest in life (Clark & Watson, 1991). As was noted by Dunbar et al. (2000) several of the HADS items would appear to fit these constructs well.

Recently, several IRT studies have indicated that the anxiety and depression scales may be combined into a single unidimensional psychological distress scale—presumably due to the high inter-factor correlations (Forjaz, Rodriguez-Blazquez, & Martinez-Martin, 2008; Pallant & Tennant, 2007; Tang, Wong, Chiu, Lum, & Ungvari, 2008; Tang, Wong, Chiu, & Ungvari, 2007). The differences in the dimensionality suggested by these methods is interesting as the number of factors is stable within methodologies, but not across.

One possible explanation for the ambiguity between studies applying different methodologies is the presence of a general factor. Two alternative models—higher-order and bifactor—have been proposed to represent the factor structure of scales with a general factor (Figure 5.1). Higher-order models are composed of first-order factors onto which the observed items load, and higher-order factors onto which the first-order factors load. The higher-order factors are causal determinants of the lower-order factors accounting for the correlation between the first-order factors, only influencing the observed variables indirectly. The three-factor models often explain the HADS factor structure in terms of the tripartite theory of depression, suggesting a possible higher-order NA factor (e.g. Dunbar et al., 2000). The bifactor model consists of general (e.g. psychological distress) and specific components (e.g. anxiety and depression). Also known as group-factor models, bifactor models were initially developed in intelligence research (Schmid & Leiman, 1957) but have recently been applied to the study of psychological distress,



(a) Bifactor **(b)** Higher-order

Figure 5.1: Representations of a bifactor and higher-order model

for example the Beck Depression Inventory (Ward, 2006; Thombs, Ziegelstein, Beck, & Pilote, 2008; Chilcot et al., 2011)[1], the combined pool of items from the Beck Depression Inventory and Beck Anxiety Inventory (Steer, Clark, Beck, & Ranieri, 1999), the Depression Anxiety and Stress Scale (Crawford & Henry, 2003) and, pertinently, to extend the tripartite theory (Simms, Gras, Watson, & O'Hara, 2008; T. A. Brown et al., 1998; Krueger & Finger, 2001). Currently no studies have applied a bifactor model to the HADS.

As well as issues with dimensionality, there are concerns with *measurement equivalence*. This relates to the extent to which comparisons across groups (e.g. defined by age, gender, disease etc.) represent *real* differences on the underlying construct, or are an artifact of the measurement process, such as differing interpretations of an item. That is, individuals with equivalent true scores should have the same probability of a particular observed score on a test (Meredith, 1993). Several studies have used CFA to compare the fit of different models across groups (Matsudaira et al., 2009; Johnston et al., 2000; Martin, Thompson, & Barth, 2008). This is termed *configural invariance*, and discussed further in section 5.3.3. Only two studies have directly assessed measurement equivalence of the HADS by examining for differential functioning of individual items across groups: comparing females with breast cancer to females in the general population (Osborne, Elsworth, Sprangers, Oort, & Hopper, 2004), and examining differences across demographic and disease activity groups in end-stage renal disease (Tang

[1] See appendix A

et al., 2008). Currently no studies have assessed measurement equivalence of the HADS in patients with a rheumatological condition, and none have employed multiple group CFA (MG-CFA), which allows for a more detailed examination of differential item functioning (DIF) (Millsap & Yun-Tein, 2004). This is particularly important given concerns about bias due to the content of some of the HADS items tapping into the somatic symptoms of RA (Pincus et al., 1996).

The aim of the current chapter is to examine the psychometric properties of the HADS in patients with RA, focusing on (i) dimensionality and (ii) measurement equivalence. Exploratory and confirmatory factor analysis will be employed to examine the dimensionality of the HADS, and compare the fit of several models indicated by previous research, as well as assessing the fit of a bifactor model. In addition, measurement equivalence will be assessed within RA by examining differential item functioning across demographic and clinical variables. Furthermore, MG-CFA models will be employed to assess measurement equivalence across chronic physical illnesses, specifically RA, renal failure and cancer, and also the stability of measurement over time within RA. The latter is pertinent to Chapter 6 where latent growth models, which assume measurement equivalence over time, are employed.

5.2 Methods

5.2.1 Sample

The data used in the analysis consists of a sub-sample of the Early RA Study (ERAS). ERAS is a multicentre prospective observational study that recruited nearly 1500 individuals with RA on first presentation to a rheumatologist, prior to the initiation of disease modifying therapy. Greater detail regarding the design of ERAS is provided in Chapter 6 and Appendix D. Individual HADS item scores, rather than sum-scores, were available for patients attending the Winchester centre only ($N = 279$). Of these patients, HADS data were never collected, or individual HADS scores were not available, for 119 individuals. For the remaining 160 individuals, one observation per individual was selected at random for the present analysis.

5.2.2 Hospital Anxiety & Depression Scale

The HADS is a self-administered scale consisting of 14-items split equally across anxiety and depression sub-scales, each with a four-point ordinal response format. To reduce the risk of a false positive bias, the scale does not assess somatic symptoms of anxiety and depression related also to physical disorder, such

as fatigue and insomnia.[2] Furthermore, severe psychopathological symptoms uncommon in nonpsychiatric patients, such as suicidality, are also not assessed. A copy of the HADS is provided in Appendix F.

The HADS has been shown to have adequate diagnostic accuracy. In their review, Bjelland et al. (2002) reported that the optimal cut-off for both the anxiety and depression scales was a score of 8 or more, across 12 studies of non-cancer medical populations (anxiety: mean sensitivity .90 [range .82, .94], mean specificity .78 [range .73, .94]; depression: mean sensitivity .83 [range .70, 1.00], mean specificity .79 [range .68, .91]). Furthermore, the same review found the HADS to have good concurrent validity, correlating highly with other measures of depression, anxiety and psychological distress. The range of correlations between the depression scale with the Beck Depression Inventory, General Health Questionnaire (GHQ-28), Symptom Check List (SCL-90) Depression scale and the Montgomery Asberg Depression Rating Scale (MADRS) were .50 to .81. For the anxiety scale, correlations with the State-Trait Anxiety Inventory (STAI), GHQ-28, SCL-90 Anxiety scale, and the Hamilton Anxiety Rating Scale (HAM-A) ranged between .34 and .81 (Bjelland et al., 2002).

5.2.3 Disease severity measures

Functional disability was operationalised using the UK version of the Health Assessment Questionnaire (HAQ) disability index (Kirwan & Reeback, 1986). The HAQ consists of 20 items concerning the respondents ability to complete certain activities of daily living (dressing & grooming, arising, eating, walking, hygiene, reach, grip and activities). Scores range between 0 and 3 with higher values indicating greater disability. Generally scores greater than 1 indicate that an individual has moderate disability, and above 2 severe disability although specific cut-offs have not been defined. Since the distribution of HAQ disability was positively skewed scores were square-root transformed for analysis.

Disease activity was assessed using the original Disease Activity Score (DAS; van der Heijde et al., 1990), a composite measure including a blood marker of inflammation—erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP)—plus separate counts of the tenderness (TJC) and swelling (SJC) of 44 specific joints (mainly of the hands, feet and wrists). Scores over 5 suggest high disease activity and scores less than 3 low disease activity.[3]

[2] Pincus et al. (1996) note that item D8 *"I feel slowed down"* should probably have been omitted from the scale based on this criteria.

[3] A DAS score of less than 1.6 corresponds to the American Rheumatology Association preliminary criteria for clinical remission (Fransen et al., 2004).

5.2.4 Statistical Analysis

There were relatively few missing responses across the HADS items for the RA sample. In total 152 (95%) of the sample had no missing item responses, four individuals had one missing response, two individuals two missing responses, one individual four missing responses and one with 6 missing responses. These were imputed using a single run of the `ice` module in Stata 10.1 (Royston, 2004). `ice` imputes responses using chained equations via Gibbs sampling, a Markov Chain Monte Carlo procedure. As the HADS response format is polytomous ordinal logistic regression models were used. This approach is acceptable when the correlations between the imputed variables are being generated (Graham, 2009).

EFA and CFA were undertaken in M*plus* 5.1 using robust weighted least squares estimation (WLSMV; B. Muthén, 1984; B. Muthén et al., 1997). This estimator was described in section 4.2.3. Briefly, WLSMV is an appropriate estimator for indicator variables with an ordinal response format. Its properties have been observed to be acceptable in a simulation study assessing similar sample size to that of the current analysis (Flora & Curran, 2004). The best fitting model was selected using conventional indices for assessing goodness-of-fit of the model to the data: χ^2 test of exact fit, root mean square error of approximation, Tucker-Lewis Index (TLI), and Comparative Fit index (CFI).[4] To aid model comparison the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) derived using maximum likelihood (ML) estimation are also presented.[5]

The models compared consisted of one-, two-, and three-factor models listed below with the loading patterns provided in Table 5.1.

[4] See section 4.2.2 for details of the assessment of model fit in latent variable models.

[5] The value of χ^2 is known to be inflated for ML with ordinal indicators, and will be further exaggerated by increasing model complexity (P. Curran, West, & Finch, 1996). Since the information criterion are related to χ^2, some caution must be taken in their interpretation. However, their use for pragmatic reasons remains important as both AIC and BIC penalise for model complexity and help avoid problems of over-fitting by using conventional goodness of fit indices only.

One-factor models:

1. Unidimensional general psychological distress factor with loadings held constant—equivalent to the one-parameter normal ogive model and comparable to the models estimated by studies of the HADS employing IRT Rasch analysis (Pallant & Tennant, 2007; Tang et al., 2007; Forjaz et al., 2008)
2. Unidimensional general psychological distress factor with loadings freely estimated (Razavi, Delvaux, Farvacques, & Robaye, 1990)—equivalent to the two-parameter normal ogive IRT model (see Takane & de Leeuw, 1987).

Two-factor models:

3. Original oblique anxiety-depression factorization based on Zigmond and Snaith (1983)
4. Two oblique anxiety depression factors with item A7 revised to load on the depression factor (Moorey et al., 1991)

Three-factor models:

5. Tri-dimensional model based on the Tripartite theory of anxiety and depression (Clark & Watson, 1991), several items forming a separate, theoretically hierarchical, NA factor (Dunbar et al., 2000). This is a special case of a hierarchical model referred to as an incomplete hierarchical model (F. F. Chen, West, & Sousa, 2006).
6. Tri-dimensional model consisting of a depression factor and with the anxiety factor subdivided into psychic anxiety and psychomotor agitation factors (Friedman et al., 2001)
7. Tri-dimensional model consisting of a depression factor and with the anxiety factor containing a separate restlessness factor (Caci et al., 2003)
8. A bifactor model, which consists of a general factor as well as (orthogonal) anxiety and depression factors

5.3 Results

5.3.1 Descriptive statistics

Table 5.2 shows the descriptive statistics for the sample at the baseline assessment. The proportion of females in the subsample was roughly two-thirds, reflecting the distribution in the full ERAS sample and the RA population in general. Age at onset and functional disability (HAQ) at baseline were similar and not significantly different from the rest of the ERAS cohort. However, disease activity as indicated by the DAS score was significantly higher in the sub-sample.

Table 5.1: Loading patterns for each of the eight dimensional structures proposed to underly the HADS

Model	Params	Factor	Item loadings
1. Pallant and Tennant (2007)	43	General distress*	A1, A3, A5, A7, A9, A11, A13, D2, D4, D6, D8, D10, D12, D14
2. Razavi et al. (1990)	56	General distress	A1, A3, A5, A7, A9, A11, A13, D2, D4, D6, D8, D10, D12, D14
3. Zigmond and Snaith (1983)	57	Anxiety	A1, A3, A5, A7, A9, A11, A13
		Depression	D2, D4, D6, D8, D10, D12, D14
4. Moorey et al. (1991)	57	Anxiety	A1, A3, A5, A9, A11, A13
		Depression	D2, D4, D6, A7, D8, D10 ,D12, D14
5. Friedman et al. (2001)	59	Anxiety	A3, A5, A9, A13
		Agitation	A1, A7, A11
		Depression	D2, D4, D6, D8, D10, D12, D14
6. Caci et al. (2003)	59	Anxiety	A1, A3, A5, A9, A13
		Restlessness	A7, A11, D14
		Depression	D2, D4, D6, D8, D10, D12
7. Dunbar et al. (2000)	59	Anxiety	A3, A9, A13
		Depression	D2, D4, D6, A7, D8, D10, D12, D14
		NA	A1, A5, A7, A11, A**, D**
8. Bifactor	70	Anxiety	A1, A3, A5, A7, A9, A11, A13
		Depression	D2, D4, D6, D8, D10, D12, D14
		General distress	A1, A3, A5, A7, A9, A11, A13, D2, D4, D6, D8, D10, D12, D14

* Equality constraint on factor loadings; ** A and D represent the latent factors loading onto the higher-order NA factor.

Table 5.2: Baseline characteristics of the sample compared to the ERAS cohort

	ERAS ($n = 1460$)		Sub-sample ($n = 160$)		significance
	Mean	SD	Mean	SD	
Female	66%		69%		$\chi^2(1) = .727, p = .394$
Age at onset (yrs)	55.34	14.61	56.48	14.12	$t(1458) = .94, p = .350$
HAQ disability (0-3)	1.15	0.77	1.09	0.74	$t(1458) = .93, p = .351$
DAS (0-10)	4.22	1.63	5.03	1.82	$t(1458) = 5.85, p < .001$

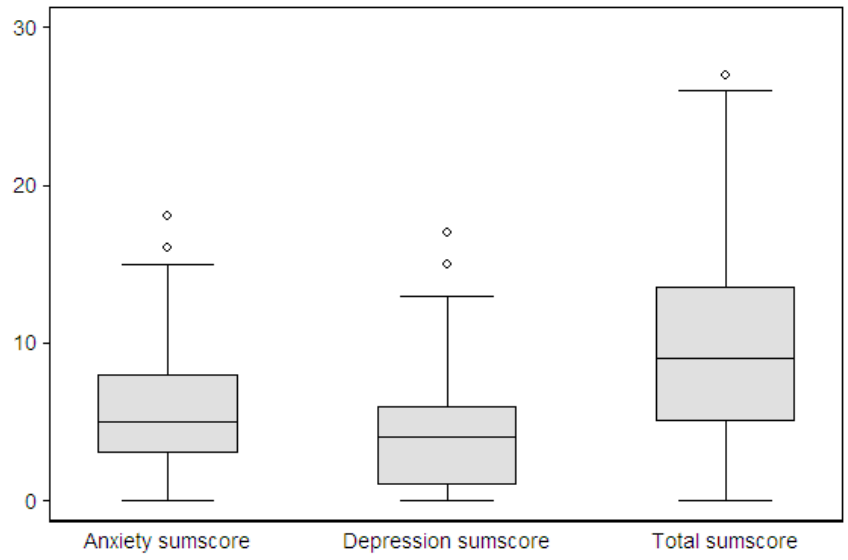


Figure 5.2: Box-plot of HADS scores

The mean age at onset was 56-years corresponding to a mean age at the assessment of 62-years, comparable with the rest of the ERAS cohort. Levels of functional disability at baseline, assessed by the HAQ, were also similar to the remainder of the ERAS cohort.

As was noted earlier, one record from the ERAS yearly assessments was selected at random for inclusion in the psychometric analysis. For these randomly selected assessments the average disease duration was 6.24-years (*SD* 4.19), HAQ disability was .83 (*SD* .77), and DAS was 3.70 (*SD* 2.18). The mean values of the HADS anxiety and depression scales were 5.8 (*SD* 3.7) and 4.4 (*SD* 3.2), respectively. Using the caseness criteria of a score greater than eight indicating psychopatholgy, 43 (27%) fulfilled the criteria for anxiety disorder and 23 (14%) fulfilled the criteria for depressive disorder. The distribution of scores is presented in Figure 5.2.

The individual HADS item responses were generally positively skewed, with scores of 2 or 3 relatively uncommon for most items (Figure 5.3). Means[6] and median values are presented in Table 5.3. On the whole anxiety items were more likely to be responded to at higher response categories (e.g. 2 or 3). Although the item most likely to be reported at higher levels was D8 *"I feel as if I am slowed down"*, with a mean of 1.58, all other items had values of 1 or lower. This resonates with the earlier suggestion of possible bias relating to this item in a similar population (Pincus et al., 1996). The item with the lowest mean value was D4 *"I can laugh and see the funny side of things"*, which was almost identical to D6 *"I feel cheerful"* and D14 *"I can enjoy a good book or radio or TV programme"*.

Due to the polytomous response format of the HADS items, polychoric correlations were calculated

[6]In classical test theory means of Likert scored items represents the items difficulty.

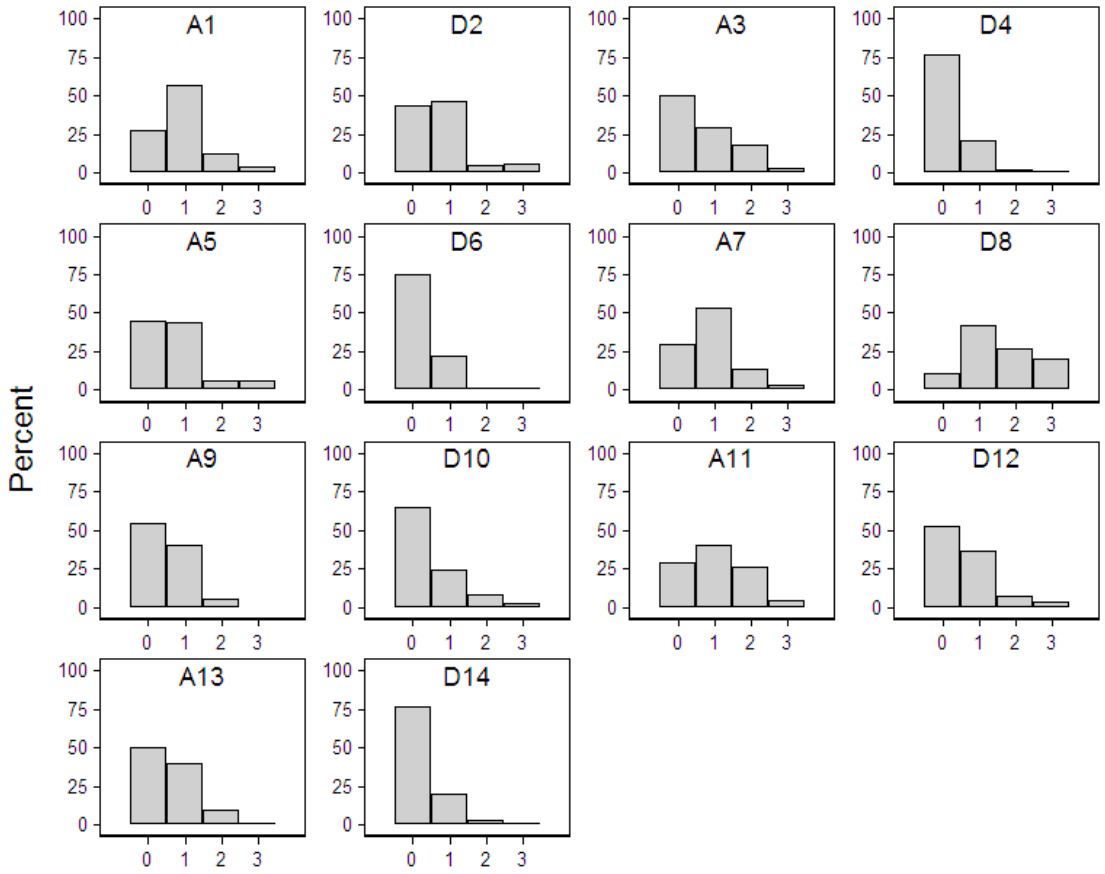


Figure 5.3: Distribution of scores across individual HADS items

Table 5.3: Descriptive statistics for HADS items

	Mean	*Median*
A1	0.93	1.00
D2	0.72	1.00
A3	0.75	1.00
D4	0.27	0.00
A5	0.73	1.00
D6	0.29	0.00
A7	0.90	1.00
D8	1.58	1.00
A9	0.51	0.00
D10	0.48	0.00
A11	1.06	1.00
D12	0.57	0.00
A13	0.61	0.50
D14	0.27	0.00

(Table 5.4). Correlations were generally moderate to high, ranging from .17 to .85. As would be expected anxiety items were generally more highly correlated with other anxiety items compared to depression items, and vice versa.

Classical item analysis of the HADS indicated that including all items in a single analysis—therefore assuming that the items measure a single unidimensional construct—resulted in a relatively high Cronbach's α, .87.[7] The item-rest correlations range between .41 and .66, and the item-total correlations .48 to .72. Moreover, Cronbach's α would have remained stable were any of the items removed.

Considering only the depression items the scale had adequate internal consistency, Cronbach's α was .81. The item-total correlations were .51 to .82, and the item-rest correlations .37 to .73. D14 "*I can enjoy a good book or radio or TV programme*" did not appear to add to the reliability of the scale, but was not detrimental either.

For the anxiety items the internal consistency was again good, Cronbach's α, .83. The item-total correlations were relatively high, .59 to .81; and the item rest-correlations were also high. Again, the reliability of the scale was fairly stable were any of the items to be removed, although A7 and A11 appeared to add little.

To summarise, the reliability of the HADS, according to classical test theory was good. The reliability of the anxiety and depression sub-scales were both greater than .8, which is broadly comparable to previous research (Bjelland et al., 2002). Furthermore, the use of the total sumscore is indicated as being appropriate, all items show relatively high correlations with the total score.[8] This supports the findings of previous research employing Rasch analysis (Forjaz et al., 2008; Pallant & Tennant, 2007; Tang et al., 2008, 2007), however dimensionality needs to be further assessed using factor analytic techniques. This is addressed in the following section.

5.3.2 Dimensionality

5.3.2.1 Exploratory factor analysis

Inspection of the Kaiser-Meier-Olkin (KMO) measure of sampling adequacy indicated that the correlation matrix was suitable for factorization. The lowest value was .70 for A9, well within the acceptable range (Kaiser, 1974). The overall statistic, .83, corresponded to a classification of the suitability of the correlation matrix for factorization as 'meritorious'.

[7] Cronbach's α is a measure of internal consistency that may be interpreted as the lower bound of the reliability of the test. Values greater than .7 are suggested as indicating acceptable reliability (Nunally & Bernstein, 1994).

[8] The higher value Chronbach's α for the total, compared to anxiety and depression sub-scales, is likely an artifact due to its relationship with test length—the Spearman-Browne prophecy

Table 5.4: Polychoric correlation matrix of HADS items

	A1	A3	A5	A7	A9	A11	A13	D2	D4	D6	D8	D10	D12	D14
A1	1.00													
A3	0.54	1.00												
A5	0.67	0.63	1.00											
A7	0.59	0.41	0.44	1.00										
A9	0.48	0.78	0.62	0.34	1.00									
A11	0.44	0.39	0.42	0.48	0.37	1.00								
A13	0.70	0.71	0.72	0.41	0.85	0.44	1.00							
D2	0.47	0.30	0.41	0.49	0.29	0.40	0.40	1.00						
D4	0.61	0.50	0.48	0.68	0.42	0.34	0.47	0.72	1.00					
D6	0.61	0.45	0.58	0.50	0.41	0.22	0.43	0.46	0.63	1.00				
D8	0.58	0.32	0.46	0.49	0.29	0.50	0.41	0.81	0.63	0.32	1.00			
D10	0.35	0.38	0.40	0.51	0.17	0.22	0.21	0.57	0.56	0.49	0.49	1.00		
D12	0.57	0.46	0.51	0.63	0.43	0.41	0.42	0.77	0.80	0.64	0.64	0.66	1.00	
D14	0.40	0.25	0.33	0.66	0.19	0.29	0.23	0.40	0.50	0.48	0.29	0.34	0.49	1.00

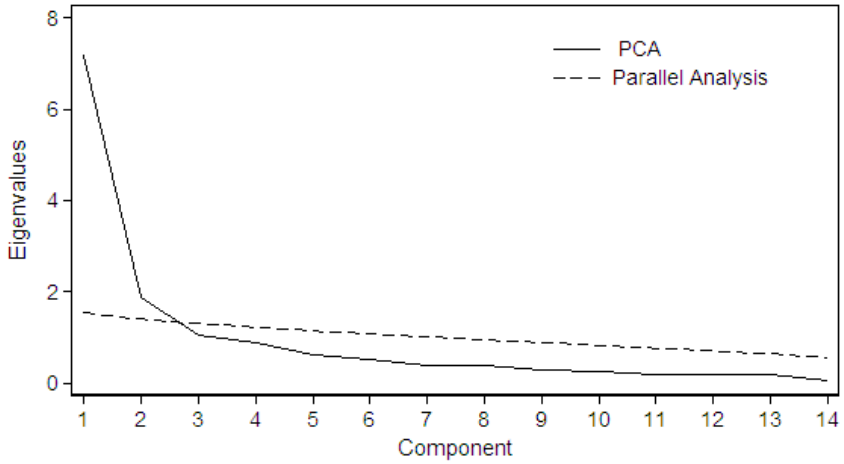


Figure 5.4: Parallel analysis for principle components averaged over 1000 replications

Principle components analysis of the polychoric correlation matrix was undertaken to identify the number of factors that should be extracted. The Kaiser criterion—extracting as many factors as there are Eigenvalues above 1—indicated the extraction of the first three principle components. However, parallel analysis using 1000 randomly drawn samples indicated that the Eigenvalue for the third component was lower than would be expected by chance (Figure 5.4), suggesting only two factors should be extracted.[9]

EFA initially suggested a general psychological distress factor upon which all items loaded >.4, and a depression group-factor onto which all of the depression items and A7 *"I can sit at ease and feel relaxed"* loaded >.4. Factor loadings are displayed in Table 5.5. The fit of the model was borderline acceptable (RMSEA = .090; CFI = .984; TLI = .977).

In order to try to extract a simple structure from the pattern of loadings an oblique geomin rotation was applied. Using an oblique rotation allows the two factors to correlate, as we would reasonably expect for the latent constructs of anxiety and depression. After rotation, the items fitted the structure as would be expected. All of the depression items loaded onto a single factor, along with two of the items from the anxiety scale, A1 and A7—the former being a double loading. Only five of the seven anxiety items loaded onto the anxiety scale. A7 loaded only onto the depression factor and A11 loaded weakly and equally on both the anxiety and depression scales.

For the rotated solution, the correlation between the two factors was .51, which is comparable to what has been previously reported (Bjelland et al., 2002; Herrmann, 1997). After oblique rotation

[9]This third factor was consistent with the third factor described by (Martin, 2005), as A7 and D14 only loaded on this factor. Previous EFA studies that have found a three-factor solution may have extracted too many factors due to reliance on the Kaiser criterion (Preacher & MacCallum, 2003)

Table 5.5: Exploratory factor analysis

	Unrotated		Rotated		Uniqueness	Structure matrix	
	Factor 1	Factor 2	Factor 1	Factor 2		Factor 1	Factor 2
A1	0.76	0.14	0.41	0.50	0.36	0.67	0.76
A3	0.78	-0.14	0.06	0.78	0.34	0.48	0.82
A5	0.77	-0.06	0.25	0.64	0.37	0.55	0.75
A7	0.59	0.42	0.64	0.16	0.46	0.72	0.44
A9	0.83	-0.32	-0.14	0.95	0.15	0.32	0.94
A11	0.48	0.12	0.36	0.27	0.70	0.48	0.46
A13	0.92	-0.33	0.00	0.92	0.16	0.42	0.96
D2	0.56	0.57	0.94	-0.14	0.23	0.81	0.36
D4	0.70	0.51	0.80	0.11	0.25	0.88	0.51
D6	0.63	0.35	0.48	0.30	0.53	0.64	0.55
D8	0.49	0.49	0.81	-0.03	0.37	0.75	0.36
D10	0.44	0.53	0.71	-0.06	0.54	0.65	0.31
D12	0.66	0.61	0.85	0.06	0.22	0.81	0.43
D14	0.44	0.40	0.56	0.03	0.67	0.54	0.34

the factors loadings no longer represent the correlations between the items and the underlying factors therefore the structure matrix, the correlations between the items and the factors is also presented in table 5.5. For the depression factor each of the depression items correlations with the factor ranged between .54 and .88. Furthermore, A1 and A7 correlated highly with the depression factor, .67 and .72 respectively. The anxiety item correlations with the anxiety factor ranged between .44 and .96. As would be expected with strong inter-factor correlations each item correlates fairly highly on the opposing factor (range .29 to .73).

In summary, the initial solution indicated a general psychological distress factor with a depression group-factor. However, following oblique rotation the anxiety-depression factor structure emerged (Bjelland et al., 2002). As with previous research item A7 was observed to load more strongly on the depression scale than the anxiety scale (Moorey et al., 1991).

5.3.2.2 Confirmatory factor analysis

While the results of the EFA presented here replicate the findings of studies employing similar methods, recent CFA research indicates a three-factor solution. CFA analysis allows for the direct comparison of the fit of these models. Eight plausible models were tested (Table 5.6).

One-factor models The initial model fitted to the data was the one-parameter normal ogive model, this is a unidimensional model with all parameter loadings held equal (Model 1). It is analogous to

Table 5.6: Goodness of fit statistics for CFA models

Model	χ^2	df	p	CFI	TLI	RMSEA	WRMR	AIC	BIC
1-factor									
1	164.4	28	0.000	0.85	0.91	0.17	1.93	3403.0	3400.4
2	155.9	25	0.000	0.85	0.91	0.18	1.56	3396.7	3392.9
2-factor									
3	107.7	26	0.000	0.91	0.94	0.14	1.25	3303.1	3299.2
4	84.6	26	0.000	0.94	0.96	0.12	1.11	3280.2	3276.3
3-factor									
5	64.2	27	0.000	0.96	0.98	0.09	0.91	3256.0	3253.9
6	74.5	27	0.000	0.95	0.97	0.11	0.98	3263.6	3259.5
7	77.8	26	0.000	0.94	0.96	0.11	1.03	3270.0	3266.0
8	40.7	26	0.033	**0.98**	**0.99**	**0.06**	**0.62**	**3241.5**	**3236.4**
Final	37.5	26	0.068	0.99	0.99	0.05	0.63	*	*

* Information criterion not computable for final model due to conditional independence assumption

the Rasch model fitted by the IRT papers (Forjaz et al., 2008; Pallant & Tennant, 2007; Tang et al., 2008, 2007). Although in these papers fit was adequate, here it was poor. The test of (non) exact fit is highly significant and the χ^2:df ratio large, indicating the test was not significant simply because it was overpowered. Furthermore, the fit statistics indicate that the degree of ill fit is quite large, with all outside acceptable fit levels.

Model 2 frees the factor loadings resulting in a significantly improved fit , $\chi^2_{\text{DIFFTEST}}(10) = 52.8, p < .001$, although the test of exact fit remained highly significant and the fit statistics outside acceptable limits. The BIC and the AIC also favoured the more complex Model 2.

Two-factor models The two two-factor models exhibited better fit to the data than the one-factor models however there was still significant ill fit. Models 3, the original Zigmond and Snaith (1983) formulation, showed worse fit compared to Model 4, which loaded A7 on the depression rather than anxiety sub-scale.

Three-factor models Four three-factor models were compared. Three of which, Models 5, 6 and 7, split the anxiety sub-scale into two factors. Model 8, a bifactor model, includes a general psychological distress factor as well as specific depression and anxiety factors. Notably, Model 5, based on the tripartite theory of depression includes a higher-order negative affectivity factor—in an incomplete hierarchical model (F. F. Chen et al., 2006). All of the three-factor models show better fit than the two and one-factor models. The goodness of fit statistics were optimal for Model 8, the bifactor model. This was supported by values of the AIC and BIC.

Final model Modifications were made to the bifactor model, Model 8, by excluding items that either did not load significantly onto the general or specific factors, furthermore modification indices were inspected and additional paths and residual correlations included where necessary. Parameter estimates are given in Table 5.7. All factor loadings on the general factor were retained. However, for the anxiety factor the loadings of A7 and A11 were non-significant and therefore removed. For the depression factor, the loadings for D6 and D14 were non-significant and also removed. Furthermore, modification indices suggested adding a residual correlation between D2 and D8. Including this path in the model significantly increased the fit of the model. Although, modification indices suggested additional residual correlations their inclusion did not improve the fit of the model values of these were less than 10 and were ignored to avoid over-fitting. The final model fitted the data well. The test of exact fit was non-significant and all measures of goodness of fit were within acceptable levels.

The general psychological distress factor explained the largest amount of the common variance (69%). The anxiety and depression group-factors were associated with relatively modest contributions to the total common variance, accounting for 17% and 13%, respectively. Furthermore, the proportion of test variance due to the general factor, ω_h, is 44%, indicating that the saturation of the HADS by the general factor is high. Item communalities ranged from 35% for A11 *"I feel restless as if I have to be on the move"* to 87% for D12 *"I look forward with enjoyment to things"*.

In conclusion, the comparison of several plausible factorizations of the underlying constructs relating to the HADS items reveals superior fit for the bifactor model. While the fit of models 5, 6 and 7 was within acceptable limits, and similar to that reported by previous CFA studies (Martin, 2005), the bifactor model produced a lower χ^2 statistic and was supported by both the AIC and BIC despite the increased model complexity.

5.3.2.3 Comparison of predicted and sumscores

In order to gauge what the general factor underlying the HADS items relates to, and to assess the magnitude of the distortion when using the HADS as a unidimensional rather than multidimensional scale, the predicted factor scores from the bifactor model were compared to the observed sumscores. The correlations between the factor scores and sumscores and are displayed in Table 5.8. The correlation between the anxiety factor and sumscore was high ($r = .50$), as was the correlation between the depression factor and sumscore ($r = .64$). However, both the anxiety and depression sumscores were more highly correlated with the general distress factor ($r = .87$ and .82, respectively), although not as highly as the total sumscore ($r = .95$). As expected the correlations between the factors are low (i.e. they are

Table 5.7: Estimated factor loadings and thresholds for bifactor model

		Factor			Threshold	
		G	A	D	0-1	1-2/3
A1	I feel tense or wound up	0.77	0.27		-0.60	0.98
A3	I get a sort of frightened feeling as if something awful is about to happen	0.56	0.60		-0.03	0.80
A5	Worrying thoughts go through my mind	0.67	0.43		-0.13	1.18
A7	I can sit at ease and feel relaxed	0.79			-0.52	0.96
A9	I get a sort of frightened feeling like butterflies in the stomach	0.47	0.82		0.08	1.65
A11	I feel restless as if I have to be on the move	0.59			-0.52	0.51
A13	I get sudden feelings of panic	0.59	0.70		0.00	1.21
D2	I still enjoy the things I used to enjoy	0.63		0.55	-0.17	1.25
D4	I can laugh and see the funny side of things	0.80		0.36	0.71	1.96
D6	I feel cheerful	0.74			0.67	1.96
D8	I feel as if I am slowed down	0.65		0.28	-1.18	0.08
D10	I have lost interest in my appearance	0.54		0.43	0.39	1.25
D12	I look forward with enjoyment to things	0.78		0.51	0.09	1.32
D14	I can enjoy a good book or radio or TV programme	0.59			0.74	1.86

Note: G = General distress; A = Anxiety; D = Depression

orthogonal).

These observations suggest that factor scores should be utilised in future research. Where this is not possible, the use of the total score is more advisable than the anxiety and depression sumscores by themselves. To be sure, the correlations do indicate that the anxiety and depression sumscores do relate the the underlying constructs. However, using the sumscores of the separate subscales will not differentiate between the specific elements of anxiety and depression from general distress, due to the saturation of the sumscores by the general factor. Further consideration of the nature of the general factor and the HADS total sumscore is provided at the end of this chapter.

5.3.3 Measurement equivalence

Moving forward, the following section tests for measurement equivalence under the assumption that the bifactor model is the correct model. Measurement equivalence relates to the condition where individuals with equivalent true scores would have the same probability of a particular observed score on an associated test (Meredith, 1993). Differences across groups, or time points, thus reflect *real* differences rather than differential item interpretation.

Table 5.8: Pearson correlations between HADS factor and summed scores

		1	2	3	4	5	6
1	Anxiety factor	1.000					
2	Depression factor	-0.148	1.000				
3	General factor	0.098	0.246	1.000			
4	Anxiety sumscore	0.496	0.022	0.872	1.000		
5	Depression sumscore	-0.103	0.640	0.815	0.582	1.000	
6	Total sumscore	0.240	0.353	0.950	0.902	0.876	1.000

Measurement equivalence has been described extensively elsewhere (e.g. Meredith, 1993; Millsap & Yun-Tein, 2004), therefore detailed discussion is not presented here. Briefly, the literature surrounding the HADS generally suggests that it conforms to the assumptions of *dimensional* and *configural* invariance.[10] That is, equal numbers of factors are observed across populations and the same items are observed to load on the same factors. However, this observation does not indicate whether items function the same way across different groups. Where individual items are found to function differently across groups this item bias is often termed differential item functioning (DIF).

5.3.3.1 Differential item functioning across demographic and clinical variables

Within the RA sample DIF for demographic and clinical variables was assessed using multiple-indicator multiple-cause (MIMC) models. This was partly due to the limited sample size. Splitting the sample into groups, for example based on gender, would have meant any MG-CFA would have lacked robustness due to the size of the sub-groups. However, the MIMC approach has the advantage that it allows for the inclusion of continuous independent variables, which meant that continuous variables could be examined without the necessity to split them into groups at some arbitrary point.

MIMC models allow for the estimation of both the direct and indirect (i.e. via the latent construct) effects of a covariate on the item responses. The assumption is that the effect of group on response is fully mediated by the underlying construct—that is, there is no direct effect. If there is a direct effect on an item, the item is said to display DIF. Biased items were identified by the examination of modification indices in models where the latent factors and observed variables were regressed on the demographic and clinical variables, but the parameters for the direct effects of these variables on the observed items was constrained to zero. Items showing DIF were added on a systematic basis using the procedure described by (Saris, Satorra, & Veld, 2009). This involves the examination of the expected parameter change for freely estimating the direct path in combination with the MI and the power of the MI test.

[10] Although differences have been observed across methodologies (c.f. Bjelland et al., 2002; Martin, 2005).

Age Age in years at the time of assessment was included in the model. Age was significantly associated with Depression, $b = 0.032, p = 0.001$, but not the general factor, $b = -0.010, p = 0.143$, or Anxiety, $b = -0.003, p = 0.715$. Examination of the modification indices indicated no problem with DIF in relation to Age.

Gender A dummy coded variable for female gender was included in the model. Females scored significantly higher on the depression, $b = 0.764, p = 0.028$, and anxiety factors $b = 0.831, p < 0.001$, compared to males, but scored lower than males on the G factor, $b = -0.440, p = 0.033$.

Inspection of the modification indices suggested freeing the path from female to D14 *"I can enjoy a good book or radio or TV programme"*. Re-estimating the model with this path freed showed that the path was significantly different from zero, $b = 0.621, p = 0.003$, and significantly improved the fit of the model, $\chi^2(1) = 7.56, p = .006$. This indicates that DIF is present between gender groups for this item. Specifically, females, compared with males at the same level on the general factor, had lower likelihood of responding in the higher categories. Holding the three factors constant at the sample mean, the probability of a male scoring 1 *"Sometimes"* compared to 0 *"Often"* on item D14 was 0.37, as opposed to 0.20 for females. This is displayed graphically in Figure 5.5. This accounts for the differences between the sexes observed on the general and depression factors in the previous model. In the re-estimated model males and females differ significantly only in terms of anxiety, $b = 0.706, p = 0.001$, and not depression, $b = 0.350, p = 0.207$, or general distress, $b = -0.251, p = 0.208$.

Functional limitation HAQ disability was significantly associated with the general factor, $b = 0.505, p = 0.001$, and Depression, $b = 0.737, p < 0.001$, but not Anxiety, $b = -0.019, p = 0.925$. Examination of the modification indices indicated no problem with DIF. The inclusion of direct paths would not result in significant improvement in fit using a likelihood ratio test.

Disease Activity Disease activity, as indexed by the DAS (Prevoo et al., 1995) was entered into the model. Individuals with higher levels of disease activity scored significantly higher on average on the depression factor, $b = 0.270, p < 0.001$, and marginally so on the general factor, $b = 0.095, p = 0.073$, but not on the anxiety factor, $b = 0.057, p = 0.332$.

Inspection of modification indices suggested freeing the path from DAS to item D8, *"I feel slowed down"*. Doing so the parameter estimate was significant, $b = 0.224, p = 0.003$, as was the change in model fit, $\chi^2(1) = 7.35, p = .007$. For item D8, holding the level of underlying psychological distress factors at the mean, the probability of scoring 1 *"Sometimes"* instead of 0 *"Not at all"* was .50 for those

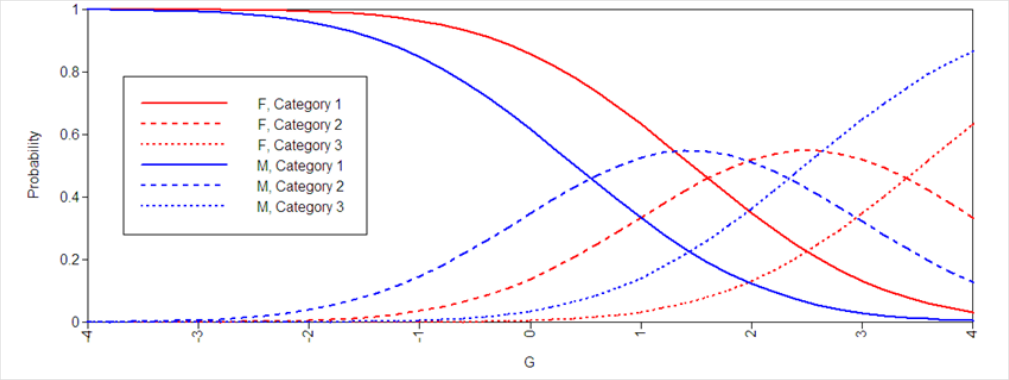


Figure 5.5: Item characteristic curve for D14, by gender

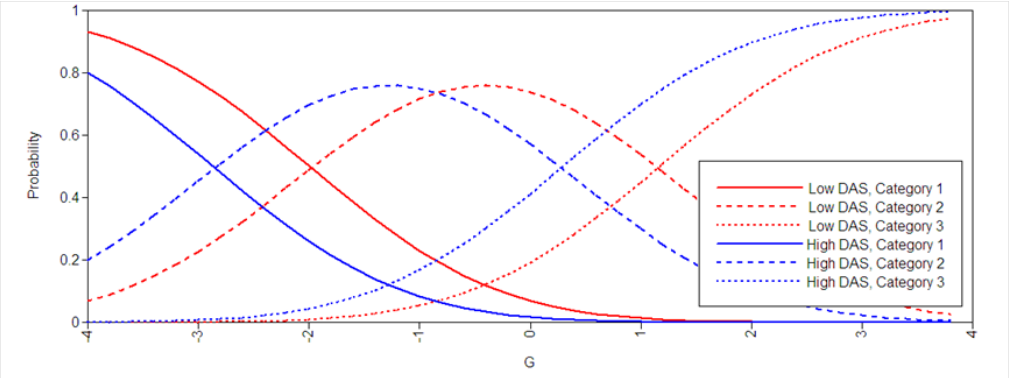


Figure 5.6: Item characteristic curve for D8, by low (mean – .5 *SD*) and high (mean + .5 *SD*) DAS groups

half a *SD* below the mean on DAS, compared to 0.68 for those half a *SD* above the mean (Figure 5.6). Despite the presence of DIF, there was little impact on the interpretation of differences on the anxiety, $b = 0.053, p = 0.364$, depression, $b = 0.200, p = 0.002$, and general distress factors, $b = 0.096, p = 0.060$.

In summary, these analyses, using MIMC models, suggest that concerns regarding item bias due to underlying level of disease severity are unwarranted. Although DIF was observed for disease activity the effect was small, and appears to contribute little to overall scores on the factors. It is unlikely that the bias will have a major impact except for those with extreme levels of disease activity.

A concern relates to linearity. MIMC models assume DIF is equal (uniform) across the distribution of the variable, however it would be plausible for a an increasing effect of the bias at higher levels of disease activity. Greater concern must be given to the finding of DIF for gender, which for D14 loading onto the depression and general factor appeared to account for the difference between the sexes on these two factors

5.3.3.2 Measurement equivalence across chronic physical conditions

The factor structure of the HADS in the RA sample was compared to patients with renal failure (RF) and cancer. The RF sample consisted of the baseline HADS assessment completed by 170 patients enrolled in an observational study being undertaken within the Renal Department at the Lister Hospital, East & North Hertfordshire NHS trust. These patients were, at the time, not receiving dialysis but were expected to require this treatment within the next 12-months. The mean age of the sample was 61.0 (*SD* 16.2), similar to that of the RA sample. The cancer sample consisted of 96 patients attending for PET-CT scans at the Paul Strickland Scanner Centre, Mount Vernon Hospital. The data was collected as part of a student project to investigate predictors of panic attack during a scan. Mean age of the group was slightly younger than the rheumatological sample used in the preceding analysis, at 50.6 years (*SD* 16.1).

CFA assessment of dimensional and configural invariance Separate CFA models were fitted based on the eight models previously assessed (Tables 5.6, 5.9 and 5.10). For dimensional invariance to hold the best fitting model for each group should include the same number of factors. Furthermore, for configural invariance the same model should fit the data best.

For all three groups, the three-factor models show better fit than the two and one factor models. For both the RA and the renal failure groups the goodness of fit statistics was optimal for Model 8, the bifactor model. Furthermore, for the renal failure group the test of exact fit was non-significant. This was supported by values of the AIC and BIC. For the cancer group however, model 5, the Tripartite model (Dunbar et al., 2000), showed the best fit, although little difference in the goodness-of-fit statistics was observed between Models 5 and 8.

For all groups modifications were made to the bifactor model, Model 8, by excluding items that either did not load significantly onto the general or specific factors, furthermore modification indices were inspected and additional paths and residual correlations included where necessary.

For the RA group, as was previously reported, all factor loadings on the general factor were retained, the loadings of items A7 and A11 on the anxiety factor fixed to zero, and the loadings for D6 and D14 on the depression factor were fixed to zero. Furthermore, a residual correlation between D2 and D8 was included. The test of exact fit for this model was non-significant and all measures of goodness-of-fit were within acceptable levels.

Similarly, for both the renal and cancer groups all items loaded significantly on the general factor and were retained, and the loadings for A11 on the anxiety factor were non-significant and thus fixed to

Table 5.9: CFA model fit statistics, renal failure group

Model	χ^2	df	p	CFI	TLI	RMSEA	AIC	BIC
1-factor								
1	142.0	34	0.000	0.82	0.89	0.14	4063	4062
2	112.8	36	0.000	0.87	0.93	0.11	4035	4033
2-factor								
3	74.6	36	0.000	0.94	0.96	0.08	3984	3982
4	78.0	35	0.000	0.93	0.96	0.09	3990	3989
3-factor								
5	61.8	35	0.003	0.96	0.97	0.07	3971	3969
6	59.7	35	0.006	0.96	0.98	0.06	3965	3964
7	69.0	35	0.001	0.94	0.97	0.08	3978	3976
8	48.3	34	0.053	**0.98**	**0.99**	**0.05**	**3955**	**3953**
Final	43.3	32	0.087	0.98	0.99	0.05	3959	3957

zero. Item A7 loaded non-significantly on the anxiety factor in only the renal failure group. Again for the depression factor, D14 did not load significantly and its loading on the factor were fixed to zero in both the renal and cancer groups. D2 was also excluded in the renal failure group, but not the cancer group. In addition, D4 and D12 were also non-significant in the renal failure group and thus their loadings on the depression factor fixed to zero. D6 was non significant and excluded from loading on the depression factor in the caner group. No residual correlations were included for the renal failure group, but a residual correlation was included between items D4 and A11 in the cancer group. The test of exact fit was non-significant for both groups and all measures of goodness of fit were within acceptable levels.

The final models for each group were similar, although the minor differences observed do pose a threat to the assumption of configural invariance. However, it is conceivable that differences may be a result of over fitting to the data, and particularly for the cancer group may result from random variation due to the relatively small sample sizes.

Multiple group CFA MG-CFA was applied to test the assumption of *strong measurement invariance*. Following the recommended strategy of B. Muthén and Asparouhov (2002)[11]. Initially a baseline non-invariant model was fitted that freely estimated the factor loadings and thresholds followed by an invariant model that constrain the factor loadings and thresholds to be equal across groups. Scale factors[12]

[11] Meredith (1993) suggests testing the equivalence of the factor loadings and intercepts in separate stages (*metric* and *strong* invariance). Millsap and Yun-Tein (2004) proposes a commensurate approach for categorical indicators but convergence problems were encountered for this approach. These issues were likely due to the small sample sizes for each group and limited number of thresholds per item (Bontempo, 2006). The alternative approach proposed by B. Muthén and Asparouhov (2002) combines the tests of *metric* and *strong* invariance, which is defensible since they have a combined impact on the item characteristic function (B. Muthén & Asparouhov, 2002).

[12] Scale factors are used in multiple group analysis when the dependent variables are categorical and a WLSMV estimator is applied. The scale factors account for "across group differences in the variances of the latent response variables for the

Table 5.10: CFA model fit statistics, cancer group

Model	χ^2	df	p	CFI	TLI	RMSEA	AIC	BIC
1-factor								
1	113.6	28	0.000	0.63	0.70	0.18	2358	2340
2	94.4	26	0.000	0.71	0.74	0.17	2335	2310
2-factor								
3	59.5	28	0.001	0.86	0.89	0.11	2272	2247
4	50.7	26	0.005	0.90	0.92	0.09	2264	2239
3-factor								
5	37.0	27	0.094	**0.96**	**0.96**	**0.06**	**2258**	**2231**
6	54.6	28	0.002	0.89	0.91	0.10	*	*
7	47.2	28	0.013	0.92	0.93	0.08	2261	2234
8	39.4	26	0.045	0.94	0.95	0.07	*	*
Final	35.3	26	0.105	0.96	0.96	0.06	**	**

* Information criterion not computable due to non convergence of ML estimation

** Information criterion not computable for final model due to conditional independence assumption of ML

and factor means were fixed at one and zero, respectively, in one group and freely estimated in the others, as is the convention to achieve model identification. Since the invariant model is nested within the baseline model the two can be compared using a χ^2 difference test.

The baseline non-invariant model specified all items to freely load onto a general factor, all depression items except D6 and D14 to load onto a depression factor, and all anxiety items except A7 and A11 to load onto an anxiety factor. In addition, a residual correlation between items D2 and D8 was included, as this was indicated by the CFA of the RA data in section 5.3.2.2 and notably it was significant for RF group although not indicated by modification indices. For the RA and RF groups the test of exact fit was non-significant, $\chi^2_{\text{RA}}(26) = 39.29, p = .057$, $\chi^2_{\text{renal}}(33) = 44.92, p = .094$. However, for the cancer group the test of exact fit was significant, $\chi^2_{\text{cancer}}(25) = 54.65, p < .001$. A requirement for invariance testing is that the baseline model is non-significant (Millsap & Yun-Tein, 2004).

The baseline MG-CFA model showed poor fit to the data, largely due to the contribution of the cancer group to the overall value of the χ^2 statistic (Table 5.11), although fit indices indicate that the degree of misfit is small. The invariance model showed significant worsening of fit, $\chi^2(36) = 84.43, p < 0.001$, and the change in the fit indices of around .02. Inspection of the parameter estimates for the non-invariance model presented in Table 5.13 indicates that this finding is likely to be due to the magnitude of the differences with the cancer group, which showed generally lower factor loadings on the general factor, concurrently higher loadings on the anxiety and depression factors, and differing thresholds (items A1, D2, A3, D8, A9, A11, D12). By contrast, the estimates were largely similar for the RA and RF groups.

observed categorical dependent variables" (p. 395 L. Muthén & Muthén, 2007). This allows for the recovery of across group differences in factor means and variances.

Table 5.11: Multi-group CFA models, RA, RF and cancer groups

Model	χ^2	df	p	CFI	TLI	RMSEA
Non-invariat	128.19	81	0.000	0.98	0.98	0.06
Invariant*	174.92	92	0.000	0.96	0.97	0.08

*$\Delta\chi^2(36) = 84.43, p < 0.001$

Table 5.12: Multi-group CFA models, RA and RF groups only

Model	χ^2	df	p	CFI	TLI	RMSEA
Non-invariant	84.17	58	0.014	0.98	0.99	0.05
Invariant*	97.48	62	0.003	0.98	0.99	0.06

*$\Delta\chi^2(16) = 23.7, p = 0.096$

A biasing factor for the cancer sample may be that the assessment was taken immediately preceding a PET-CT scan. At this time levels of anxiety—particularly symptoms of autonomic arousal that several anxiety items assess—are likely to be raised, and it may be that the test is being influenced to a greater extent by state levels of anxiety than in the RA and renal failure groups. Resultantly, it was deemed appropriate to exclude the cancer group from the analysis and examine measurement invariance across the RA and renal failure groups separately (Table 5.12). The test of exact fit for the non-invariant model remained significant considering only the RA and renal failure groups. However, the fit indices indicated the fit to the data was acceptable. On constraining the factor loadings and thresholds to be equal, the worsening in fit was non-significant, $\chi^2(16) = 23.7, p = 0.096$, and only marginal reduction was observed in the goodness of fit indices.

It would appear that while the assumption of invariant factor loadings and thresholds does not hold when considering the cancer group, this assumption is tenable when considering the RA and RF groups.

5.3.3.3 Measurement equivalence over time

It is important that the HADS actually measure the same underlying latent constructs with time. If not, it may result in comparisons between time points being misleading, as changes, or lack of, may be due to changes in the measurement of the underlying constructs rather than changes in the constructs themselves. Resultantly any longitudinal modelling may be biased.

The HADS sumscores have been found to have good test-retest reliability (Herrmann, 1997), and Osborne et al. (2004) found no evidence for DIF when considering time from diagnosis using a MIMC model approach, however I have found no study reporting an assessment of measurement invariance over time. For the findings of the following chapters to be robust this must be assessed. This section

Table 5.13: Parameter estimates for the non-invariance model for the RA, renal failure (RF) and cancer (CA) groups

		Group	Factor			Threshold	
	Item		G	A	D	0–1	1–2/3
A1	I feel tense or wound up	RA	0.77	0.27		-0.60	0.98
		RF	0.68	0.27		-0.67	0.70
		CA	0.34	0.68		-1.26	0.67
A3	I get a sort of frightened feeling as if	RA	0.56	0.60		-0.03	0.80
	something awful is about to happen	RF	0.52	0.64		-0.25	0.63
		CA	0.24	0.73		-0.85	-0.08
A5	Worrying thoughts go through my mind	RA	0.67	0.43		-0.13	1.18
		RF	0.62	0.48		-0.33	0.63
		CA	0.59	0.61		-1.10	0.21
A7	I can sit at ease and feel relaxed	RA	0.79			-0.52	0.96
		RF	0.83			-0.27	1.02
		CA	0.86			-0.81	0.85
A9	I have lost interest in my appearance	RA	0.47	0.82		0.08	1.65
		RF	0.59	0.64		0.09	1.47
		CA	0.23	0.60		-0.64	1.05
A11	I feel restless as if I have to be on the move	RA	0.59			-0.52	0.51
		RF	0.36			-0.43	0.63
		CA	0.25			-0.97	0.46
A13	I get sudden feelings of panic	RA	0.59	0.70		0.00	1.21
		RF	0.59	0.49		0.06	1.16
		CA	0.45	0.63		-0.55	1.10
D2	I still enjoy the things I used to enjoy	RA	0.63		0.55	-0.17	1.25
		RF	0.54		0.13	-0.59	0.51
		CA	0.31		0.57	-0.16	1.38
D4	I can laugh and see the funny side of things	RA	0.80		0.36	0.71	1.96
		RF	0.75		0.33	0.61	1.67
		CA	0.63		0.26	0.37	1.26
D6	I feel cheerful	RA	0.74			0.67	1.96
		RF	0.79			0.10	1.81
		CA	0.93			0.43	1.45
D8	I feel as if I am slowed down	RA	0.65		0.28	-1.18	0.08
		RF	0.45		0.28	-1.57	-0.24
		CA	0.22		0.32	-1.15	0.16
D10	I have lost interest in my appearance	RA	0.54		0.43	0.39	1.25
		RF	0.52		0.92	0.19	0.91
		CA	0.50		0.40	0.37	1.05
D12	I look forward with enjoyment to things	RA	0.78		0.51	0.09	1.32
		RF	0.71		0.01	0.10	1.08
		CA	0.51		0.65	0.03	1.01
D14	I can enjoy a good book or radio or TV	RA	0.59			0.74	1.86
	programme	RF	0.50			0.68	1.57
		CA	0.63			0.78	1.86

Note: G = General distress; A = Anxiety; D = Depression

Table 5.14: Multi-group CFA models using delta parametrisation

Model	χ^2	df	p	CFI	TLI	RMSEA
Non-invariance	89.36	55	0.002	0.97	0.98	0.08
Invariance	111.12	54	0.000	0.95	0.96	0.10

*$\chi^2(18) = 14.62, p = 0.688$

addressed this issue by considering measurement invariance between the baseline and 1-year follow-up assessments for the members of the ERAS cohort for whom individual item responses were available. As with the previous MG-CFA analysis the procedure described by B. Muthén and Asparouhov (2002) was applied. From the 160 individuals all individuals completing a HADS at either the baseline or 1-year follow-up assessment were used, $N = 100$ and 99 observations respectively (96 at both).[13]

The baseline non-invariant model with the same bifactor structure as described in the previous section was used, again factor loadings and thresholds were freely estimated across the two repeated assessments. Despite the small sample size, the test of exact fit was highly significant, although the CFI and TLI were within acceptable levels (Table 5.14). An invariant model with factor loadings and thresholds constrained to be equal across the two repeated assessments was then estimated. A χ^2 difference test revealed no significant worsening of fit for the invariant model, $\chi^2(18) = 14.62, p = 0.688$, and negligible changes in the fit indices indicating the assumption of measurement invariance holds. However, it is important to be mindful that with such small sample sizes the power to detect meaningful measurement invariance is likely to be low.

Table 5.15 displays the parameter estimates for the non-invariant model. Inspection of these estimates reveals that for the general factor the factor loadings were relatively similar. The trend was for higher values at the second assessment. The differences were larger for the specific factors, indicating a possible issue with measurement invariance when considering the depression or anxiety factors in isolation.

Generally, the threshold parameters were similar, with differences ranging -.39 to +.49 (*NB*. 1 = 1 *SD*). There appeared to be a systematic shift further up the distribution for the second threshold parameter only at the second time point. Fifteen of the 28 threshold parameters changed by less than a fifth of a standard deviation, while six changed by more than a third of a *SD* up the latent construct.

[13] As the HADS was only included in the set of data collected around 1990, HADS scores were not available for those recruited between 1986 and that time. The rationale for using these time-point rather than later time where more data are available is that it is changes early in the course of the disease that are of most importance and it is at that time that the threat to measurement invariance is strongest, for example disease-modifying treatment was typically initiated between these two assessments.

Table 5.15: Parameter estimates for the time non-invariant model

		Time	Factor			Threshold	
	Item		G	A	D	0–1	1–2/3
A1	I feel tense or wound up	Baseline	0.60	0.51		-0.74	1.04
		1-year	0.64	0.42		-0.87	1.22
A3	I get a sort of frightened feeling as if	Baseline	0.66	0.40		0.08	0.92
	something awful is about to happen	1-year	0.78	0.50		0.01	0.94
A5	Worrying thoughts go through my mind	Baseline	0.57	0.52		-0.13	0.84
		1-year	0.67	0.39		-0.01	1.33
A7	I can sit at ease and feel relaxed	Baseline	0.80			-0.92	0.84
		1-year	0.86			-0.43	1.22
A9	I get a sort of frightened feeling like butterflies	Baseline	0.44	0.64		0.20	1.48
	in the stomach	1-year	0.47	0.84		0.03	1.87
A11	I feel restless as if I have to be on the move	Baseline	0.43			-0.44	0.58
		1-year	0.59			-0.45	0.60
A13	I get sudden feelings of panic	Baseline	0.53	0.70		0.13	1.34
		1-year	0.65	0.48		0.08	1.55
D2	I still enjoy the things I used to enjoy	Baseline	0.46		0.36	-0.50	1.13
		1-year	0.49		0.55	-0.16	1.22
D4	I can laugh and see the funny side of things	Baseline	0.85		-0.01	0.61	1.75
		1-year	0.87		0.28	0.76	2.05
D6	I feel cheerful	Baseline	0.76			0.67	1.88
		1-year	0.79			0.90	2.05
D8	I feel as if I am slowed down	Baseline	0.68		-0.06	-1.48	-0.13
		1-year	0.64		0.07	-1.22	0.19
D10	I have lost interest in my appearance	Baseline	0.51		0.26	0.52	1.56
		1-year	0.66		0.30	0.60	1.16
D12	I look forward with enjoyment to things	Baseline	0.76		0.84	0.08	1.34
		1-year	0.67		0.53	0.19	1.55
D14	I can enjoy a good book or radio or TV	Baseline	0.58			0.77	1.65
	programme	1-year	0.77			0.90	2.05

Note: G = General distress; A = Anxiety; D = Depression

5.4 Discussion

This chapter has examined the psychometric properties of the HADS. Previous research has indicated that there may be issue concerning dimensionality using this instrument, and also that some of the items of the instrument may be biased, differentially assessing the underlying constructs of anxiety and depression for different individuals.

For the patients with RA (and renal failure) the bifactor model provides superior fit to the HADS item covariance structure compared to alternative formulations, such as the original anxiety-depression formulation (Zigmond & Snaith, 1983) and three-factor solutions centering around the tripartite theory of anxiety and depression (Dunbar et al., 2000; Friedman et al., 2001; Caci et al., 2003). The finding of a bifactor structure reconciles the conflicting results of previous studies applying different methodologies. Despite the competing models identified, several studies using alternate methodologies have indicated a general factor: the first unrotated factor in EFA studies indicates a general factor but the aim of finding a simple structure leads to rotation and the anxiety-depression factorization (Herrmann, 1997); CFA studies have supported a general NA factor (Martin, 2005; Dunbar et al., 2000; Desmond & MacLachlan, 2005; Martin et al., 2003; McCue et al., 2006; Rodgers et al., 2005; Barth & Martin, 2005; Martin, Thompson, & Chan, 2004; Martin, Tweed, & Metcalfe, 2004; Martin et al., 2008; Pallant & Bailey, 2005; Wang, Lopez, Thompson, & Martin, 2006); and IRT studies applying Rasch models find that a unidimensional solution is appropriate (Forjaz et al., 2008; Pallant & Tennant, 2007; Tang et al., 2007, 2008).

Previous CFA studies have indicated at a possible higher-order factor, but have failed to consider a bifactor solution. Although, the general conclusion has been that a tripartite like structure exists, these conclusions are dubious since model fit is often only marginally better for this compared to competing models. This would seem to suggest model mis-specification.

IRT studies find that a unidimensional solution is appropriate, however these apply fairly restrictive Rasch models (Pallant & Tennant, 2007; Tang et al., 2008, 2007). Although multivariate IRT models exist, they are rarely used in practice and have thus far not been considered for the HADS. IRT approaches have been criticized for the reliance on unidimensionality (Reise, Morizot, & Hays, 2007) and it would seem that those conducted on the HADS have not been sensitive enough to identify the anxiety and depression group factors.

The remaining issue concerns the interpretation of the general factor. The general factor may measure general psychological distress or may reflect NA, a a “common, underlying disposition of somatopsy-

chic distress" that subsumes a wide range of negative emotions (Watson & Clark, 1984). Although several items that are closely related to the NA construct had high loadings on the general factor and low loadings on the anxiety factor (restlessness and tension: A1, A7 and A11; worry: A5), all items had high loadings on the general factor. This would seem to suggest that although the general factor does capture elements of NA it is a measure of general psychological distress.

This interpretation of the general factor and support for a bifactor structure is provided by recent research extending the Tripartite theory. Simms et al. (2008) used IRT based full-information factor analysis on the Inventory of Depression and Anxiety Symptoms (IDAS). The authors found that a bifactor solution fitted the data better than a unidimensional Rasch model, identifying 13 factors relating to symptom groups such as suicidality, dysphoria, panic and generalized anxiety. Comparing the general factor to other instruments they concluded that the general factor measured general distress, although was strongly associated with anxiety, depression and NA. It would seem likely that this is also true of the HADS.

The group-factors do however appear to be good markers for the Tripartite constructs of autonomic anxiety and anhedonic depression. The highest loading items on the anxiety factor were for items A3 *"I get a sort of frightened feeling as if something awful is about to happen"*, A9 *"I get a sort of frightened feeling like butterflies in the stomach"* and A13 *"I get sudden feelings of panic"*, which assess somatic responses to anxiety and panic. Moreover, items A1 *"I feel tense and wound up"*, A7 *"I can sit at ease and feel relaxed"* and A11 *"I feel restless as if I have to be on the move"* exhibit low loadings on the anxiety factor and are removed due to non-significant paths in the final RA model.

According to the Tripartite theory, the prevailing component of depression is anhedonia characterized by low positive affectivity—a loss of pleasure and interest in life (Watson et al., 1995). For the depression factor items D2 *"I still enjoy the things I used to enjoy"* and D12 *"I look forward with enjoyment to things"* typify anhedonia and have the highest loadings on the depression factor. Furthermore, item D8 *"I feel slowed down"* which concerns psychomotor retardation exhibited only a low loading on the depression factor.

The correlations observed between the general and specific factors and the sumscores indicate that the HADS sumscores, although capturing some of the specific variance in item responses associated with anxiety and depression, predominantly tap into the the general psychological distress factor. As such, the HADS total sumscore rather than the individual anxiety and depression sumscores will be utilized in the analyses in following chapters.

In terms of measurement equivalence, the results presented no major cause for concern. While prob-

lems were uncovered with the cancer group, it is likely that the higher psychological distress experienced within cancer patients was due to increased levels of state anxiety.

The HADS was intended to be administered in hospital clinics, as such it was designed to avoid being biased by the elevated levels of anxiety often concomitant in this setting. This was the setting in which the RA and renal failure patients completed the questionnaire. However the cancer patients were administered the HADS shortly before a PET-CT, a procedure which requires them to be injected with a radioactive isotope and be confined to a small space for an extended period of time—not to mention the reason for the scan being to inform them whether their treatment had caused their tumor to shrink. It may be that the high state anxiety as a result of the immediate situation impacted on the interpretation of the HADS items, such that the "last two weeks" reference frame was not adhered to. Supporting this proposition, mean sum-score anxiety levels were 8.1 (*SD* 3.7) for the cancer group compared to 5.8 (*SD* 3.7) and 5.9 (*SD* 4.0) for the RA and renal failure groups, respectively. Whereas, mean levels of the depression sum-score were similar across the three groups (cancer: 4.5 [*SD* 3.2]; RA: 4.4 [*SD* 3.2]; renal: 5.5 [*SD* 3.2]). This does however raise some concern regarding the ability of the HADS to differentiate between trait and state components of psychological well-being.

A limitation of the analysis is that the group sizes were small. While Flora and Curran (2004) did report WLSMV estimation to work acceptably well in simulations with similar sized groups, the study did not assess models with a structure as complicated as a bifactor structure. Furthermore, the examination of measurement equivalence typically requires larger sample sizes than is required for CFA with ordinal indicators alone. This limits the statistical power of the test for an invariant structure across groups. However, in line with previous research the violations of measurement equivalence uncovered were relatively small (Osborne et al., 2004; Tang et al., 2008). Whats more, the cumulative bias observed for individual items is likely to have only a minor impact on scores on the general factor, or indeed the HADS total sumscore.

A further limitation is that there was no other measure of psychological distress or indicator for NA, such as an assessment of neuroticism, with which to examine the convergent validity of the HADS.

In summary, the data presented in this chapter support the utility of the HADS among a chronically ill populations assessed in outpatient clinics during routine appointments. The bifactor structure provides an acceptable empirical explanation of the HADS item covariance structure and allows a conceptual interpretation that reconciles the ambiguous findings of previous studies.

As it is not be possible to use individual item responses in the remainder of this dissertation, the HADS total score will be used as a marker for the individuals level of general psychological distress. The

use of the sumscores for the separate anxiety and depression scales is limited by the level of saturation of the general factor and so are not considered separately. That is, the anxiety and depression scales provide an assessment of autonomic anxiety and anhedonic depression that incorporates large elements of general psychological distress. Using the total score provides a broader assessment of psychological distress that incorporates symptoms of autonomic arousal and anhedonia. Further reasons to favour the use of the total sumscore, include a decreased likelihood of bias as a result of DIF, increased precision of measurement and a less skewed distribution.

The following chapter examines changes in psychological well-being using the HADS total score over an extended period of time in the ERAS cohort.

Chapter 6

The course of psychological distress

6.1 Introduction

This chapter examines changes in psychological well-being during the RA disease course, addressing the first objective of this dissertation (see section 3.5.3). Data from the ERAS cohort is used to examine the rate of change over-time, including whether any change is constant or varies as a function of disease duration, and factors that affect the rate of change over time. In addition, heterogeneity in changes is assessed to see if the data was is appropriately described using a single trajectory or whether multiple groups of patients with distinct trajectories provides a better explanation. Following from the findings of Chapter 5, the HADS total score will be used as a measure of general psychological distress incorporating symptoms of anhedonia depression and autonomic arousal.

Psychological distress in RA is typically high compared to the general population, with rates of depressive disorder roughly 2-4 times higher (Katon & Schulberg, 1992; Dickens et al., 2002). Despite a large number of studies assessing the prevalence of psychological disorder in RA, few studies have appropriately considered how, or why, levels of psychological distress change over time. Longitudinal studies examining changes in psychological distress in RA studies were reviewed in Chapter 3. To recap, these studies typically fall into two types.

Firstly, several studies examined changes in the average level of distress over time, using repeated measures ANOVA, t-tests or descriptive data (e.g. means and standard deviations). The vast majority of these studies found levels of distress to be stable over time, that is, no change in distress over time was observed at the group level (e.g. Brekke et al., 2003). The other type of study typically used regression analysis—such as using the change in distress between two time points as the dependent variable, residualised change score analysis, or path analysis—finding that certain covariates predict

changes in distress over time, that is at the individual level covariates explain the heterogeneity in change (e.g. Treharne et al., 2007; Schiaffino et al., 1998).

Although these two approaches at first appear to present conflicting findings, it is important to note that no difference in the average level of distress over time does not rule out important within individual changes. The first type of analysis simply is not intended to identify such individual level heterogeneity. For example, there may be equal numbers of individuals experiencing worsening or improvement in distress over the time period, which sums to zero creating the impression of no change when the analysis uses only the marginal means.

Considering further studies that examine changes in the average level of distress over time there is another serious flaw in the design of the vast majority of studies. As was discussed in Chapter 3, the major limitation is the failure to adequately control for disease duration in either the design or the analysis. Most studies include patients irrespective of their disease duration, the failure to control for disease duration in further analysis means that the finding of no change over time is meaningless. More specifically, the inclusion of individuals' with wildly varying disease durations means that assessments of change in psychological distress from $t = 1$ to $t = 2$ for the group are not sensible, since individuals are at different stages of the disease course and we might expect psychological distress to change differently at different times.

In section 3.3 the distress data from 14 studies that restricted the inclusion criteria to only those with recent onset disease were pooled. This suggested a potentially non-linear trend of reducing distress over time. This was supported by a further study that found lower levels of distress in 134 RA patients with early versus long-standing disease Treharne et al. (2007).

In addition, one study of patients early in the disease course identified distinct trajectories of psychological distress following the onset of RA. Persson et al. (2005) first split their sample of 158 patients with recent onset RA at the median baseline level of distress and then by whether levels of psychological distress decreased over time. Those below the median at baseline showed little change is distress over time. However, for individuals scoring above the median baseline level of distress there was a clear differentiation into a group with a decline in distress over time (38%) and those with consistently high levels of psychological distress (12%). This finding suggests heterogeneity in the psychological response to the onset of RA. However, the groups derived are likely to be a result of the process used to define them and these findings need to be confirmed.

In a recent study, Morris et al. (2011) employed cluster analysis to identify three distinct long-term patterns of depressive symptoms (low/none 66%, intermittent 25%, chronic 9%). However, this study

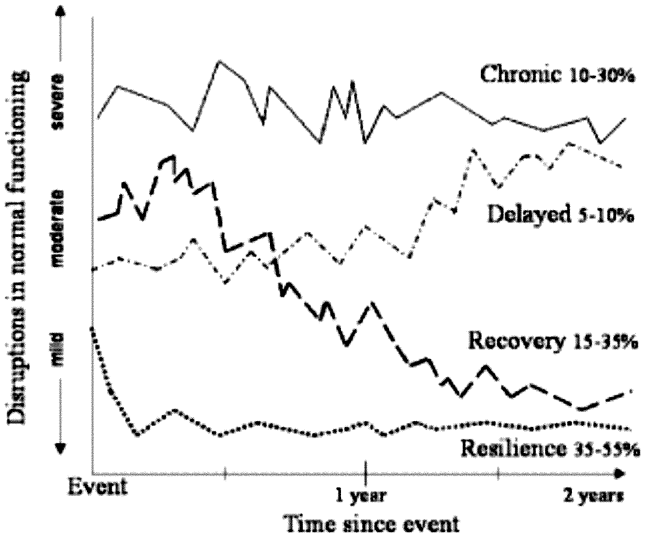


Figure 6.1: Prototypical trajectories of disruption in normal functioning following a loss or potential trauma: source Bonanno (2005, p.136)

was limited by the large range in disease duration for the sample at study entry, on average greater than 10-years. Resultantly, their analyses would not be able to identify changes that may occur early in the disease course.

Several studies of psychological distress in individuals following breast cancer surgery, heart surgery or a myocardial infarction have attempted to define distinct trajectories using sophisticated analytical methods. Prior to discussing these studies it is useful to introduce a psychological model that postulates different trajectories that should be identified.

Bonanno (2005) describes four response trajectories following a traumatic life experience (Figure 6.1): (i) many individuals are 'resilient' to the effects of the stressor, experiencing little or no disruption in functioning; (ii) a further group consists of individuals initially experiences high levels of distress but who recover in a relatively short period;[1] (iii) some individuals however experience a 'chronic' disruption in functioning and experience persistently high levels of distress caused by the traumatic experience; (iv) while a final group initially have a delayed disruption in functioning. Although initially developed for major traumatic events, such as an act of terrorism, these response trajectories may generalise to other situations. As has already been noted the onset of a chronic physical illness may be considered a stressful life-event, characterised by recurrent stressful situations associated with the symptoms of the condition (De Ridder et al., 1998; Moos & Schaeffer, 1984; Zautra, 1996).

Lam et al. (2009) assessed depression on four occasions in the 8-months following surgery for breast cancer in 285 women from Hong Kong. Using growth mixture modelling they identified 4 distinct

[1] According to resilience theory this group is also resilient (Ryff, Singer, Love, & Essex, 1998).

trajectories relating to Bonanno's model: chronic distress (15%), resilient (67%), recovered (12%), and delayed-recovered (7%). The delayed-recovered group showed initial levels of depression that were comparable to the resilient group, but were raised at the 1-month and 4-month time points before reducing at the 8-month-timepoint. Compared to the resilient group the chronic distress group had lower baseline levels of optimism (OR=.62 [.51-.77]), worse physical symptoms (OR=1.28; 95% CI: 1.18, 1.34), and issues with treatment decision-making (expectancy-outcome incongruence: OR=1.45; 95% CI: 1.28, 1.65). Similarly, the recovered group also had worse baseline physical symptoms (OR=1.22; 95% CI: 1.13, 1.33) and more treatment decision-making difficulties (OR=1.44; 95% CI: 1.27, 1.64) but did not have worse optimism (OR=.90; 95% CI: .72, 1.11). The "delayed-recovered" group reported worse physical symptoms (OR=1.23; 95% CI: 1.13, 1.34]), and lower satisfaction with the medical consultation (OR=.77; 95% CI: .66, .89).

Another study also using a sample of women with breast cancer again provided support for this model. Helgeson, Snyder, and Seltman (2004) examined psychological and physical adjustment following surgery and initiation of chemotherapy for breast cancer (N=363). Using latent class growth analysis the authors identified four latent trajectory classes in SF-36 mental component scores. The largest class representing a "resilient" group consisted of 43% of individuals who had the lowest levels of distress throughout the study. A second group of around 18% showed showed minor ups and downs. Both groups appeared to show a small increase in psychological well-being over time. Around 27% of individuals showed poor psychological well-being over the first that substantially improved over time. The final group showed an immediate and substantial decline over time (13%).

These two studies of cancer patients conform approximately to the predictions of the Bonanno model. However, studies in individuals with cardiovascular disease have not provided the same level of support. Martens, Smith, Winter, Denollet, and Pedersen (2008) used latent class growth analysis to examine trajectories of depressive symptoms in myocardial infarction patients over 1-year ($N = 287$). They identified a 4-class solution that was differentiated only by initial level of distress (i.e. stable over time: non-depressed, mildly depressed, moderately depressed and severely depressed).

In a similar study, B. M. Murphy, Elliott, Worcester, et al. (2008) used growth mixture modelling to identify two common trajectories in both anxiety and depression symptoms in 226 women over 12-months following myocardial infarction or coronary bypass surgery. The majority of patients showed relatively low levels of anxiety and depression with an improvement in psychological functioning over time (Anxiety 84%, Depression 89%). The other classes representing only a small number of individuals showed a worsening of symptoms of anxiety and depression. The same research group examined trajec-

tories of depression and anxiety in 184 individuals following coronary artery bypass surgery (B. M. Murphy, Elliott, Higgins, et al., 2008). Using growth mixture modelling they identified non-linear patterns of change (cube-root). Two trajectory classes were identified regarding anxiety: remitted-minor (92%) and remitted-major (8%)). However, three depression trajectories were identified: remitted-minor (72%), partially remmited-major (14%), and worsening-minor (14%). Anxiety class membership was related only to presurgery depression. Remitted-minor depression was associated with older age. Partially remitted major was associated with being unpartnered, smoking, high presurgery anxiety, cholesterol, angina, and earlier surgery. Low ejection fraction and worse physical function was associated with the minor-worsening class.

Although, the studies involving patients with cardiovascular disease have not shown the same robust level of support for the Bonanno model as the two cancer studies the resilient group was consistently observed across all studies. It may be that the three cardiovascular disease studies did not have large enough sample sizes to be able to detect all four classes.

6.1.1 Aims & Objectives of the chapter

This second empirical chapter will examine the longitudinal trajectories of psychological distress assessed using the HADS in the ERAS cohort. Initially the shape of the trajectory will be assessed by examining different non-linear trajectories with latent curve models (LCMs). After finding the best fitting trajectory covariates will be added to the models to assess their impact on the initial levels of psychological distress and changes over time. The unconditional model will then be extended to examine whether latent classes of trajectories exist using growth mixture modelling (GMM). This will be theoretically driven by past research. Additionally, a sensitivity analysis will be undertaken to assess the impact of missing data on the models (particularly the dropout mechanism).

6.2 Methods

6.2.1 Sample

The sample used in the current analysis consisted of a sub-sample of individuals from the ERAS cohort. This is a prospective inception cohort initiated in 1986, with participants recruited from rheumatology clinics at 9 UK hospitals. Inclusion criteria for the study were all adults (≥18-years) meeting the American College of Rheumatology criteria for the diagnosis of Rheumatoid Arthritis, with symptoms of less than 2-years and prior to the initiation of disease-modifying medication. Between 1986 and 1994, 1460

individuals were recruited and continue to be followed up yearly. Further details on the ERAS cohort are provided in Appendix D.

Three of the ERAS centres Grimsby, Winchester and Basingstoke collected information on psychological distress using the Hospital Anxiety and Depression Scale ($N = 421$). In addition, a further 363 individuals were recruited from the Winchester centre after 1994 although they were not included in the ERAS database. For these individuals only the core clinical data and HADS scores were collected. The total sample size was 784.

The maximum number of years of follow up was 19 (Median = 7). Due to very few individuals completing more than 15 years follow-up only information collected at visits up to this point was used, resulting in a total of 6167 follow-up visits completed. The pattern of dropout and questionnaire non-completion (intermittent missingness) is displayed graphically in Figure 6.2

Since the ERAS study is a longitudinal cohort with a large number of individuals recruited over a long period of time right censoring is common. Of the initial 784 individuals only 63 (8%) completed the full 15-years of follow-up. Of the remaining 721 individuals, 236 were lost to follow-up (151 died, 45 moved, 35 can't/won't, 5 discharged/remission) and 485 remained within follow-up but had not completed 15-years follow-up at the time of the last follow-up assessment.

Intermittent missingness was also common, partly due to the decision to include the HADS in the data collection procedure in 1989, several years after the initiation of the study. Excluding missing data as a result of right censoring (i.e. dropout or death), 400 (42%) had no missing HADS data during the course of follow up, with 571 (60%) with less than one-third of missing data. The dropout rate was relatively low, with the majority of losses to follow-up due to death. However, as a result of the length of the period of recruitment, there are large differences in the total number of years that individuals have been followed up. Figure 6.2 shows the number of individuals completing each year of follow-up and for each year then number that completed the HADS. Overall, no HADS data was collected for 25% of completed visits. The amount of missing HADS data ranged between a maximum of 32% at year 1 and minimum of 18% at year 6.

6.2.2 Measures

Data concerning the main study variable of psychological distress, the HADS (Zigmond & Snaith, 1983)[2], assessed at yearly intervals was used in the analysis. The previous chapter identified a bifactor structure underlying the HADS and that the total score appears to give a consistent estimate of general psycholog-

[2]The HADS was described in section 5.2.2

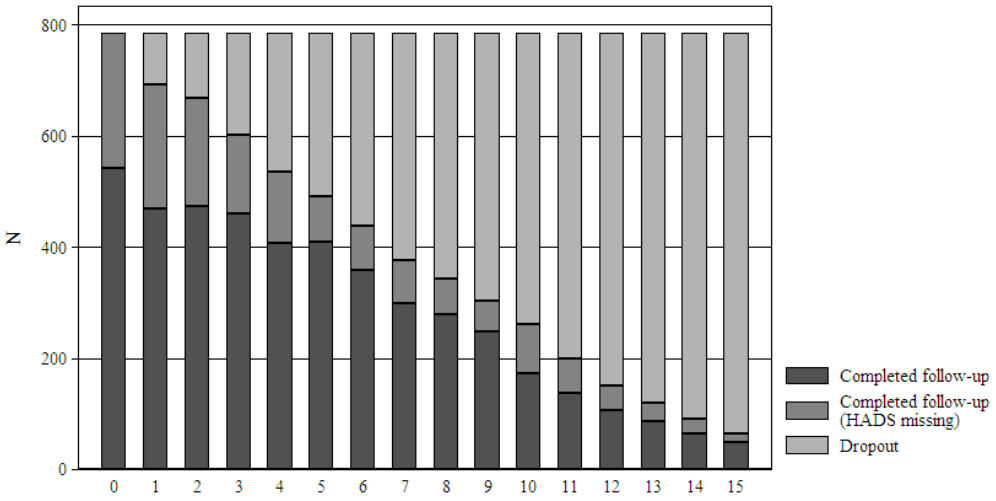


Figure 6.2: Frequency of completed follow-up visits and completed HADS for each follow-up visit

ical distress incorporating specific features of anxiety (autonomic arousal) and depression (anhedonia). Since only sum-scores for the anxiety and depression subscales were available the total sum-score was used rather than estimates of the three separate constructs.

With regard to covariates listed below, unless otherwise stated the values of the covariates at the baseline assessment were used in the analysis.

Functional limitation Functional disability was operationalised using the UK version of the Health Assessment Questionnaire (HAQ) disability index (Fries et al., 1980; Kirwan & Reeback, 1986). The HAQ consists of 20 items concerning eight activities of daily living (dressing & grooming, arising, eating, walking, hygiene, reach, grip and activities). Items are scored on a four-point ordinal scale ranging from 0 'without any difficulty' to 3 'unable to do'. In addition, for each activity respondents also report whether they receive assistance from other people or use assistive devices. The aggregated score is the average of the maximum rating within each of the eight activities of daily living adjusted for the use of devices and assistance. Scores range between 0 and 3 with higher values indicating greater disability. Generally scores greater than 1 indicate that an individual has moderate disability, and above 2 severe disability although specific cut-offs have not been universally agreed. Since the distribution of HAQ disability was positively skewed scores were square-root transformed for analysis.

Disease activity The original Disease Activity Score (DAS; van der Heijde et al., 1990) is a composite measure including a blood marker of inflammation—erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP)—plus separate counts of the tenderness (TJC) and swelling (SJC) of 28 specific joints

(mainly of the hands, feet and wrists). Scores for the DAS range between 0 and around 10 (although there is technically no upper limit since ESR and CRP are unbounded), with scores of over 5 indicating high disease activity and scores less than 3 low disease activity.[3] DAS scores were approximately normally distributed. However, CRP, ESR, SJC and TJC were all positively skewed and were square-root transformed where used in the analysis.

Pain A 100mm visual analogue scale (VAS) anchored at 0 "No pain at all" and 100 "Worst pain ever" was used to assess the patients level of bodily pain in the clinic. VAS pain scores followed a uniform distribution.

Morning stiffness The amount, in hours, of early morning stiffness (EMS), an indicator of disease activity, was also recorded. Responses were positively skewed and therefore were square-root transformed.

Comorbidity Comorbidity was assessed using the Charlson comorbidity index (Charlson, Pompei, Ales, & MacKenzie, 1987). This is essentially a weighted count of comorbidities that have been found to be related to mortality (e.g. cancer, heart disease, diabetes, renal failure etc). For the current analysis, Charlson scores were dichotomised as the presence or absence of at least one Charlson comorbidity.

Socio-economic status Social class was assessed using the Registrar Generals social class categories. This information was only available for those in the ERAS database, and is therefore missing for the additional individuals. This index is based on the persons current occupation. For those not currently in employment social class was based on their spouses occupation or their occupation during their last period of employment. Those in the former typically consisted of females who declared themselves to be housewives and the latter males or females who were unemployed or retired. Information on work status was also available.

The level of social deprivation was measured using the Carstair Index based on the level of social deprivation by post-code area. Again, this was only available for those in the main ERAS cohort. The variable was dichotomised with the lowest 2 quintiles defined as socially deprived.

6.2.3 Statistical analysis

The change in psychological distress over time will be assessed using LCMs. This method was introduced in section 4.3 and so is only briefly described here. LCMs extend the simple linear regression model to

[3] A DAS score of less than 1.6 corresponds to the American Rheumatology Association preliminary criteria for clinical remission (Fransen et al., 2004).

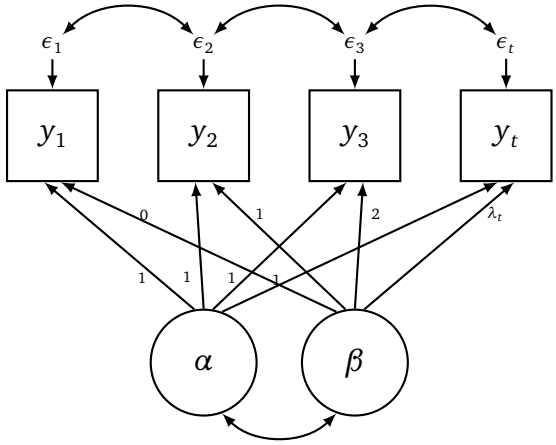


Figure 6.3: Linear latent growth curve model with autocorrelated errors

allow for the multi-level nature of longitudinal data, corresponding to the equation system

$$\begin{aligned} y_{it} &= \alpha_i + \lambda_t \beta_i + \epsilon_{it} \\ \alpha_i &= \mu_\alpha + \zeta_{\alpha i} \\ \beta_i &= \mu_\beta + \zeta_{\beta i} \end{aligned} \tag{6.1}$$

This model may be estimated as a special case of confirmatory factor analysis (Bollen & Curran, 2006; McArdle & Epstein, 1987), expressed as a path diagram in Figure 6.3. The intercept factor α_i represents the level of the outcome variable y_{it}—distress as indicated by the HADS total score—at the baseline assessment since $t_1 = 0$, and the (linear) slope factor α_i the rate of change in y_{it} for each one unit increase in time t. Scores on these factors are allowed to vary across individuals, and are a function of the mean intercept μ_α and slope μ_β and an individual specific disturbances $\zeta_{\alpha i}$ and $\zeta_{\beta i}$, respectively.

Potential non-linear trajectories in distress were assessed by comparing a linear model with a model including a quadratic slope factor, various non-linear transformations of λ_t, and using the free-loading method proposed by Meredith and Tisak (1990). All models allowed for an auto-correlated error structure since this was observed to increase model fit in preliminary analysis.

Although the LCMs allow variation in the intercept and slope between individuals, it is assumed that all individuals come from a common population that can be approximated by a single growth trajectory, defined by μ_α and μ_β. GMM relaxes this assumption using latent trajectory classes, which allow for different groups of individual growth trajectories to vary around different means. GMM was described in detail in section 4.3.3. To briefly recap, equation 6.1 can be extended through the inclusion

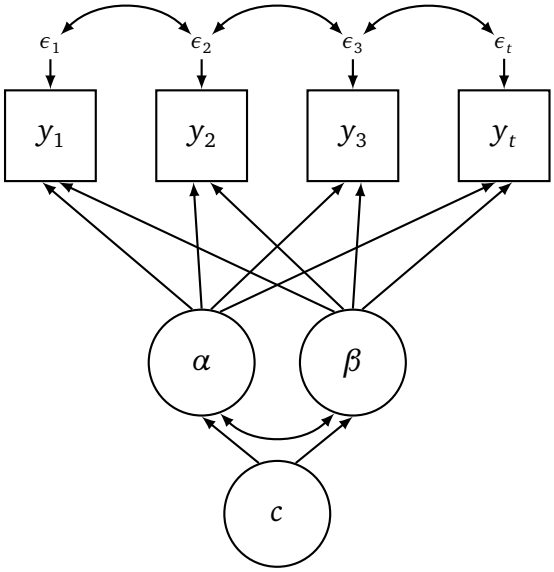


Figure 6.4: Growth mixture model

of categorical latent variable c, with k levels ($k = 1, 2, \ldots, K$)

$$
\begin{aligned}
y_{it} &= \sum_{k=1}^{K} \Pr(c = k)[\alpha_{ki} + \lambda_{kt}\beta_{ki} + \epsilon_{kit}] \\
\alpha_{ki} &= \mu_{\alpha k} + \zeta_{\alpha ki} \\
\beta_{ki} &= \mu_{\beta k} + \zeta_{\beta ki}
\end{aligned} \tag{6.2}
$$

where the subscript k indicates the that parameters are allowed to vary across latent classes. The result is separate trajectories for each latent class, each with its unique estimates of variances and covariate influences (B. Muthén, 2006b). This model is expressed as a path diagram in Figure 6.4.

6.3 Results

6.3.1 Demographic and clinical characteristics

Table 6.1 shows the demographic and clinical characteristics for the sample. The distribution of demographic characteristics was similar to the full ERAS cohort. The clinical and demographic profile was similar to the full ERAS cohort (for figures of the full ERAS cohort see Table 5.2). As a multi-centre inception cohort ERAS provides an accurate representation of the UK RA population. There is a 2:1 female-male ratio, and the average age at diagnosis is in the mid 50's. The sample was predominantly

white and around 40% left school at or before the age of 16. The only variable that showed any difference from the full ERAS cohort was HAQ disability. The current sample showed lower HAQ (.74 vs. 1.15; Cohen's $d = .35$). It is not clear why this difference is observed particularly since all other clinical variables were comparable. It is useful to note that HAQ disability exhibited considerable heterogeneity across centres. Those from the Winchester centre, from which the majority of these patients were drawn, on average reported lower levels of functional limitation than from other centres.

At the baseline assessment the number of individuals above the caseness criteria for the individual HADS sub-scales (>8) was 27.3% for anxiety and 16.1% for depression. Furthermore, 11.0% scored above both cut-offs. These figures are similar to those reported using the smaller sample of patients for whom item responses were available in the previous chapter.

6.3.2 Descriptive analysis

Pair-wise correlations between HADS total scores at different visits indicated an autoregressive structure, with first-order correlations above .7, except for baseline (Table 6.2). The correlations between the baseline HADS total score and subsequent assessments were smaller compared to other assessments ($r \approx .5$), and remained stable over time. The N contributing to each correlation are also shown. Over time the numbers reduce dramatically, with no one from the baseline visit also being assessed at the 15-year visit (NB. the missing data pattern is non-monotone).

Examination of the mean levels of distress at each follow-up shows that on average scores were highest at the baseline assessment and there was possibly a reduction over time. However, the magnitude of the change is relatively small with the difference between the highest ($t_0 = 11.4$) and lowest ($t_{14} = 8.0$) scores being only 3.4 units—around half a standard deviation. This observation was confirmed by the examination of Figure 6.5. Since different individuals are contributing to assessments at different time points this trend may be artefactual, as a result of individuals who were followed up for longer periods being on average less depressed.

Figure 6.6 shows individual trajectories for HADS total scores over the 15-years of follow-up. The overlaid LOWESS smoothed line shows a decreasing trend over time. However, there is a large amount of variability within individual trajectories. Although not particularly clear, large increases and decreases in scores over time can be observed.

Further clarity is provided by Figure 6.7, which shows the individual trajectories for 20 randomly selected individuals. The plot shows several different trajectory types. Several individuals show fairly consistent levels of psychological distress over time (e.g. 7210, 7233, 7248, 7256). One individual,

Table 6.1: Demographic and baseline clinical characteristics ($N = 784$)

	N	Mean	SD	Min	25th %ile	Median	75th %ile	Max	Skewness	Kurtosis
Demographic										
Age	779	56.99	15.05	15	46	57	69	93	-0.25	0.5
Female	784	67%								
Height (m)	668	1.65	0.09	1.45	1.58	1.64	1.71	1.93	0.43	0.32
Weight (kg)	671	72.11	14.78	42.3	60.8	70.6	80.5	157	0.74	-1.24
BMI	770	26.51	4.84	15.92	23	25.93	29.17	47.4	0.87	-1
White	760	98%								
Married	641	71%								
Low education (None/<CSE)	369	41%								
Social class (IV/V)	369	60%								
Socially deprived (Carstair)	380	32%								
Working	377	43%								
Smoker	784	23%								
Clinical										
HADS anxiety	542	6.33	4.12	0	3	6	9	17	0.6	0.26
HADS depression	542	5.11	3.55	0	2	5	7	19	0.75	-0.3
HADS total	542	11.44	6.81	0	6	10	15	34	0.67	-0.06
Morning stiffness (hours)	784	1.76	1.8	0	1	1	2	9	2.15	-4.73
HAQ disability	784	0.74	0.68	0	0.21	0.54	1	3	1.19	-0.81
VAS pain	784	49.88	27.79	0	27	50	72	100	0.04	1
DAS	778	4.33	1.76	0.13	3.81	5.07	6.47	9.4	-0.11	0.57
Tender joint count	783	18.75	15.26	0	6	15	27	67	0.94	-0.2
Swollen joint count	784	16.69	14.43	0	5	13	26	59	0.86	0.03
ESR	779	38.44	28.1	1	16	32	57	133	0.81	0.03
CRP	627	34.33	40.22	0	6	18	47	278	2.07	-5.6
Charlson comorbidity	386	20%								

Table 6.2: Pairwise correlations (below diagonal), contributing N (above diagonal), means and standard deviation's for HADS total score over 15-years

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HADS-T 0yr	*542*	425	394	351	274	252	205	166	147	121	90	64	37	20	5	0
HADS-T 1yr	0.55	*469*	372	331	263	241	204	161	145	121	92	68	40	25	8	3
HADS-T 2yr	0.52	0.76	*474*	379	311	290	241	194	175	146	115	86	59	42	24	15
HADS-T 3yr	0.57	0.75	0.75	*460*	340	323	279	226	199	172	137	107	77	58	39	29
HADS-T 4yr	0.46	0.71	0.76	0.78	*407*	327	289	242	209	181	134	107	76	59	40	30
HADS-T 5yr	0.49	0.71	0.70	0.74	0.79	*409*	314	263	239	206	149	117	87	67	50	38
HADS-T 6yr	0.47	0.64	0.73	0.71	0.76	0.81	*358*	268	239	213	153	123	91	73	55	40
HADS-T 7yr	0.50	0.65	0.71	0.75	0.75	0.75	0.80	*299*	246	211	152	122	91	73	53	41
HADS-T 8yr	0.50	0.58	0.70	0.72	0.77	0.73	0.75	0.78	278	223	164	132	102	83	59	45
HADS-T 9yr	0.42	0.47	0.67	0.67	0.71	0.65	0.72	0.74	0.83	*247*	167	133	103	83	60	47
HADS-T 10yr	0.55	0.54	0.61	0.72	0.65	0.68	0.62	0.68	0.78	0.75	172	*134*	104	85	62	48
HADS-T 11yr	0.50	0.49	0.62	0.63	0.72	0.67	0.67	0.74	0.73	0.74	0.73	*137*	100	83	60	46
HADS-T 12yr	0.48	0.41	0.64	0.60	0.72	0.74	0.67	0.65	0.68	0.76	0.73	0.80	*107*	79	59	47
HADS-T 13yr	0.46	0.53	0.68	0.63	0.69	0.70	0.59	0.75	0.68	0.77	0.68	0.67	0.85	*86*	62	48
HADS-T 14yr	-0.07	0.04	0.62	0.51	0.62	0.62	0.50	0.71	0.69	0.83	0.72	0.62	0.76	0.88	*64*	48
HADS-T 15yr	.	-0.03	0.66	0.52	0.73	0.62	0.52	0.59	0.64	0.71	0.68	0.63	0.65	0.80	0.84	*49*
Mean	11.44	9.78	9.21	9.96	10.17	10.05	9.50	9.93	9.29	9.34	8.80	8.67	9.07	8.37	8.04	9.86
SD	6.81	6.85	6.72	7.11	7.11	6.94	6.62	6.83	6.88	7.04	6.86	6.92	7.00	6.68	6.08	6.51

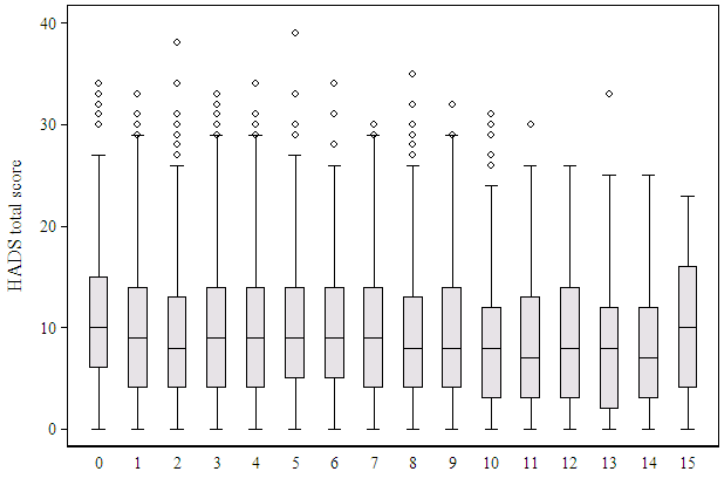


Figure 6.5: Box-plots of observed HADS total scores for each year of follow up

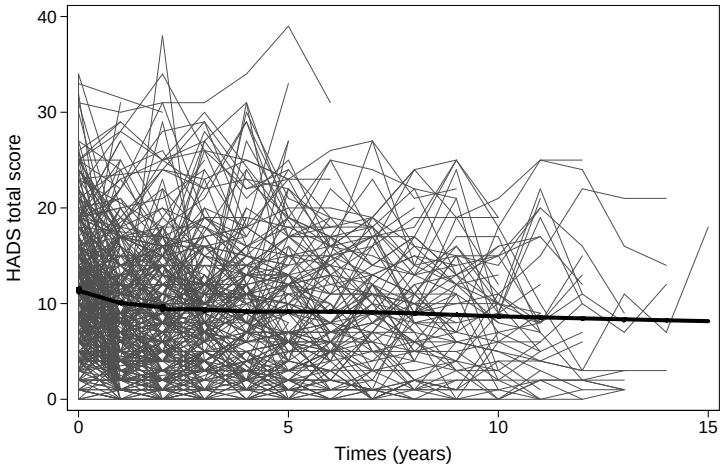


Figure 6.6: Observed HADS total score trajectories with overlaid LOWESS smoothed line

7218, shows a rather chaotic pattern. There also seems to be a consistent pattern in some individuals for a decrease in psychological distress over time notably over the first few years of the disease (e.g. 7152, 7170, 7172, 7175, 7177, 7207, 7247, 7278).

6.3.3 Latent curve model

LCMs were fitted to the HADS total scores. Initially unconditional (i.e. without covariates) LCMs were fitted to examine the shape of the mean psychological distress trajectory over the course of follow-up. After the best fitting function of time was identified covariates were added to the model, a conditional LCM.

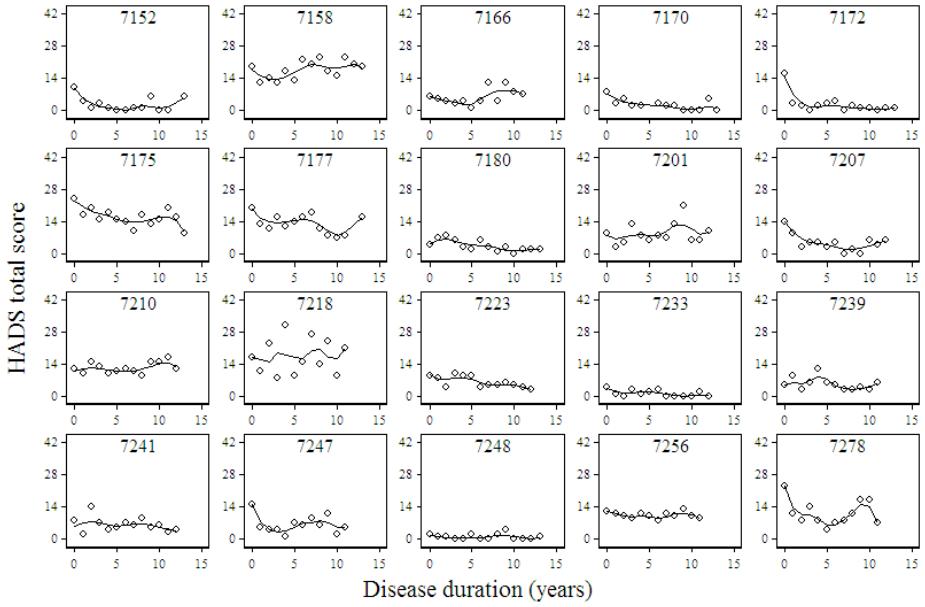


Figure 6.7: Observed HADS total score trajectories with overlaid LOWESS smoothed line for 20 randomly selected individuals (of those with less than 5 missing data points): bandwidth .50

6.3.3.1 Unconditional latent curve model

Several different models allowing for different trajectory shapes were fitted to the data. Based on the descriptive analysis several non-linear models allowing for non-linear monotonic changes with a deceleration in the rate of change over time were fitted to the data: square-root, logarithmic, reciprocal and exponential. All models were fitted allowing for autocorrelation between residuals. All of the models had similar goodness-of-fit statistics but the reciprocal function was selected by RMSEA, TLI and both information criterion (Table 6.3).

All models had a negative estimate of the slope factor indicating a reduction in levels of psychological distress over time (Table 6.4). Inspection of the model-implied trajectories from the fixed portion of the model in Figure 6.8 indicates that this reduction typically occurs during the first few years after disease onset, as was indicated in the descriptive analysis.

For the model with the reciprocal functional form of time, the mean value of the random intercept factor was 11.29, which is close to the value of 11.44 reported in Table 6.2. The variance of the intercept was significant indicating that there was significant heterogeneity in the baseline level of depression. The mean of the random slope factor was significant negative, -1.74, indicating the average total change as $t \rightarrow \infty$. Half of this change is expected to occur during the first year, two-thirds by the second year and so on. This relates to an overall reduction in the HADS for the sample of - 1.58 units over the period of follow-up (Cohens' $d = -.23$). The majority of this change occurred during the first few years following

Table 6.3: Unconditional latent curve model fit

	Free-loading	Linear	Quadratic	Square-root	Logarithmic	Reciprocal	Exponential
χ^2	276	333	291.7	318.8	306.8	298.7	305.9
DF	102	116	112	116	116	116	116
CFI	**0.955**	0.944	0.954	0.948	0.951	0.953	0.951
TLI	0.947	0.942	**0.951**	0.946	0.949	**0.951**	0.949
RMSEA	0.047	0.049	**0.045**	0.047	0.046	**0.045**	0.046
-2LL	**26751**	26808	26767	26794	26782	26774	26781
AIC	26851	26880	26847	26866	26854	**26846**	26853
BIC	27084	27048	27033	27034	27022	**27014**	27021

Note. Emboldened figures represent the best fitting model.

diagnosis: -0.87 units between diagnosis and 1-year follow-up and -1.31 units by 3 years. Furthermore, the variance of the slope was significant indicating heterogeneity in the rate of change over time.

The correlation between the random intercept and slope for the best fitting model with reciprocal functional form was -.31 ($p = .02$), indicating that individuals with increased psychological distress at baseline were more likely to experience a reduction over time.

Figure 6.9 shows the estimated (i.e. model-implied) individual trajectories for the same 20 randomly selected individuals used in Figure 6.7 plotted alongside their observed scores. The estimated trajectories tend to fit the observed scores relatively well for most people, although there is often much within person variability. It is important to remember that LCMs try to fit a smooth trajectory to the scores, however HADS scores, by design, are influenced cross-sectionally by other factors, such as disease activity at that time. Inclusion of these cross-sectional associations is likely to improve the fit of the model.

Checking the assumptions of the LCM (stated above) indicated no cause for concern. Specifically, (i) residuals were approximately normally distributed within each year; (ii) residuals showed homoscedasticity within each year; and (ii) standardizing residuals, only 46 (1%) had an absolute value greater than 3, as would be expected.

6.3.3.2 Conditional latent curve models

To examine the effect on initial level and change in distress, the intercept and slope factors were regressed onto a selection of covariates. Initially covariates were entered into separate models to examine the effect unadjusted for other variables (Table 6.5). Continuous covariates were centered at their means to maintain the interpretability of the intercept and slope factors.

Gender and social class showed significant effects on intercept, indicating worse psychological distress for those who were female and for individuals in more disadvantaged social classes. Furthermore,

Table 6.4: Parameter estimates (and standard errors) for unconditional latent curve models with correlated residuals

	Linear	Free-loading	Quadratic	Square-root	Logarithmic	Reciprocal	Exponential
μ_α	10.37 (0.24)	11.32 (0.30)	10.62 (0.25)	10.55 (0.25)	10.82 (0.26)	11.29 (0.28)	11.34 (0.28)
$\mu_{\beta 1}$	-0.06 (0.03)	-1.52 (0.40)	-0.18 (0.08)	-0.37 (0.14)	-0.49 (0.14)	-1.74 (0.34)	-1.5 (0.29)
$\mu_{\beta 2}$			0.01 (0.01)				
$COV(\alpha, \beta 1)$	0.17 (0.20)	-13.38 (7.01)	0.42 (0.68)	0.11 (1.04)	-1.08 (1.30)	-10.48 (6.56)	-14.21 (10.40)
$COV(\alpha, \beta 2)$			-0.06 (0.05)				
$COV(\beta 1, \beta 2)$			-0.05 (0.02)				
$VAR(\alpha)$	31.43 (2.25)	38.37 (6.26)	28.55 (2.69)	30.29 (2.43)	30.06 (2.85)	33.93 (5.46)	39.37 (10.14)
$VAR(\beta 1)$	0.13 (0.03)	28.12 (12.15)	0.82 (0.23)	3.36 (0.69)	3.96 (0.80)	32.99 (8.51)	28.36 (10.84)
$VAR(\beta 2)$			0.00 (0.00)				

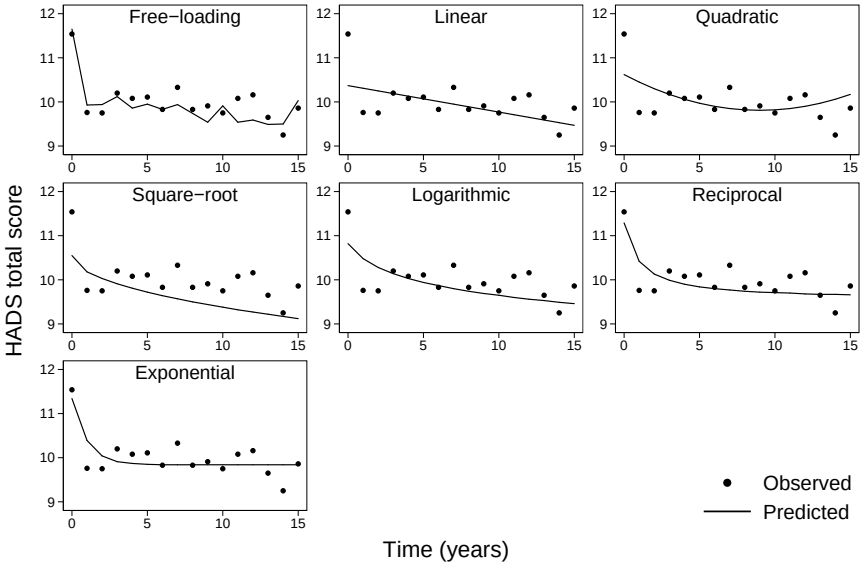


Figure 6.8: Predicted HADS total scores for each model

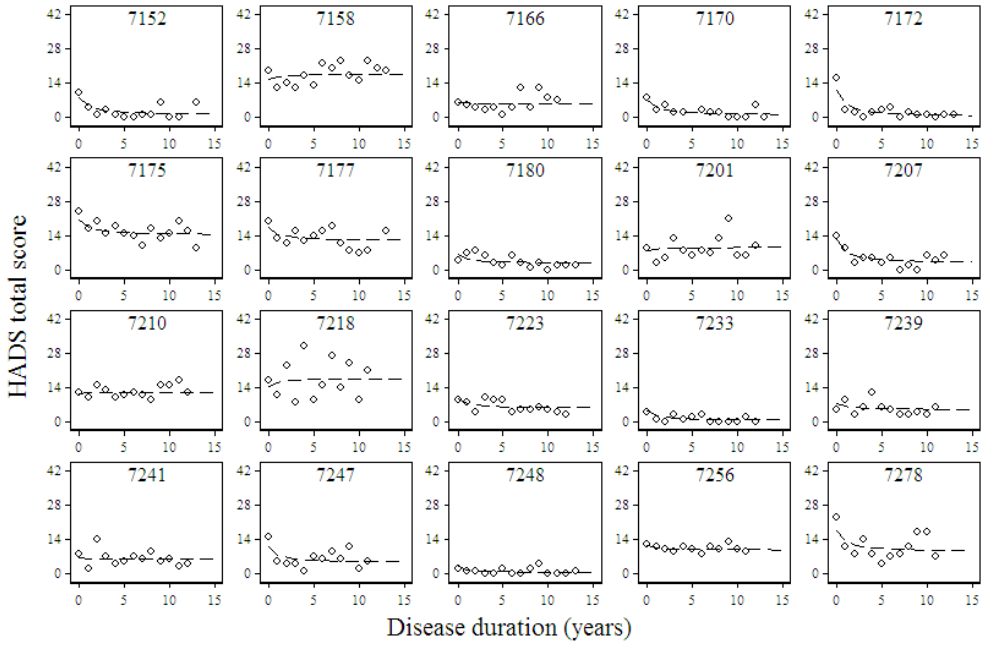


Figure 6.9: Model implied trajectories for a 20 randomly selected individuals, dashed lines represent model-implied trajectories

individuals with more severe disease also showed worse levels of psychological distress with duration of early morning stiffness, HAQ disability, tender and swollen joint counts, Disease Activity Score and pain all related to the random intercept.

There was a significant effect of age on the slope factor with older individuals more likely to show less improvement in distress over time. All of the measures of disease severity at baseline were estimated to have negative relationships with the random slope (i.e. more improvement), although only early morning stiffness, CRP, and pain were significant. This suggests that those with more active disease at baseline, and worse psychological distress, were more likely to experience an improvement in distress with time.

Table 6.6 shows the estimates from a multivariate model with all covariates added together. Due to missing data for some covariates (see Table 6.5) the model would have included only 215 cases.[4]. As a result multiple imputation was employed using the `ice` package in Stata, that implements imputation by chained equations (Royston, 2004). Ten imputed datasets were generated with missing values imputed. Continuous variables were modelled using linear regression and binary variables using logistic regression. The LCMs were then estimated using M*plus* 5.1 and combined within M*plus* 5.1 using Rubin's rules (i.e. the coefficients were averaged and the standard errors adjusted). The HADS total scores over follow up were not imputed since they are handled appropriately via the full information maximum likelihood estimator.

A restricted number of covariates were entered into the model. Several of the disease severity variables were excluded due to high correlations, and furthermore DAS being a composite of three of the variables. CRP was removed from the final model as it contained a lot of missing values and the effect was strongly, although not significantly, in the opposite direction as was previously observed (i.e. high CRP related to better psychological distress).

In the conditional model the mean of the random intercept (μ_α) was 9.52 and the mean of the random slope (μ_β) was -.71. The slope was non-significantly different from 0 indicating that in the reference group trajectories were stable over time. This represents patients that were female, not social disadvantaged, non-smokers, that were not working, and had levels of the other variables at the sample mean.

Concerning the random intercept, there was little change in the estimates of the effect of social class and early morning stiffness on the random intercept compared to the figures presented in Table 6.5.

[4]Although FIML uses all available data for the dependent vriables, the estimation is conditional on the covariates resulting in listwise deletion for observations with missing covariates

However, the effect of sex was reduced to non-significant ($p = .460$). This may be due to males being less likely to suffer from early morning stiffness and on average having less severe disease in general. It would seem then that the effect of gender on psychological distress may be mediated via disease severity. Furthermore, when early morning stiffness was included in the model, the effects of other measures of disease severity were non-significant.

Only gender and DAS were observed to be significantly related to the random slope factor. Males showed a significantly worse trajectory of psychology distress although the difference compared to females was small. Disease activity score also showed a small but significant effect, whereby individuals with higher disease activity had worse psychological distress with a faster rate of improvement in those with higher DAS at baseline.

Figure 6.10 graphically depicts the model-implied trajectories. The reference line represents the model-implied trajectory at the mean of all continuous variables and where all binary variables are held at 0 (i.e. female, social Class I-III, non-smoker, not working). The dashed lines represent varying the factor whilst holding others constant. For continuous variables, the lines represent a 1SD increase in continuous covariates or a change from yes to no for binary covariates. It is clear that the two most important factors are the duration of early morning stiffness and the individual's social class. The effects are mainly on baseline levels, with little variation over time. However the slope at 1SD above the mean for EMS was almost 0. Also for those in social class IV or V there was a slightly increased reduction, possibly related to the fact that they were higher in the first place and therefore more likely to reduce (regression to the mean).

6.3.3.3 Time varying covariates

To examine whether the effect of HAQ disability, disease activity and pain on psychological distress was stable over time the effects were entered into the LCM as time varying covariates. This enables for the examination of any differential effect of these variables over time.

The square-root of HAQ disability score was included as time varying with distress being regressed on it at each time point. The parameter estimates were all very similar and hence were constrained to be equal. Although the change in the model fit was significantly worse, $\chi^2(15) = 32.4, p = .007$, the BIC indicated the constrained model was more parsimonious (35013 vs.34945). The constrained parameter estimate was significant, $b = 5.42, \text{SE} = 0.23$, and similar to the effect observed for the intercept regressed onto baseline HAQ disability score.

In a separate model, DAS was included as a time-varying-covariate with distress at each time point

Table 6.5: Parameter estimates (and standard errors) for separate conditional LCMs, with correlated residuals, including covariates with complete cases

	N	α	β
Age	779	-0.02 (0.02)	**0.08 (0.02)**
Male	784	**-1.98 (0.58)**	0.48 (0.72)
BMI	770	0.09 (0.06)	0.13 (0.07)
Socially deprived (Carstair)	380	0.24 (0.89)	1.04 (1.02)
Education (None/<CSE)	369	0.09 (0.96)	1.75 (1.08)
Social class (IV/V)	369	**2.49 (0.96)**	-0.52 (1.15)
Smoker	723	1.09 (0.65)	0.66 (0.80)
Working	377	-1.07 (0.96)	-1.59 (1.42)
Early morning stiffness (hours)	784	**1.99 (0.38)**	**-1.74 (0.48)**
HAQ disability	784	**4.97 (0.63)**	-1.02 (0.79)
ESR	779	0.09 (0.12)	-0.22 (0.15)
CRP	627	0.14 (0.10)	**-0.29 (0.12)**
Tender joint count	784	**1.05 (0.14)**	-0.12 (0.18)
Swollen joint count	784	**0.31 (0.14)**	-0.02 (0.17)
DAS	779	**0.75 (0.14)**	*-0.74 (0.17)*
VAS pain	784	**0.09 (0.01)**	**-0.04 (0.01)**

**Note*. Figures in bold are significant at the 5% level.

Table 6.6: Parameter estimates (and standard errors) for conditional LCMs, with correlated residuals, including multiply imputed covariates

	α	β
Age	0.03 (-0.04)	0.08 (-0.04)
Male	0.03 (-0.05)	**0.16 (0.08)**
BMI	0.59 (-0.41)	-0.82 (-0.58)
Social class (IV/V)	**2.28 (0.90)**	-1.37 (-1.00)
Smoker	0.75 (-0.59)	1.28 (-0.85)
Working	-0.35 (-1.52)	-0.41 (-1.73)
Early morning stiffness (hours)	**2.76 (0.95)**	1.014 (-0.89)
HAQ disability	0.05 (-0.23)	-0.04 (-0.27)
DAS	**0.07 (0.01)**	**-0.04 (0.02)**
VAS pain	-0.13 (-0.11)	-0.24 (-0.17)

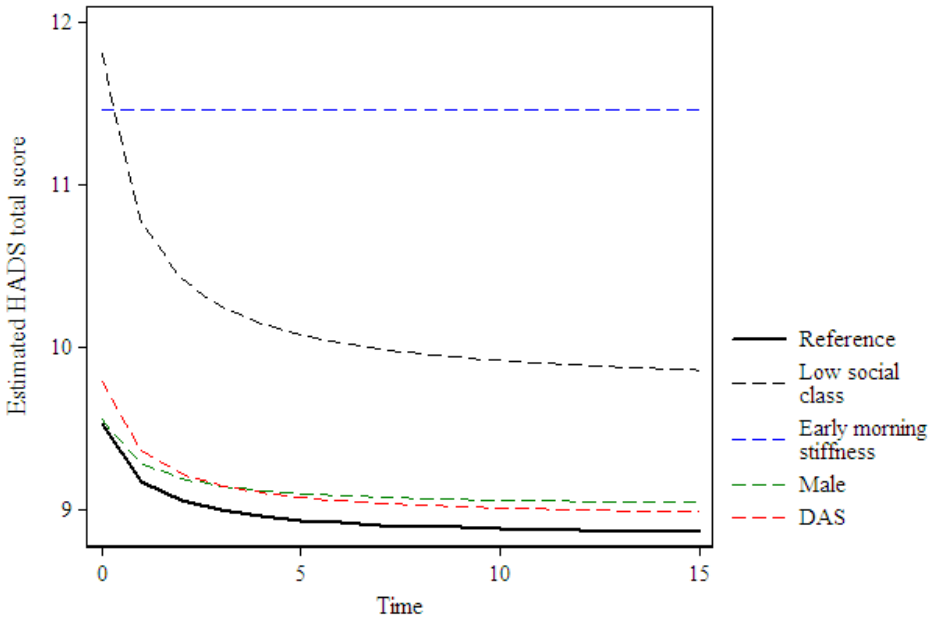


Figure 6.10: Model implied trajectories of psychological distress, at specified levels of selected covariates (Reference relates to trajectory for all continuous variables at mean and dichotomous variables held at 0)

regressed onto the DAS at the same time point. Again, the parameter estimates were all similar. Constraining them to be equal resulted in a non-significant reduction in model fit, $\chi^2(15) = 19.7, p = .184$, with the BIC indicating increased model parsimony (54349 vs.54268). The constrained parameter estimate was significant $b = 0.87, \text{SE} = 0.05$, and again was similar to the effect observed for the random intercept regressed on baseline DAS.

VAS pain score was also entered into the growth model including age and sex as a time varying covariate. The parameter estimates were all similar and the model with them constrained to be equal was not of significantly worse fit, $\chi^2(15) = 24.0, p = .065$, and the parsimony was improved (BIC: 85553 vs.85476). The parameter estimate for the constrained model was significant, $b = 0.07, \text{SE} = 0.003$, and similar to the effect observed for the random intercept regressed onto baseline VAS pain score.

The estimated parameters for HAQ, DAS and VAS pain entered as time varying covariates were all similar over time. Constraining them to be equal did not appear to reduce model fit in a substantive way. The regression of the time varying covariate at baseline on baseline total HADS score is equivalent to the regression on the intercept of the LCM, and the parameter estimates were comparable. Hence, it would seem that the effect of each of these process variables is stable over time and therefore does not need to be included in the model as time-varying.

6.3.4 Growth mixture model

GMMs were fitted to the data to assess whether changes in distress in the sample were adequately described by a single overall trajectory or whether multiple distinct subgroups exhibiting distinct patterns of change were present. Initially, this was done without covariates as this approach has been shown to enable more precise selection of the appropriate number of classes (Tofighi & Enders, 2006). Due to the large amount of missing data after 10-years of follow-up and the apparent stability of the trajectories the following analysis was restricted to the follow-ups recorded over the first 10-years since disease onset. Sensitivity analysis, using all data up to 15-years gave comparable results. However, there were issues with model convergence, namely the time to achieve convergence was substantially longer and there were issues with local maximum for models with larger numbers of latent classes.

The fit of models with 1 through 6 latent classes was assessed using standard model comparison techniques, such as information criterion and the Lo-Mendell-Rubin likelihood ratio (LMR) test. For each model the reciprocal functional form of time was estimated, with first-order correlated residuals.

Although the log-likelihood and the AIC favoured the 6-class model both have been shown to over-select the number of classes (Nylund et al., 2007; Tofighi & Enders, 2006). The consistent AIC (CAIC) which takes the sample size into account and the BIC, which have been found to perform relatively well (Nylund et al., 2007; Tofighi & Enders, 2006), both favoured a 4-class solution. Furthermore, the LMR test also indicated a 4-class solution. The parameter estimates for the growth factors of the 4-class solution are given in Table 6.8 and the estimated trajectories plotted in Figure 6.11.[5]

The 4-class model specifies the majority of individuals as being in a class with consistently low levels of psychological distress that would appear to conform to Bonanno (2005) *resilient* trajectory (68%). This class experienced a small but significant reduction in psychological distress over the period (Cohen's $d = -.23, p < .001$). The other three classes were of roughly equal size. One class consisted of individuals with consistently high levels of psychological distress (*chronic*; 12%). Although, the magnitude of the expected change, μ_β, in this class was similar to the resilient class it was non-significant (Cohen's $d = -.31, p = .081$). A further class consisted of individuals with high levels of psychological distress at the time of diagnosis that decreased to normal levels (*recovered*; 9%). Unsuprisingly the slope parameter for this class was highly significant (Cohen's $d = -2.28, p < .001$). Each of these groups was also observed in the 3-class model. The fourth class, which was not identified in the 3-class model, consisted of individuals with psychological dsitress levels that were, on average, similar to the resilient

[5]For the 4-class model a global maxima was achieved using 100 randomly selected starting values and 10 final stage optimizations. Seven of the ten optimizations converged on the same log-likelihood solution. Sensitivity analysis comparing models where the time trajectories were estimated using the free-loading method gave comparable results.

Table 6.7: GMM fit

# Classes	1	2	3	4	5	6
Parameters	26	29	32	35	38	41
Entropy	.	0.678	**0.726**	0.666	0.635	0.640
AIC	24386	24324	24299	24274	24266	**24260**
CAIC	24533	24488	24481	**24472**	24482	24492
BIC	24507	24459	24449	**24437**	24444	24451
LMR	.	0.0171	0.025	**0.0451**	0.6657	0.3505

Table 6.8: GMM estimates of growth factors

Class	Chronic	Resilient	Recovered	Delayed
μ_α	21.45 (1.08)	8.70 (0.33)	20.05 (1.30)	8.55 (1.04)
$\mu_{\beta 1}$	-1.85 (1.32)	-1.68 (0.49)	-15.59 (1.96)	10.22 (2.03)
$COV(\alpha, \beta 1)$	10.30 (2.78)	10.30 (2.78)	10.30 (2.78)	10.30 (2.78)
$VAR(\alpha)$	4.34 (2.14)	4.34 (2.14)	4.34 (2.14)	4.34 (2.14)
$VAR(\beta 1)$	4.97 (3.60)	4.97 (3.60)	4.97 (3.60)	4.97 (3.60)

group but dramatically increased over the period of follow-up (delayed; 11%). Again the value of the random slope parameter was higly significant (Cohen's $d = 1.40, p < .001$).

The trajectories of the 5-class model were also inspected. In addition to the four trajectory groups observed in the 4-class model, an additional class with stable and moderate levels of psychological distress was observed. This appeared to mainly consist of individuals previously in the resilient class. Fit indices and the LMR likelihood ratio test indicated that this further separation was not necessary and merely constitutes and over extraction of classes.

6.3.4.1 Predictors of latent class membership

To identify variables that were associated with latent class membership the means across latent classes, estimated using posterior-probability based imputation, were compared (Table 6.9). As well as the overall test for a significant difference between the classes three pair-wise comparisons are of interest. Firstly, in what characteristics do the two classes with initially low levels of distress differ compared to the two classes with initially high levels of distress? Secondly on what characteristics do the resilient and delayed classes differ? And finally on what characteristics do the chronic and recovered classes differ?

Overall, differences between classes tended to be characterised by clinical rather than demographic features. Moreover, for clinical features, differences were observed for self-reported features (early morning stiffness, HAQ disability, tender joint count and VAS pain all $p < .05$) rather than objective measures, such as ESR, CRP and the clinicians' report of the number of swollen joints.

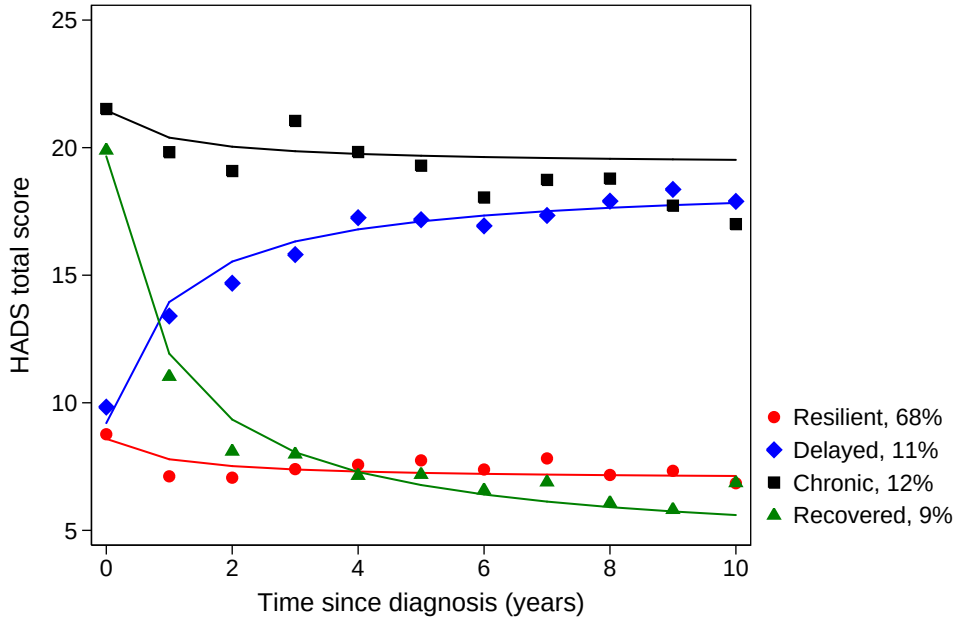


Figure 6.11: Predicted trajectories of 4-class GMM. Markers are sample means weighted by class probabilities and solid lines are model-implied trajectories.

Grouping the classes by the initial level of psychological distress the resilient and delayed classes, compared to the chronic and recovered classes, tended to be younger, male and from a more advantaged social class. Furthermore they were less likely to report severe disease as indexed by self-reported measures. For example, the chronic class had higher initial levels of HAQ disability compared to the resilient ($\chi^2(1) = 11.94, p = 0.001$) and delayed classes ($\chi^2(1) = 4.18, p = 0.041$); the resilient class significantly lower baseline VAS pain compared to the chronic ($\chi^2(1) = 20.290 =, p < 0.001$) and recovered classes ($\chi^2(1) = 7.30, p = 0.007$); and the resilient class had significantly fewer tender joints at baseline compared to the chronic ($\chi^2(1) = 23.21, p < 0.001$) class with the difference compared to the recovered class on the margins of significance ($\chi^2(1) = 3.01, p = 0.083$). Since the number of tender joints is used in the calculation of the DAS, the difference observed may account for the significant difference in DAS observed between the chronic and resilient classes ($\chi^2(1) = 5.36, p = 0.02$).

Considering the resilient and delayed classes, both of which had low levels of psychological distress initially, only the comparison for the number of tender joints was significant ($\chi^2(1) = 3.88, p = 0.049$). There was a (non-significant) trend for individuals in the delayed class to be female, have less education, disadvataged social class, smoke, not be in work and have worse disease severity as indexed by the number of tender joints and VAS pain. Although noteworthy due to the difference being in the expected direction, no conclusion may be drawn from this observation.

Compared to the recovered class the chronic class were more likely to be from a deprived area, smoke, have less education ($\chi^2(1) = 3.52, p = 0.061$) and report worse disease, as indexed by HAQ disability ($\chi^2(1) = 4.18, p = 0.041$), the number of tender joints ($\chi^2(1) = 5.12, p = 0.024$), and VAS pain.

In summary, the largest group of individuals had on average consistently low levels of psychological distress, accounting for around two-thirds of the sample. This does not mean that individuals in this class did not experience psychological distress it is simply that on average distress was low to moderate, although may have been high at times, for example as a result of a disease flare. The chronic group on average experienced consistently high levels of psychological distress. This does not necessarily mean that these individual were clinically depressed or anxious at all time points, but that in general they tended to experience higher levels of anxiety or depression, or both.

6.3.5 NMAR sensitivity analysis

Due to the proportion of missing data a sensitivity analysis was conducted examining for possible bias introduced into the growth parameter estimates by the missingness mechanism being *not missing at random* (NMAR). For example, it is plausible that individuals with higher levels of psychological distress are more likely to have worse levels of disease and other coexistent medical comorbidities and therefore more likely to dropout of the study through death or being unable to attend clinic. As is the convention, intermittent missingness is assumed to be MAR with sources of NMAR coming from dropout (B. Muthén et al., 2011).

Issues concerning missing data and appropriate analytical methods were introduced in section 4.4.2. The approaches used for modelling NMAR mechanisms are complicated involving, in this instance, the joint modelling of the growth model and the dropout model. The generalised latent variable modelling framework is extremely flexible and allows for fitting several such models. A full investigation of such models requires a dissertation length investigation in itself. The following analyses are therefore relatively simple sensitivity analyses to ensure that the dropout mechanism does not overly influence the estimates of the growth parameters.

6.3.5.1 Selection models

Initially the Diggle and Kenward (1994) and Wu and Carroll (1988) selection models were considered. As was previously discussed selection models consider dropout conditioned on the observed data. The Diggle and Kenward (1994) selection model was the first to be considered. Applying this model to the

Table 6.9: Means (standard errors) of demographic and clinical variables across latent classes using posterior probability based multiple imputations

Class	Resilient	Delayed	Recovered	Chronic	χ^2	p
Age	57.06 (0.72)	58.53 (1.94)	55.27 (2.66)	56.52 (1.83)	1.73	0.630
Male	0.35 (0.02)	0.29 (0.07)	0.28 (0.06)	0.28 (0.05)	1.19	0.755
BMI	26.34 (0.22)	27.20 (0.68)	25.82 (0.64)	27.27 (0.61)	2.94	0.402
Socially deprived (Carstair)	0.33 (0.03)	0.31 (0.08)	0.26 (0.33)	0.33 (0.09)	0.61	0.895
Education	0.38 (0.03)	0.56 (0.09)	0.43 (0.11)	0.47 (0.10)	1.02	0.796
Social class (IV/V)	0.56 (0.03)	0.67 (0.08)	0.70 (0.12)	0.72 (0.09)	2.66	0.447
Smoker	0.22 (0.02)	0.27 (0.06)	0.21 (0.06)	0.32 (0.06)	2.44	0.486
Working	0.46 (0.03)	0.31 (0.08)	0.43 (0.11)	0.38 (0.09)	0.72	0.870
Early morning stiffness (hours)	1.03 (0.04)	0.99 (0.09)	1.20 (0.11)	1.21 (0.09)	8.70	**0.034**
HAQ disability	0.69 (0.02)	0.81 (0.05)	0.81 (0.06)	0.89 (0.05)	8.94	**0.030**
ESR	5.76 (0.11)	5.62 (0.32)	6.08 (0.37)	5.44 (0.31)	2.55	0.467
CRP	4.97 (0.17)	4.79 (0.49)	5.59 (0.53)	4.65 (0.44)	3.07	0.381
Tender joint count	3.68 (0.08)	4.24 (0.23)	4.14 (0.25)	4.77 (0.21)	14.75	**0.002**
Swollen joints	3.50 (0.09)	3.63 (0.28)	3.63 (0.27)	3.83 (0.27)	1.03	0.795
DAS	5.01 (0.20)	5.31 (0.41)	5.75 (0.92)	5.60 (0.17)	3.14	0.371
VAS pain	46.11 (1.30)	53.03 (3.64)	58.67 (4.33)	61.03 (2.96)	17.37	**0.001**

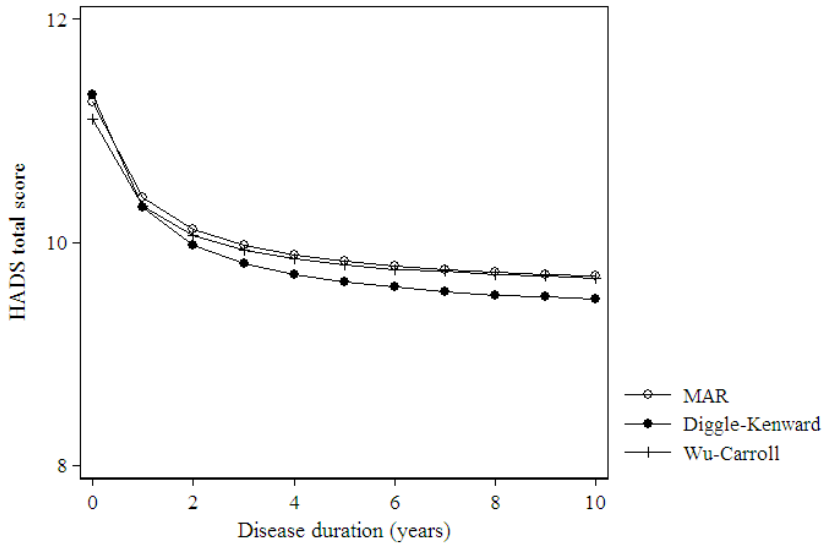


Figure 6.12: Estimated HADS total score mean trajectories for MAR, Diggle-Kenward and Wu-Carroll selection models

data, the estimated association between the level of psychological distress and dropout was small and non-significant ($OR_{y_t} = 0.96, p = 0.319$), suggesting that the MAR assumption holds. Furthermore, the estimate of the lagged effect of psychological distress on dropout was also non-significant ($OR_{y_{t-1}} = 1.04, p = .179$) indicating that psychological distress was not predictive of future dropout.

The Wu and Carroll (1988) model also supported the assumption that the data was MAR. No significant effect of either the random intercept ($OR = 1.11, p = .094$) or the random slope ($OR = 0.92, p = .324$) on dropout was observed.

The number of parameters and the information criterion for the MAR, Diggle-Kenward and Wu-Carroll models are shown in Table 6.10. The Diggle-Kenward model was indicated as being the best fitting model by the AIC, BIC and sample size adjusted BIC, whereas the MAR model is indicated as being the best fitting model by the consistent AIC. The estimated mean psychological distress trajectory for the Diggle-Kenward model and the Wu-Carrol model are shown in Figure 6.12. The estimated trajectories of the Wu-Carroll and the MAR model are almost identical. The Diggle-Kenward model indicates a slightly greater reduction in psychological distress over time ($\mu_\alpha = 2.02$), although the magnitude of the difference is small.

Table 6.10: Selection models fit statistics

	MAR	Diggle-Kenward	Wu-Carroll
Params	27	28	28
AIC	27794	**27789**	27822
CAIC	**27947**	27948	27980
BIC	27921	**27920**	27952
sBIC	27834	**27831**	27864

Table 6.11: Pattern-mixture model fit statistics

	MAR	PMM	Roy 2c	Roy 3c	Roy 4c	Roy 5c
Params	16	35	29	42	55	68
AIC	24384	24392	24324	24307	24293	**24289**
CAIC	**24474**	24591	24488	24545	24621	24674
BIC	**24458**	24556	24459	24503	24550	24606
sBIC	24407	24444	**24367**	24369	24375	24390

6.3.5.2 Pattern-mixture models

Next the pattern-mixture models were considered, which model the observed data conditional on the missing data. Both the conventional pattern-mixture model[6] and the Roy (2003) latent dropout pattern-mixture model were fitted to the data.

Table 6.11 shows the the fit of the conventional pattern-mixture model, and the Roy latent dropout pattern-mixture model with $C = 2, 3, 4, 5$. In addition, the fit statistics for a MAR model are presented where the model is specified with the same log-likelihood metric by constraining the random effect mean estimates to be equal. The information criterion support different models. The AIC indicates that best fitting model is the Roy model with 5 latent classes, however the AIC has been shown to over select the number of classes in growth mixture models and should therefore be treated with caution (Tofighi & Enders, 2006). The consistent AIC and the BIC, which have both shown more acceptable properties, indicate the MAR model, whereas the sample size adjusted BIC selects the 2-class Roy model. Inspection of the individual trajectories for each dropout pattern shows similar trends for 9 of the 11 patterns with no obvious time trend (Figure 6.13). Mixing over the trajectories gives an estimate of the overall growth trajectory that is almost identical to the MAR estimate (Figure 6.14).

Although not indicated by the fit indices it is of interest to consider the Roy 4-class dropout pattern-mixture model in relation to the 4-class GMM that was identified in the previous section since the Roy model provides a sensitivity analysis for the MAR assumption of the GMM. Similar latent classes of

[6]The model was specified with respect to dropout rather than general item missingness. As such one pattern was considered for individuals dropping out of the study at each year of follow-up.

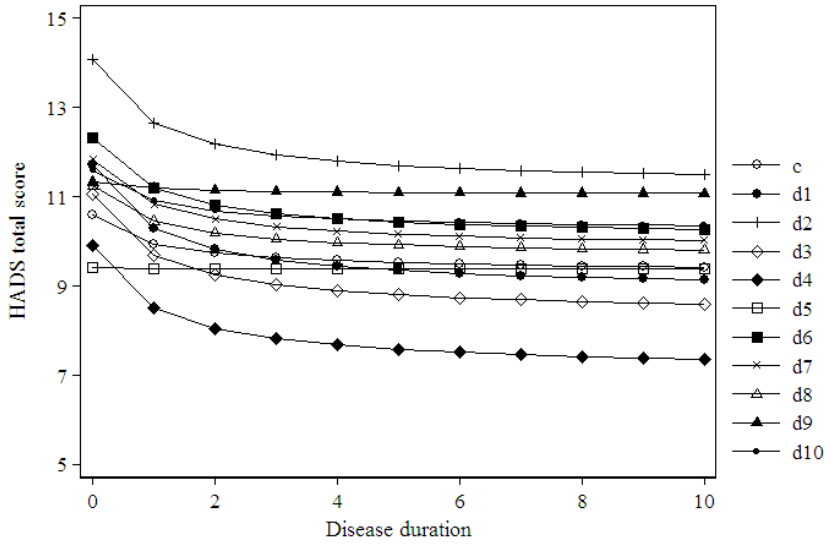


Figure 6.13: Estimated HADS total score trajectories for each dropout pattern-mixture model

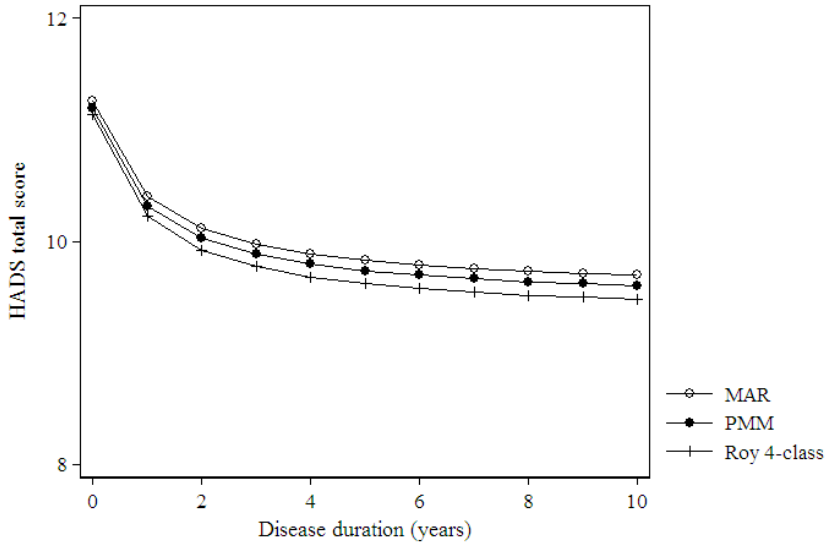


Figure 6.14: Estimated HADS total score

growth trajectories are identified by the model with little change in the proportion of people in each class. Respectively, for the MAR model and the 4-class latent class dropout model the number in each of the classes was resilient 68% & 66%, chronic 12% & 11%, recovered 9% & 9%, delayed 11% & 14%. The overall trajectory mixing across these latent classes is shown in Figure 6.14. The mean of the random intercept is similar to that of the MAR model but the mean of the random slope indicates a slightly greater average reduction in distress ($\mu_\beta = 1.98$) similar to that of the Diggle-Kenward selection model.

Sensitivity analysis exploring a number of NMAR dropout mechanisms supports the validity of the estimates under the assumption that the missingness mechanism is MAR. Caution is still needed concerning the interpretation of the results in light of the proportion of missing data since the sensitivity analysis assumed that the intermittent missingness mechanism was MAR. Furthermore, since the missing data mechanism can never be known there are an infinite number of possible NMAR mechanisms. (B. Muthén et al., 2011) describes several extensions of the selection and pattern-mixture models assessed that add extra complexity to the models estimated, for example by allowing for separate latent classes for the growth and dropout parts of the model, that may provide more appropriate sensitivity analyses. However, a fuller investigation of NMAR mechanisms is beyond the scope of this dissertation and further models are not considered.

6.4 Discussion

This chapter explored the shape of the trajectories of psychological distress over the fifteen years from diagnosis of RA. Analyses employing LCM's confirmed the initial findings of the descriptive analysis, the mean trajectory showed a slight decrease initially that stayed stable over time. There was however much inter-individual heterogeneity. Male sex, social class IV or V and factors relating to severity of disease symptoms were related to higher initial levels of psychological distress. Moreover, worse disease severity at baseline was associated with a greater decline in psychological distress over time. Growth mixture modeling was employed to assess whether the data were appropriately described using a single trajectory. Four trajectories, relating to the Bonanno (2005) response to trauma model, were found to provide the most parsimonious grouping of the individual trajectories. Self-reported somatic symptoms explained differences between the classes. Finally, sensitivity analysis exploring the assumptions concerning the missing data mechanism indicated that the assumption that data were *MAR* was sound.

While there have been a large number of studies examining psychological distress and adjustment in RA none have examined changes in distress over such long periods of time or employed appropriate

longitudinal models to examine change. The finding of a reduction in distress in the years following diagnosis is in line with previous research using appropriate methodologies (e.g. Ødegård et al., 2007; Schieir et al., 2009, see section 3.3), and fits more broadly with the literature concerning adjustment to life with a chronic illness (Stanton, Revenson, & Tennen, 2007). Furthermore, in line with other studies psychological distress cross-sectionally levels of psychological distress were associated with demographic characteristics such as sex and socio-economic status, and with clinical features relating the severity of disease symptoms. For example, Treharne et al. (2007) found that cross-sectionally older age and worse HAQ disability were associated with increased levels of psychological distress, and Schiaffino et al. (1998) found lower education and more active disease were related to worse psychological distress. Examination using time-varying covariates indicated that the cross-sectional association between variables was stable across time, confirming previous reports (Covic, Pallant, Conaghan, & Tennant, 2007; Smedstad et al., 1997).

Growth mixture modelling revealed that four trajectories, comparable to those predicted by the Bonanno response to trauma model (Bonanno, 2005), best summarized the distributions over time. The largest group, consisting of around two-thirds of the sample, was resilient to the traumatic effects of the disease with consistently low levels of psychological distress over time. Another group however experienced chronic disruption in psychological well-being. Two further groups showed opposite reactions. One showed a short-lived episode of high distress with recovery to normal levels after a couple of years, whereas the other group experienced an insidious increase in distress over time.

The resilient group was the largest consisting of around two-thirds of the sample. This is larger than expected under Bonanno's model but seems reasonable since the severity of the traumatic experience, development of a chronic physical illness, is less than the model was typically intended for (e.g. a terrorist attack). The figures is towards the upper limit of the proportion observed in studies applying similar methods to other clinical populations (Helgeson et al., 2004; Lam et al., 2009; A. A. Kaptein & Weinman, 2004; Martens et al., 2008; B. M. Murphy, Elliott, Higgins, et al., 2008). This is not entirely surprising since, despite its impact on health-related quality of life, it seems unlikely that diagnosis of RA is potentially as traumatic an experience as a myocardial infarction or breast cancer surgery. Furthermore, consistent with several of these studies the majority of the change occurred early in the course of the disease (Helgeson et al., 2004; Lam et al., 2009; K. I. Kaptein, Jonge, Brink, & Korf, 2006). This would explain the apparent stability observed in the majority of longitudinal studies of individuals with established RA (see section 3.3).

The current study identified differences between the groups at the time of presentation to the

rheumatologist in terms of subjective self-reported disease symptoms—pain, stiffness and functional impairment—rather than objective measures of disease activity. One explanation is that differences result from some negative dispositional reporting style. There has been considerable discussion of such an effect in the literature, and is generally referred to as negative affectivity (NA). The previous chapter indicated that it is likely that the HADS, which assesses general psychological distress, in part captures some of this negative affectivity. While NA may account for some of the association between the level of psychological distress at baseline and self-reported symptoms, it does not account for differences between the resilient and delayed classes or between the chronic and recovered classes, whom showed similar levels of distress at baseline but experienced different changes.

It seems likely that psychological factors play an important role role in driving the changes in distress. For example, negative illness perceptions such as the over interpretation of symptoms may help to maintain levels of psychological distress or act as a vulnerability factor that increases the level of psychological distress over time (Leventhal, Diefenbach, & Leventhal, 1992). Alternately, there may be a difference in the coping strategies employed with, for example, avoidant and denial working in the short term but causing problems later in the disease (Scharloo et al., 1999; Lowe et al., 2008; G. K. Brown, Nicassio, & Wallston, 1989).

An alternative and equally plausible explanation is physiological. It may be that the classes experience different disease trajectories. For example, the delayed group may experience a disease that is initially relatively benign but is fast progressing and has severe impact on quality of life in general. Vice-versa it may be that those in the recovered group initially experience a very severe disease but one that is well managed by treatment and disease progression is relatively slow. This explanation is limited by the null finding for baseline differences in objective measures of disease severity between these two classes. In reality it seems likely that there is an interplay between the psychosocial and physiological factors that drives the levels of psychological well-being.

There are a number of strengths and limitations of the current study. The major strength relates to the design of the study and the methods of analysis used. The combination of a large sample of individuals followed, since diagnosis, for a long period with advance longitudinal modeling techniques allows for a greater insight into the response to the development of RA than previous studies.

The main limitation of the study relates to the amount of missing data. As with all longitudinal studies there was a large number of individuals that had dropped out of the study. Furthermore, specifically for the HADS questionnaire there was relatively large amounts of intermittent missingness. Despite this limitation the findings of the models are likely to be fairly robust. The models used assume that data

were MAR, which is less restrictive than the MCAR assumption of more traditional analytic methods. Furthermore, sensitivity analysis examining whether the dropout mechanism was likely to be NMAR indicated that any violation of the models assumptions was limited and would have little impact on the substantive results. However, one needs to be mindful that the NMAR condition is untestable and the missing data mechanism may still be non-ignorable leading to biased results. Full investigation of such mechanisms is beyond the scope of this dissertation.

A further limitation is that the analytical methods employed presupposes a longitudinal course. The HADS is intended as a prolonged state measure of psychological distress with a reference frame of two-weeks. As such, it is likely to be influenced by trait and state factors. Since RA generally follows a flaring-remitting pattern, it seems likely that psychological distress will be affected by current levels of somatic symptoms. This would add to the measurement error when trying to define trajectories. However, analysis investigating the cross-sectional association between functional impairment, pain and disease activity using time-varying-covariates showed similar associations and no improvement in model fit compared to regression on the random intercept. Further, analysis jointly modeling distress with the disease course is likely to provide greater insight.

Knowledge of the factors associated with distinct psychological response trajectories may help guide targeted interventions to groups of individuals that would benefit most, with potential benefits to quality of life and clinical outcomes. Specifically the results suggest targeting those with worse self-reported somatic symptoms that experience less of an improvement in well-being than one might expect following the initiation of disease-modifying treatment. Indeed randomised controlled trials of psychological therapies in RA samples have observed greater improvements in somatic symptoms as well as depression in treatment versus control groups (Sharpe et al., 2003, 2008; Knittle et al., 2010; Pradhan et al., 2007; Zautra et al., 2007; Dixon et al., 2007). Psychological or behavioural interventions soon after diagnosis, such as tailored CBT targeting somatic symptoms, may help to reduce psychological distress in this condition. It is important however to note that a substantial number of individuals with high levels of distress early in the course of the disease will resolve without intervention. Nevertheless, for an equally large number of individuals distress will remain chronically high. These individuals are most likely to be vulnerable to poor disease outcomes and be a greater burden on health services (Katon et al., 2007; Sharpe et al., 2008).

The remaining two empirical chapters will extend the findings of the current chapter. The next chapter will examine the synchronous relationship between psychological distress and disease symptoms using the same cohort. Joint models of disease progression according to somatic symptoms and trajec-

tories of psychological distress will provide greater insight into the impact of the physiological aspects of the disease on distress. The proceeding chapter will examine the role of psychosocial factors, particularly illness perceptions and coping strategies, on changes in psychological distress using a smaller sample with shorter follow-up duration.

Chapter 7

The longitudinal association between distress and somatic symptoms

7.1 Introduction

In the previous chapter it was shown that psychological distress in RA follows a non-linear pattern with rapid improvements observed early in the course of the disease that stabilise two to three-years following diagnosis. This is perhaps due to psychological adaptation to the disease and the individual's ability to cope with the stress associated with the somatic symptoms of the disease improving in efficiency and efficacy (Stanton et al., 2007). Alternatively, these changes may be due to better control of the disease through effective therapeutic management of the disease activity that causes these somatic symptoms. The current chapter will extend these findings and explore the evidence in relation to these explanations by examining in greater detail the association between changes in psychological distress and the common somatic symptoms of pain and functional limitation. The aim is to provide greater insight into the strength of the association between psychological distress with pain and functional limitation, as well as into the direction of causality.

Numerous studies have examined the longitudinal association between function and psychological distress in RA. The findings of these studies were reviewed in detail in Chapter 3 and are now briefly discussed to provide the background and motivation of the current chapter.

Strong cross-sectional associations have beeen observed for psychological distress with pain (G. K. Brown, Nicassio, & Wallston, 1989; Evers et al., 1997; Hawley & Wolfe, 1988; Schiaffino et al., 1991; Sharpe et al., 2001; Smedstad et al., 1997; Thyberg et al., 2009) and functional limitation (G. K. Brown, Nicassio,

& Wallston, 1989; Chaney et al., 2004; Demange et al., 2004; Evers et al., 1997; Hawley & Wolfe, 1988; Nicassio & Wallston, 1992; Schiaffino et al., 1991; Sharpe et al., 2001; Smedstad et al., 1997), even after controlling for demographic and clinical characteristics. However, findings regarding longitudinal associations are rather less conclusive. After controlling for earlier distress, of the 18 studies examining a longitudinal effect of pain on distress only 8 (44%) reported a significant effect (section 3.4.3.1). The proportion was similar for functional limitation, with 6 out of 15 studies (40%) reporting a significant longitudinal effect (section 3.4.3.2). Obviously, judgments based on the number of studies reporting a significant result are not robust. Although no formal meta-analysis was conducted, inspection of the reported effect sizes indicated that any longitudinal effect was likely to be weak. This is perhaps not unsurprising since for these studies the duration between measurement occasions ranged from 6-months to 18-months.

Three of the studies included in the above number used auto-regressive cross-lagged path models (G. K. Brown, 1990; Schieir et al., 2009; Smedstad et al., 1997).[1] Two of these studies examined the cross-lagged effects between pain and psychological distress (G. K. Brown, 1990; Schieir et al., 2009). G. K. Brown (1990) reported a weak positive cross-lagged effect of pain on psychological distress (CESD) in 233 RA patients assessed at three-waves each six-months apart ($\rho_{t_2} = .23$ & $\rho_{t_3} = .26$). No cross-lagged effects were observed for depression on pain. Conversely, however Schieir et al. (2009) found a weak positive cross-lagged effect of psychological distress (CESD) on pain ($\rho_{t_2} = .28$) in 180 RA patients, assessed on two occasions 6-months apart, but no effect of pain on psychological distress. Only one study employing cross-lagged path analysis examined the longitudinal association between psychological distress and functional limitation. In a study of 216 RA patients assessed on three equally spaced occasions over 2-years, Smedstad et al. (1997) found that psychological distress (AIMS depression) was predicted by prior functional limitation (HAQ), albeit very weakly and only between the first two time-points ($\rho_{t_2} = .13$). Anxiety (AIMS anxiety), however, was not predicted by prior functional limitation. Furthermore, no effect of psychological distress in terms of anxiety or depression was predictive of future functional limitation. Only tentative conclusions can be drawn from the findings of these studies, but it would seem that any longitudinal association between psychological distress with pain or functional limitation is weak and likely to be bidirectional.

Although excluded from the review chapter it is appropriate to discuss the findings from experimental research in relation to the causal relations between psychological distress and somatic symptoms.

[1] (G. K. Brown, Nicassio, & Wallston, 1989) also reported on a cross-lagged path model but the same data was used in path analysis reported by (G. K. Brown, 1990) so was excluded.

Considering first experimental studies based on clinical trials of disease modifying drugs, it is clear that treatments that are effective in reducing somatic symptoms such as pain and functional limitation concurrently reduce levels of psychological distress (e.g. Westhovens et al., 2006). The reverse is also true, studies of antidepressant usage suggest that, as well as reducing levels of distress, somatic symptoms are improved (e.g. Frank et al., 1988; Lynch, 2001). These findings provide further support for a bidirectional causal relationship between distress and functional limitation.[2]

Returning to the weak cross-lagged effects observed, that such small effect sizes are observed is not surprising since studies consider whether the level of psychological distress at one time point is predicted by levels of pain and functional limitation 6-months or even a year earlier. It is more appropriate to consider whether changes in psychological distress occur synchronously with changes in pain and functional limitation. Only one study examined the relationship between changes in psychological distress and changes in symptoms. In a study of 319 RA patients followed for three-years, Katz (1995) observed that individuals experiencing an increase in symptoms of depression (GDS) there was a fourfold increase in the odds of experiencing a worsening of functional limitation over the same period (OR= 3.96; 95% CI: $1.01, 15.67$). Clearly, this is an area that needs further examination.

An appropriate analytic strategy not currently employed in the rheumatological literature is to use bivariate latent curve models (LCM) to examine intra-individual changes in function and psychological distress. These models extend the standard LCM model (see section 4.3) to jointly model two longitudinal processes. Examining the covariance's between the resulting random effects, which indicate the baseline level and rate of change in function and distress for the individual, will provide greater insight into the relationship between distress and function as well as the direction of causality. A recent development extending LCM through the inclusion of a nested autoregressive path model—autoregressive latent trajectory (ALT) modelling—may provide further useful information (Bollen & Curran, 2004; P. J. Curran & Bollen, 2001). Specifically, it may also provide information regarding the direction of the causal effect between psychological distress, pain and functional limitation.

7.1.1 Aims & Objectives of the chapter

The overarching aim of this chapter is to examine the synchronous association between psychological distress with pain and functional limitation over a period of 5-years following the diagnosis of RA,

[2]This assumes that the effect of DMARDs on distress is mediated through disease activity and the associated reduction in functional limitation, and that the effect of antidepressants is mediated by changes in the levels of neurotransmitters in the brain that reduce symptoms of depression. It is possible that either DMARDs or antidepressants may have a more direct effect on distress or disease activity, respectively (Lynch, 2001; Straub & Cutolo, 2001), but this is beyond the scope of this chapter.

using data from the ERAS cohort. With respect to this aim, there are three specific objectives: (i) to quantify the strength of the cross-sectional relationship between psychological distress, pain, and functional limitation; (ii) examine whether changes in psychological distress occur in synchrony with changes in pain and functional limitation; and (iii) assess the ability of pain and functional limitation at a previous time point to predict changes in psychological distress at a later time point, and *vice-versa*. These objectives map to the second objective of the dissertation, outlined in section 3.5.3.

7.2 Methods

7.2.1 Sample

As in the previous chapter, the sample used in the current analysis consisted of a sub-sample of individuals from the ERAS cohort ($N = 784$). For the present analysis data over the five-years following diagnosis was used—the reason for this discussed later, in section 7.2.3. The recruitment procedure, demographic profile and pattern of dropout for the sample were described in detail in Chapter 6 so are not discussed in detail here. At the five-year assessment 534 (68%) remained in the sample. Missing data concerning psychological distress was common, ranging between 32% at 1-year to 17% at 5-years for those completing follow up. For pain and functional limitation however data was far more complete. At the baseline assessment there were no missing values and at the later assessments there were less than 5% for those remaining at follow-up.

7.2.2 Measures

Psychological distress The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) total score was used as a measure of psychological distress. As in the previous chapter, since only sum scores for the anxiety and depression subscales were available the total score was used as a measure of general psychological distress incorporating specific features of anxiety (autonomic arousal) and depression (anhedonia).

Functional limitation Functional disability was operationalised using the UK version of the Health Assessment Questionnaire (HAQ) disability index (Fries et al., 1980; Kirwan & Reeback, 1986). The HAQ consists of 20-items concerning eight activities of daily living: dressing & grooming, arising, eating, walking, hygiene, reach, grip and activities. Items are scored on a four-point ordinal scale ranging from zero “without any difficulty” to three “unable to do”. In addition, for each activity respondents also

report whether they receive assistance from other people or use assistive devices. The aggregated score is the average of the maximum rating within each of the eight activities of daily living adjusted for the use of devices and assistance. Scores range between zero and three with higher values indicating greater limitation. Generally, scores greater than 1 indicate that an individual has moderate disability, and above two severe disability.

Pain A 100mm visual analogue scale (VAS) anchored at zero 'No pain at all' and 100 'Worst pain ever' was used to assess the patients level of bodily pain in the clinic. VAS pain scores followed a uniform distribution.

Disease activity The original version of the Disease Activity Score was used to measure disease activity (van der Heijde et al., 1990). This is a composite measure including either erythrocyte sedimentation rate (ESR) (or C-reactive protein [CRP]) plus a count of the number of tender (TJC) and/or swollen joints (SJC) of 44 specific joints (mainly the hands, feet and wrists). Scores for the DAS range between zero and around ten (although there is technically no upper limit since ESR and CRP are unbounded), with scores of over five indicating severe disease and scores less than three low disease activity.[3] DAS scores were approximately normally distributed. However, CRP, ESR, SJC and TJC were all positively skewed and were square-root transformed when used separately in the analysis.

Early morning stiffness The amount, in hours, of early morning stiffness (EMS), an indicator of disease activity, was also recorded. Responses were positively skewed and therefore were square-root transformed.

Comorbidity Comorbidity was assessed using the Charlson comorbidity index (Charlson et al., 1987). This is essentially a weighted count of comorbidities that have been found to be related to mortality (e.g. cancer, heart disease, diabetes, chronic obstructive pulmonary disease etc.). For the current analysis, Charlson scores were dichotomised as the presence or absence of at least one Charlson comorbidity.

Socio-economic status SES was assessed at baseline according to the Registrar General's classification for social class, the Carstair Index of social deprivation based on the patients post-code area and their highest level of educational qualification. All were dichotomized, social class IV or V categorized as "low social class", patients living in areas falling in the lowest 2 quintiles of the Carstair Index were defined as

[3] A DAS score of less than 1.6 corresponds to the American Rheumatology Association preliminary criteria for clinical remission (Fransen et al., 2004).

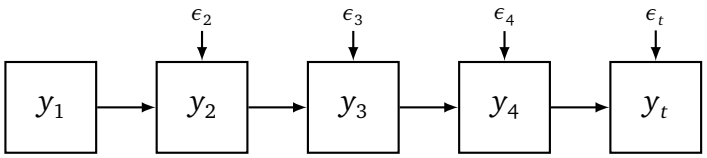


Figure 7.1: Autoregressive model

"socially deprived", and 'left school with no educational qualifications' categorized as "low education". In addition, work status (employed/unemployed) was also used. This information was only available for those in the ERAS database, and is therefore missing for the additional individuals (see section 6.2.1 and Appendix D).

7.2.3 Autoregressive latent trajectory models

There are two main approaches to the analysis of longitudinal repeated data (Raykov, 1998). As well as the LCM, discussed extensively in Chapter 4, a further approach, generally referred to as autoregressive (AR) modelling, is also widely used. AR models are commonly employed in the analysis of long time-series, for example the autoregressive moving average (ARMA) model which combines an autoregressive component with a moving average part is widely used in the field of economics. The AR model is also applicable for shorter time-series; indeed the residualised change model widely used in the social sciences to examine change over two measurement occasions is the most basic form of the AR model. The standard (simplex) AR model can be expressed as

$$y_{it} = \alpha_t + \rho_{t(t-1)} y_{it-1} + \epsilon_{it} \tag{7.1}$$

where y_{it} are the observed values on variable y for person i at time t, α_t is the intercept, $\rho_{t(t-1)}$ is the autoregressive parameter representing the strength of the association between the value of y at a previous time-point y_{it-1} on its current value y_{it}. All of the parameters are allowed to vary across time-points.

For $t = 1$ the autoregressive term $\rho_{t(t-1)} y_{it-1}$ is not included in the model since no predictor is available. That is, to avoid problems of infinite regress, the first observation y_{i1} it is treated as predetermined. The simplex AR model is depicted graphically in Figure 7.1. Furthermore, the univariate AR model can easily be extended to include a second autoregressive process with cross-lagged effects (Figure 7.2).

The AR model has been widely criticised (e.g. Marsh & Grayson, 1994). The main issue is that the AR model is based on covariance stability and therefore cannot take in to account the underlying

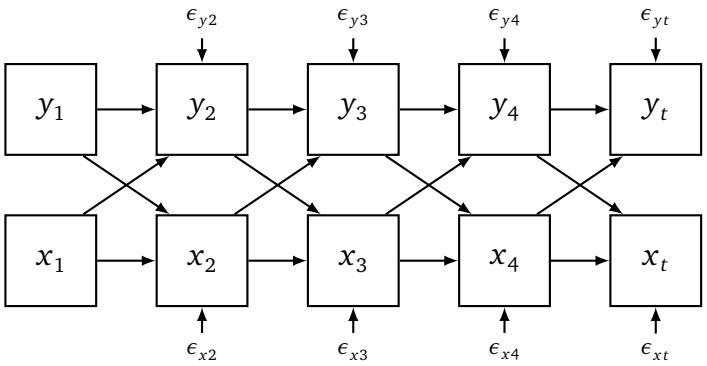


Figure 7.2: Autoregressive cross-lagged model

trajectory of the variable of interest. Furthermore, the time specific intercepts α_t and autoregressive parameters $\rho_{t(t-1)}$ are *fixed effects* and thus do not account for intra-individual differences in change. In contrast, the LCM model incorporates *random effects* for the growth parameters allowing them to vary across individuals. For this reason the use of LCMs have become increasingly popular in recent years.

A limitation of the LCM model is that, usually, only overall intra-individual trajectories are estimated, thus autocorrelations between time-points are not accounted for. Deviations from the intra-individual trajectories are treated as random errors. However, in many situations it is likely that these deviations are substantively meaningful. For example, RA follows a flaring-remitting course, during a disease flare physical ability is likely to be impaired irrespective of the underlying trajectory of physical ability that is associated with the progression of the condition. Furthermore, it is likely that individuals experiencing a flare at one time point will have an increased propensity for a flare at other time points. Morin, Maïano, Marsh, Janosz, and Nagengast (2010, p.8) explain that "such time-specific, state-like, relations may indeed be quite strong and/or vary across time and thus potentially bias the estimation of the full trajectories by causing them to be 'absorbed' by the remaining parameters of the model". Although, it is possible to incorporate autocorrelations between adjacent time-points within the LCM model,[4] a more flexible alternative is to incorporate an AR model within the LCM model (P. J. Curran & Bollen, 2001; Bollen & Curran, 2004).[5]

Although the AR and LCM models are often seen as competing approaches, Bollen and Curran (2004, p.336) have shown how they can be seen as "special cases of a more encompassing model that [they] call the autoregressive latent trajectory (ALT) model". Combining the notation used in equations 4.5 and 7.1 the ALT model for $t > 1$ can be expressed as

[4] The LCM models estimated in Chapter 6 incorporated an autocorrelated error structure
[5] Hamaker (2005) notes the equivalence of the ALT and the LCM with an autocorrelated error structure

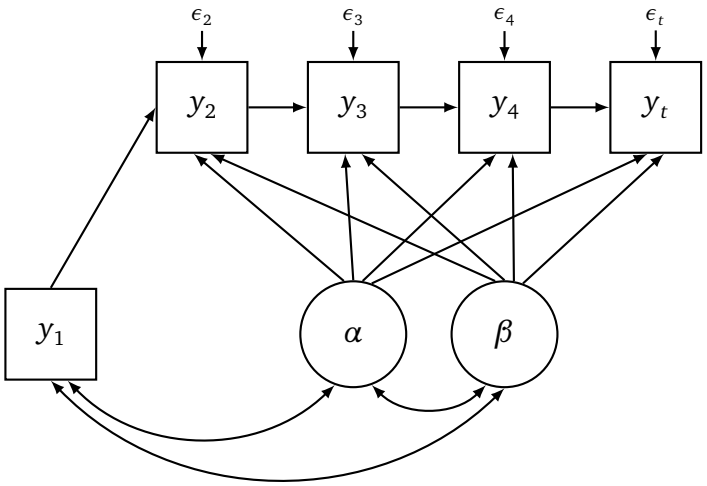


Figure 7.3: Autoregressive latent trajectory model

$$y_{it} = \alpha_i + \lambda_t \beta_i + \rho_{t(t-1)} y_{t-1} + \epsilon_{it} \tag{7.2}$$

$$\alpha_i = \mu_\alpha + \zeta_{\alpha i} \tag{7.3}$$

$$\beta_i = \mu_\beta + \zeta_{\beta i} \tag{7.4}$$

As in the AR model, the first time-point is treated as predetermined and is therefore not included in the LGM part of the model. The ALT model is depicted graphically in Figure 7.3. In this model the specifications are similar to the standard LCM, except the correlation between the first time-point, the intercept factor and the slope factor are always estimated. For identification, linear ALT models require at least five time-points, although additional constraints can be added to allow the identification of models with three or four time-points. Additional details of these models and the assumptions underlying them are described in detail by P. J. Curran and Bollen (2001) and Bollen and Curran (2004).

As with the standard AR model and the LCM model, extending the model from one process to two is possible. However, due to the increased complexity of the ALT model (i.e. the number of parameters being estimated) problems with convergence are common. Bollen and Curran (2004) recommend a systematic approach whereby the unconditional univariate LGM and AR models are first examined and then combined as a univariate ALT model, with the best fitting model selected for inclusion in the bivariate model. Then unconditional bivariate LCM and AR models incorporating cross-lagged effects are estimated, which are combined as an an unconditional bivariate ALT model. Prior to the inclusion of covariates, constraints on parameters usually need to be applied to improve the parsimony of the

model—such as, incorporating equality constraints for the time specific uniqueness correlations, the autoregressive parameters and the cross-lagged parameters. In addition to these constraints, Voelkle (2008) recommends restricting the number of assessment occasions included in the model to ensure that the LCM part of the model is correctly specified,[6] hence the decision to restrict the current analysis to 5-years.

The ALT model provides a useful framework to examine longitudinal processes, in particular when we are concerned with two processes that we expect to be related. Specifically, the ALT model allows for the researcher to distinguish between LCM and AR models. Morin et al. (2010) argue that the ALT model allows for the disaggregation of state and trait processes due to the differential interpretation of the AR parameters for the ALT compared to the AR model. Whereas for the AR model in which the AR parameters reflect inter-individual rank order stability, for the ALT model the AR parameters reflect 'the impact of individual state-like deviations from the overall trajectories' (Morin et al., 2010, p.9).

In relation to the objectives of this chapter, fitting bivariate ALT models for psychological distress separately with pain and functional limitation will allow for the assessment of the strength of the association for the underlying trajectories. Controlling for the underlying trajectories, it will be possible to assess whether there are time-specific correlations, as well as autoregressive and cross-lagged effects for the variables.

7.3 Results

7.3.1 Demographic and clinical characteristics

The baseline demographic profile of the sample was described in Chapter 6. Briefly, the average age at onset was 57.0-years (SD = 15.1), 67% were female, 41% and 60% were classed as educationally or socioeconomically disadvantaged, respectively, 43% were in paid employment, and 24% were smokers. On average, invididuals experienced symptoms for 7-months prior to their first presentation to the rheumatologist, at which time they were recruited to the ERAS cohot. The average scores for psychological distress, pain, and functional limitation at baseline and over the five-years following diagnosis are given in Table 7.1. For all, levels were raised at the baseline assessment, with a dramatic reduction over the first year and then stable and possibly increasing levels thereafter.

[6] In a simulation study Voelkle (2008) shows that misspecification of the LCM part of the ALT model will bias parameter estimates in the AR part. This is because the AR part of the model is concerned with the residualised values of y_{it} after accounting for the underlying trajectory, misspecification of the LCM model directly influences the residuals thus biasing the AR parameter estimates. Voelkle (2008) recommends restricting the number of occasions used in ALT models since obtaining a well specified LCM is more difficult with increasing numbers of occasions included.

7.3.2 Preliminary analyses

7.3.2.1 Correlations

The pattern of correlations shown in Table 7.1 would appear to suggest that at the time of diagnosis when levels of pain, functional limitation and psychological distress are typically high there is only modest association between between the three domains (r = .28 to .40). After 1-year of follow-up, when most patients have started disease-modifying therapy, the association is stronger and remains stable over time (r = .43 to .57). For pain, functional limitation and psychological distress an individual's position in the distribution of scores on the same variable is highly related across time points. Furthermore, an individual's position in the distribution of scores on an alternate variable at the same time is strongly positively related, and moderately so for different time points.

The correlations for 1-year change scores showed moderate associations between changes in psychological distress accompanying changes in pain (r = .20 to .35) and functional limitation (r = .24 to .36). Changes in disability and pain were also positively correlated (r = .34 to .53). This highlights the issue that changes in the somatic symptoms of the condition tend to be associated with concurrent changes in psychological distress.

7.3.2.2 Growth mixture modelling

A report based on a growth mixture modelling (GMM) analysis of the functional limitation data over 10-years is presented in Appendix A. As with the GMM of the HADS distress data, four latent trajectory classes were identified as providing the best fit to the data. The trajectories for each class are shown in Figure 7.4. Confirming previous research, a 'j-shaped' trajectory described the average trajectory for the cohort as a whole and for the largest of the four distinct trajectories (46%). For this class, there was an initial improvement in functional limitation, presumably due to the initiation of disease-modifying therapy, followed by a gradual and insiduous decline. Three further trajectories accounting for over half of the cohort, however, did not follow this prototypical trajectory. Two classes also showed an initial improvement in functioning but with stable levels of either low or no limitation. For around one-fifth of individuals however there was no improvement in function with levels of functional limitation staying stable and high throughout the period of follow-up. Compared to the prototypical trajectory, individuals with consistently high levels of functional limitation were more likely to be female, have lower educational attainment, less likely to work and have worse disease severity. Those in the no or low limitation classes were more likely to be younger, male, from a higher social class, be in paid

Table 7.1: Correlations and descriptive statistics for HADS distress, HAQ disability and VAS pain ($N = 784$)

	HADS-0	HADS-1	HADS-2	HADS-3	HADS-4	HADS-5	HAQ-0	HAQ-1	HAQ-2	HAQ-3	HAQ-4	HAQ-5	Pain-0	Pain-1	Pain-2	Pain-3	Pain-4	Pain-5
HADS 0yr	1																	
HADS 1yr	0.55	1																
HADS 2yr	0.54	0.77	1															
HADS 3yr	0.59	0.76	0.75	1														
HADS 4yr	0.51	0.71	0.76	0.78	1													
HADS 5yr	0.54	0.69	0.71	0.76	0.79	1												
HAQ 0yr	0.28	0.23	0.21	0.27	0.20	0.17	1											
HAQ 1yr	0.24	0.44	0.34	0.39	0.35	0.34	0.64	1										
HAQ 2yr	0.24	0.43	0.43	0.40	0.40	0.37	0.61	0.85	1									
HAQ 3yr	0.25	0.40	0.36	0.45	0.43	0.38	0.59	0.82	0.88	1								
HAQ 4yr	0.26	0.41	0.37	0.42	0.49	0.41	0.59	0.79	0.84	0.90	1							
HAQ 5yr	0.27	0.38	0.37	0.42	0.44	0.44	0.58	0.77	0.83	0.87	0.90	1						
Pain 0yr	0.40	0.19	0.28	0.30	0.24	0.22	0.36	0.14	0.14	0.14	0.16	0.13	1					
Pain 1yr	0.20	0.45	0.39	0.34	0.38	0.34	0.15	0.48	0.46	0.43	0.43	0.41	0.24	1				
Pain 2yr	0.27	0.32	0.50	0.36	0.45	0.35	0.16	0.37	0.49	0.44	0.42	0.47	0.26	0.57	1			
Pain 3yr	0.19	0.32	0.38	0.47	0.44	0.38	0.18	0.37	0.43	0.52	0.51	0.50	0.26	0.49	0.55	1		
Pain 4yr	0.20	0.39	0.39	0.37	0.53	0.43	0.19	0.41	0.45	0.49	0.57	0.52	0.24	0.53	0.50	0.59	1	
Pain 5yr	0.17	0.30	0.38	0.36	0.46	0.46	0.16	0.38	0.42	0.47	0.48	0.56	0.16	0.46	0.55	0.49	0.62	1
Mean	11.68	9.81	9.72	10.21	10.23	10.31	0.73	0.55	0.55	0.60	0.64	0.68	49.88	30.91	30.22	31.47	31.99	32.51
Var	47.89	46.70	47.35	52.38	51.30	52.40	0.46	0.42	0.42	0.50	0.55	0.62	772.44	651.21	689.10	762.81	772.06	725.90
SD	6.92	6.83	6.88	7.24	7.16	7.24	0.68	0.65	0.65	0.71	0.74	0.79	27.79	25.52	26.25	27.62	27.79	26.94
Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Max	34.00	33.00	38.00	33.00	34.00	39.00	3.00	3.00	3.00	3.00	3.00	3.00	100.00	100.00	100.00	100.00	100.00	100.00

employment and have milder disease severity.

Table 7.2 shows the marginal distribution for the most likely classes from the separate GMMs for functional limitation and psychological distress. There is a clear association between the most likely class memberships. There was a larger proportion of individuals in the delayed and chronic psychological distress classes who were also in the moderate-increasing and high-stable functional limitation classes. This indicates that changes in functional limitation and psychological distress do appear to occur concurrently. The findings of the GMM models are not discussed further, since the bivariate ALT models provide greater insight into the temporal association and synchronicity of change between psychological distress and the somatic symptoms of the disease.

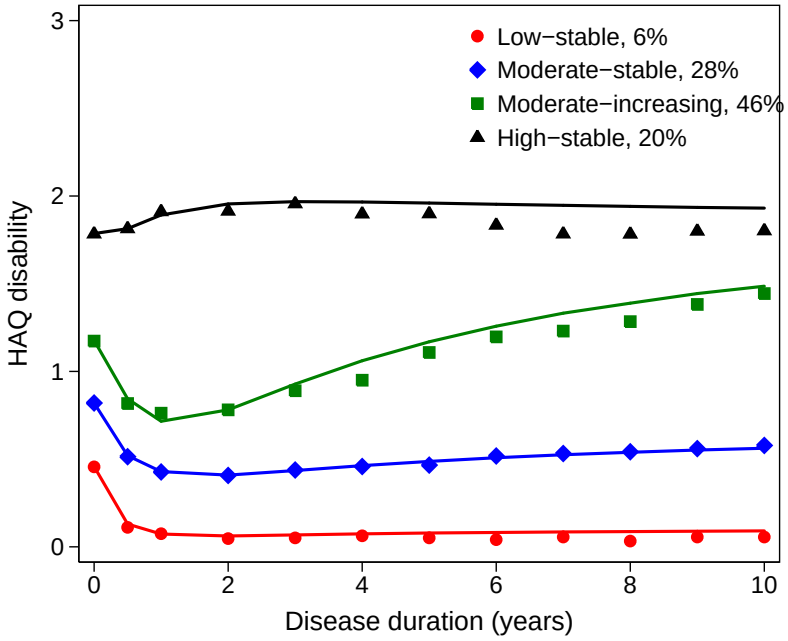


Figure 7.4: Predicted trajectories for the 4-class growth mixture model for HAQ disability

Table 7.2: Marginal distribution of the most-likely class for functional limitation GMM within most-likely class for psychological distress GMM

	HAQ disability class			
HADS distress class	Low-stable	Moderate-stable	Moderate-increasing	High-stable
Resilient	12%	36%	37%	16%
Recovered	8%	54%	38%	0%
Delayed	0%	17%	34%	48%
Chronic	0%	11%	30%	59%

7.3.3 Autoregressive latent trajectory models

The ALT models for psychological distress were estimated following the framework described by Bollen and Curran (2004) that was introduced in section 7.2.3. This involves first examining the fit of univariate AR models, then univariate LCMs and finally univariate ALT models. Following this framework should ensure that neither the AR nor the LCM part of the ALT model is misspecified for psychological distress, pain or functional limitation. Reducing the likelihood of misspecification and convergence issues when combined into a bivariate ALT model for psychological distress with pain or functional limitation.

7.3.3.1 Univariate autoregressive models

Separately fitting AR models to the pain, disability and distress data over the five years following disease onset indicated poor fit for each model (Table 7.3). For each model, the χ^2 test of exact fit was significant with the ratio of the χ^2 statistic to the degrees of freedom being large. Furthermore, values of the Comparative Fit Index (CFI), Tucker-Lewis Index (TLI) and the root mean square error of approximation (RMSEA) were outside acceptable limits of fit.[7] This would indicate that fixed effects for the autoregressive association do not adequately account for underlying inter-individual changes, and that other factors may be important in the prediction of pain, distress and disability at future time points. It is important to note that for each of the models strong autoregressive effects for each of the variables was indicated, with standardized paths $\rho \approx .60$ for pain, $\rho \approx .85$ for disability, and $\rho \approx .75$ for distress. This suggests that for pain, functional limitation and distress prior status is a strong predictor of status 1-year later.

7.3.3.2 Univariate latent curve models

LCMs using linear, polynomial and the free-loading method were considered. Voelkle (2008) has shown that misspecification of the LCM part of the model can lead to major problems in the LCM and autoregressive parts of the ALT model, hence considerable attention was given to ensuring that they were correctly specified.

Pain The univariate LCM for pain assessed at the one through five-year measurement occasions with random intercept and linear slope factors exhibited poor fit to the data by the χ^2 test of exact fit. However, the RMSEA, CFI and TLI goodness-of-fit statistics all suggested acceptable fit, indicating that the degree of misfit was not large. Including a random quadratic slope factor did not significantly

[7] See section 4.2.2 for details of the assessment of model fit in latent variable models.

Table 7.3: Results from the unconditional univariate Latent Curve Models (LCM), Autoregressive Models and Autoregressive Latent Trajectory (ALT) Models

	χ^2	DF	p	CM	$\Delta\chi^2$	DF	p	BIC	CFI	TLI	RMSEA
VAS pain											
1. Autoregressive	181.7	10	0					33921	0.845	0.768	0.148
2. LCM, linear	31	10	0.001					26368	0.98	0.98	0.053
3. LCM, quadratic	25.7	6	0	1	5.27	4	0.26	26389	0.981	0.969	0.067
4. LCM, free	23.7	7	0.001	1	7.18	3	0.066	26379	0.981	0.971	0.065
5. ALT	16.5	8	0.036					33769	0.992	0.986	0.037
6. ALT, nested LCM model	33.7	13	0.001	5	17.28	5	0.004	33753	0.981	0.978	0.045
HAQ disability											
1. Autoregressive	183.5	10	0					4249	0.956	0.933	0.149
2. LCM, linear	43.4	10	0					2896	0.99	0.99	0.067
3. LCM, quadratic	26.9	6	0	1	16.5	4	0.002	2906	0.994	0.99	0.069
4. LCM, free	23.7	7	0.001	1	19.7	3	0	2896	0.993	0.995	0.057
5. LCM, 2-year free	29.4	9	0.001	1	14	1	0	2889	0.994	0.994	0.055
6. Univariate ALT	13	8	0.111					4092	0.999	0.998	0.028
7. Univariate ALT, nested LCM	60.7	13	0	6	47.6	5	0	4106	0.988	0.986	0.068
HADS distress											
1. Autoregressive	226.6	10	0					17108	0.873	0.81	0.169
2. LCM, linear	9.9	10	0.448					13456	1	1	0
3. LCM, quadratic	5.6	6	0.467	1	4.3	4	0.368	13478	1	1	0
4. LCM, free	5.8	7	0.559	1	4.1	3	0.253	13471	1	1	0
5. ALT	11.7	8	0.167					16907	0.998	0.996	0.025
6. ALT, nested LCM model	13.9	13	0.378	5	3.7	5	0.594	16876	0.999	0.999	0.01

Note. CM = comparison model

improve the fit of the model over the linear LCM (Table 7.3). Neither did freeing the loadings on the random slope. Thus the linear LCM (Model 2) for pain was accepted as the best fitting model and implemented as the LCM part of the ALT model.

Functional limitation The univariate LCM of HAQ disability with a linear rate of change between one and five-years showed significant misfit to the data. Both the model including a random quadratic slope parameter and a model allowing the loadings on the slope parameter to be freely estimated provided significant improvement in model fit, assessed by χ^2 difference tests (Table 7.3). A model allowing for a linear trend between 1 and 5-years except for year 2 where the loading on the random slope variable was freely estimated was observed to fit the data better than the linear model, but provided no significant reduction in fit when compared to the full free-loading model. Despite showing significant misfit to the data, model five for HAQ disability was selected as the LCM for the HAQ in the ALT model since the goodness of fit indices were optimal. The estimated trajectory for the linear latent curve model for pain against the observed data is shown in Figure 7.5.

Psychological distress The univariate linear LCM for psychological distress assessed at the one through and 5-years follow-up assessments showed no significant misfit to the data (Table 7.3). Furthermore, allowing for a quadratic growth factor or for the loadings on the slope growth factor to be freely-estimated resulted in no significant improvement in fit. Therefore, the linear LCM (Model 2) for psychological distress was selected for inclusion in the ALT model.

7.3.3.3 Univariate autoregressive latent trajectory models

Unconditional ALT models were estimated separately for pain, functional limitation and psychological distress. Since the ALT model cannot be directly compared to either the AR or LCMs they were compared against the ALT model with the AR paths fixed to zero, this is referred to by Bollen and Curran (2004) as the 'nested LCM'. It follows that if the χ^2 difference test is non-significant then the inclusion of the AR paths is unnecessary and the LCM model adequately describes changes from one point to the next.

Pain The univariate ALT model for pain showed good fit to the data. Although the χ^2 test of fit was significant, the value of the χ^2 statistic was relatively low as was its ratio to the degrees of freedom. Examining the fit against the nested LCM alternative indicated superior fit for the full ALT model (Table 7.3). The estimated trajectory for pain for the full ALT model is shown in Figure 7.5. The blue triangles represent the means for the observed data and the spikes 95% confidence intervals of these means. The

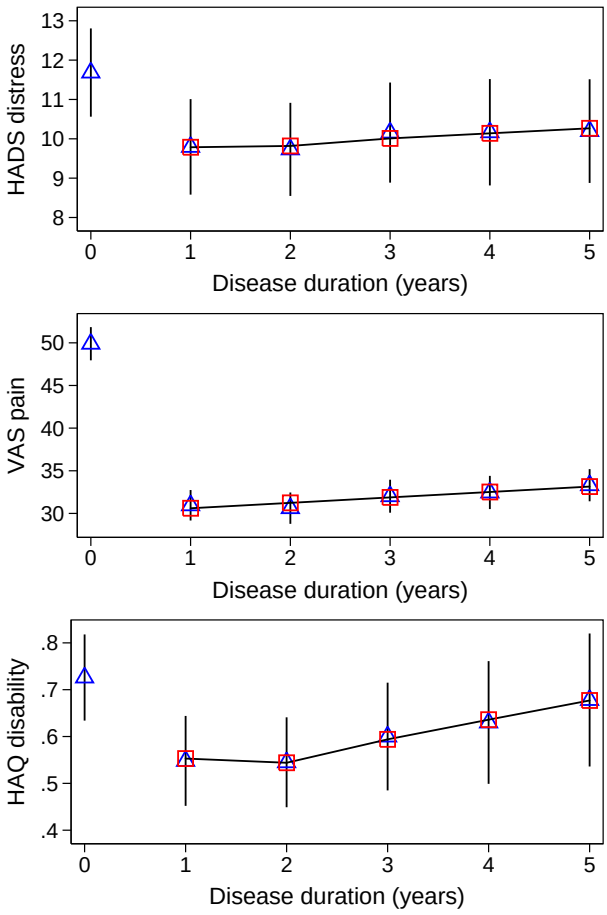


Figure 7.5: Predicted trajectories for the univariate autoregressive latent trajectory models. Triangles with error bars represent sample means with 95% CI. Connected boxes represent the model implied trajectories between the one and five-year assessments.

connected red squares represent the predicted trajectories. At baseline the mean level of pain was 49.89 (95% CI: 47.95, 51.84), reducing to 30.61 (95% CI: 28.85, 32.36) after 1-year following the initiation of disease-modifying therapy. Between 1 and 5-years after diagnosis pain increased on average by 0.64 (95% CI: 0.09, 1.19). The variances of both the random intercept and slope factors were significant, indicating heterogeneity in both the level of pain at 1-year and the rate of change in pain between 1 and 5-years in the sample.

Functional limitation The χ^2 test of fit for the univariate ALT model of functional limitation was non-significant, which considering the size of the sample suggests excellent fit to the data. Furthermore, the goodness-of-fit indices also indicated excellent fit to the data. The test of the nested LCM against the full ALT model was highly significant, indicating that the inclusion of the autoregressive effects was appropriate.

The estimated overall trajectory of functional limitation for the full unconditional univariate ALT model is shown in Figure 7.5. The mean HAQ functional limitation score at baseline was 0.73 (95% CI: 0.69, 0.77). This reduced to 0.44 (95% CI: 0.39, 0.49) after 1-year of follow-up, presumably due to the initiation of disease-modifying treatment. Between 1 and 5-years following diagnosis the average annual rate of progression of functional limitation was .034 units per year (95% CI: 0.029, 0.039), except for the change from 1 to 2-years which was notably reduced in comparison to the change observed at other years, .019 (95% CI: 0.014, 0.024). The variances of both the random intercept and slope factors were again significant. This suggests that there is considerable individual variability around the level of limitation at 1-year and in the rate of change between 1 and 5-years, consistent with the earlier findings of the GMM (section 7.3.2.2)

Psychological distress For psychological distress the full unconditional univariate ALT model exhibited excellent fit to the data according to the χ^2 test of fit and the goodness-of-fit indices. The test of the full model against the nested LCM model indicated no significant worsening of fit when the autoregressive paths were excluded. This suggests that after accounting for the latent trajectory part of the model the size of the residuals are small and it does not seem necessary to incorporate systematic autoregressive effects as was observed for both pain and functional limitation.

The estimated trajectory for the ALT model against the observed values of psychological distress are shown in Figure 7.5. The mean HADS psychological distress score at baseline was 11.66 (95% CI: 11.12, 12.20). This reduced to 9.60 (95% CI: 8.71, 10.50) after 1-year of follow-up. Between 1 and

5-years following diagnosis the average annual rate of change in psychological distress was significant and positive 0.124 (95% CI: 0.001, 0.247). This is in contrast to the estimates from Chapter 6 where reductions over this period were indicated. It is important to note that the magnitude of the change is small, equivalent to a standardized mean difference for the 1 to 5-year assessments of just 0.073. Thus it seems appropriate to conclude that levels of psychological distress are relatively stable over the period of 1 to 5-years following diagnosis. However, since the variance of the random linear slope factor was significantly greater than zero it seems that there is heterogeneity in the rate of change over 5-years, consistent with the findings of the GMM reported in the previous chapter.

7.3.3.4 Bivariate autoregressive latent trajectory models

As recommended by Bollen and Curran (2004) prior to estimating the bivariate ALT models bivariate AR models incorporating cross-lagged effects and bivariate LCMs were considered. As well as comparing the ALT model with the nested LCM, as before, separate models were estimated fixing first the AR paths for psychological distress and then the AR paths for either pain or functional limitation to zero. Furthermore, models fixing the random linear slope factor variance to zero and excluding this factor altogether were also considered. From the best fitting of these models further constraints were considered to improve model parsimony. This involved testing the equality of the time specific correlations, testing the equality of the AR paths, and testing the equality of the cross-lagged paths. The bivariate ALT models for psychological distress with pain and psychological distress with functional limitations are now discussed.

Pain and psychological distress The model fit statistics for all bivariate models involving pain and psychological distress are listed in Table 7.4. The AR model with cross-lagged effects (Model 1) exhibited poor fit to the data as indexed by the χ^2 test of exact fit and the goodness-of-fit indices. The bivariate LCM model (Model 2) however provided an acceptable fit to the data by the goodness-of-fit indices, although the χ^2 statistic was significant.

The bivariate ALT model (Model 3) showed excellent fit to the data as indicated by the goodness-of-fit indices, furthermore, the χ^2 difference test against the nested LCM (Model 4) was significant indicating that the inclusion of the AR paths was required. Comparing models that separately fixed the AR paths for psychological distress (Model 5) and pain (Model 6) to zero indicated that, consistant with the univariate analysis, the AR paths could be excluded for psychological distress without significant loss of model fit.

Next, fixing the variance of the distress slope factor to zero (Model 7) and excluding the distress

Table 7.4: Results from the bivariate Latent Curve Models (LCM), Autoregressive Models and Autoregressive Latent Trajectory (ALT) Models for VAS pain and HADS distress

	χ^2	DF	p	CM	$\Delta\chi^2$	DF	p	BIC	CFI	TLI	RMSEA
1. Autoregressive, with cross-lags	401.8	40	0.000					50649	0.887	0.816	0.107
2. LCM	164	41	0.000					39565	0.958	0.954	0.064
3. ALT, full model	47.2	28	0.013					50374	0.994	0.986	0.030
4. ALT, nested LCM	294.4	54	0.000	3	247.3	26	0	50448	0.925	0.909	0.075
5. ALT-3, no autoregressive paths for HADS	53.3	33	0.014	3	6.2	5	0.291	50347	0.994	0.987	0.028
6. ALT-5, no autoregressive paths for pain	73.9	38	0.000	5	20.6	5	0.001	50334	0.989	0.981	0.035
7. ALT-5, no slope variance for HADS	64.6	39	0.006	5	11.3	6	0.081	50318	0.992	0.987	0.028
8. ALT-5, no slope for HADS	64.8	40	0.008	5	11.5	7	0.119	50312	0.992	0.987	0.028
9. ALT-5, no slope variance for pain	73.1	39	0.001	5	19.8	6	0.003	50327	0.989	0.982	0.033
10. ALT-5, no slope for pain	75.1	40	0.001	5	21.7	7	0.002	50322	0.989	0.982	0.033
11. ALT-5, fixed time specific correlations	58.4	37	0.014	5	5.1	4	0.275	50325	0.993	0.988	0.027
12. ALT-11, + fixed autoregressive paths for pain	66.7	41	0.007	11	8.3	4	0.081	50307	0.992	0.987	0.028
13. ALT-12, + fixed pain → HADS paths	71.6	45	0.070	12	4.9	4	0.299	50285	0.992	0.988	0.027
14. ALT-13, + fixed HADS → pain paths	73.3	49	0.014	13	1.6	4	0.802	50260	0.992	0.990	0.025
15. ALT-14, no slope variance for HADS	84.7	55	0.006	14	11.4	6	0.076	50232	0.991	0.989	0.026
16. ALT-14, no slope for HADS	99.9	56	0.000	14	26.7	7	0.000	50240	0.986	0.984	0.032
17. Conditional ALT-14	110.3	90	0.072					65303	0.994	0.990	0.017

Note. CM = comparison model

Table 7.5: Results from the bivariate Latent Curve Models (LCM), Autoregressive Models and Autoregressive Latent Trajectory (ALT) Models for HAQ disability and HADS distress

	χ^2	DF	p	CM	$\Delta\chi^2$	DF	p	BIC	CFI	TLI	RMSEA
1. Autoregressive, with cross-lags	428.1	40	0.000					21141	0.934	0.893	0.111
2. LCM	152.3	40	0.000					16167	0.979	0.976	0.062
3. ALT, full model	40.9	28	0.055					20834	0.998	0.995	0.024
4. ALT, nested LCM	347.7	54	0	3	206.6	26	0	20867	0.967	0.961	0.068
5. ALT-3, no autoregressive paths for HADS	42.2	33	0.132	3	1.1	5	0.956	20801	0.998	0.997	0.019
6. ALT-5, no autoregressive paths for HAQ	82.6	38	0.000	5	40.5	5	0.000	20809	0.992	0.987	0.039
7. ALT-5, no slope variance for HADS	53.5	39	0.061	5	11.3	6	0.079	20773	0.998	0.996	0.022
8. ALT-5, no slope for HADS	53.9	40	0.070	5	11.7	7	0.109	20767	0.998	0.996	0.021
9. ALT-5, no slope variance for HAQ	71.4	39	0.001	5	29.2	6	0.000	20791	0.995	0.991	0.033
10. ALT-5, no slope for HAQ	71.7	40	0.002	5	29.5	7	0.000	20784	0.995	0.991	0.032
11. ALT-5, fixed time specific correlations	46.3	37	0.142	5	4.1	4	0.394	20779	0.998	0.997	0.018
12. ALT-11, + fixed autoregressive paths for HAQ	55.5	41	0.065	11	9.2	4	0.056	20761	0.998	0.996	0.021
13. ALT-12, + fixed HAQ → HADS paths	57	45	0.108	12	1.6	4	0.817	20736	0.998	0.997	0.018
14. ALT-13, + fixed HADS → HAQ paths	61.6	49	0.106	13	4.6	4	0.331	20714	0.998	0.997	0.018
15. ALT-14, no slope var for HADS	86.7	55	0.004	14	25.1	6	0	20699	0.995	0.994	0.027
16. ALT-14, no slope for HADS	91	56	0.002	14	29.4	7	0.000	20697	0.994	0.993	0.028
17. Conditional ALT-14	108.7	91	0.099					414456	0.997	0.995	0.016

Note. CM = comparison model

slope factor entirely (Model 8) did not result in a significant reduction in model fit. This suggests no significant change in distress or individual variation in the rate of change in distress between 1 and 5-years. Since this finding was in contrast to the univariate ALT model, the findings of the previous chapter and, furthermore, would result in not being able to compare the rate of change in distress with the rate of change in pain neither constraint was retained.

Fixing the variance of the pain slope factor to zero (Model 9) and excluding the pain slope factor entirely (Model 10) did result in a significant reduction in model fit. As was indicated by the univariate model, this suggests heterogeneity within the rate of change in pain across individuals between 1 and 5-years. Neither constraint was retained in later models.

The progressive inclusion of equality constraints for the time specific correlations (Model 11), the AR paths (Model 12) and the cross-lagged paths (Models 13 & 14) resulted in no significant loss of model fit. Moreover, the constrained cross-lagged paths for pain → distress and for distress → pain were non-significant indicating no cross-lagged effects. Following the inclusion of the equality constraints loss of fit through fixing the distress slope variance to zero (Model 15) or excluding the distress slope factor entirely (Model 16) was retested. This time excluding the distress slope resulted in a significantly poorer fit. Fixing the slope factor variance to 0 resulted in a marginally significant loss of fit. Therefore, it was decided it is appropriate to keep these in the model. Model 14 was selected as the final ALT model to which predictor variables would be added. This model (Model 17) had excellent fit to the data according to the goodness-of-fit indices and although the χ^2 test of exact fit, which was non-significant.

The standardized parameter estimates for Model 14 are displayed in Figure 7.6—note that non-significant paths are not displayed. The time specific correlations between distress and pain were moderate ($r = .30$) but were lower than those shown in Table 7.1. This is to be expected since these correlations represent the associations between the residuals after accounting for the latent trajectory part of the model. The correlation between the two random intercept factors was higher ($r = .46$) and equivalent to the associations observed in Table 7.1. The correlation between distress at the first time-point and the random intercept for distress was high ($r = .59$), whereas correlation between pain at the same time-point and the random intercept for pain was weak ($r = .19$). Both were equivalent to the correlation between the observed scores at the same time-points. The consistency between the estimated model parameters and the observed correlations support the good fit of the model.

Relating to the second objective of this chapter, there was a strong positive correlation observed between the random slope factors for distress and pain ($r = .42$). This indicates that changes in pain occur synchronously with changes in psychological distress. Furthermore, the cross-lagged effects were

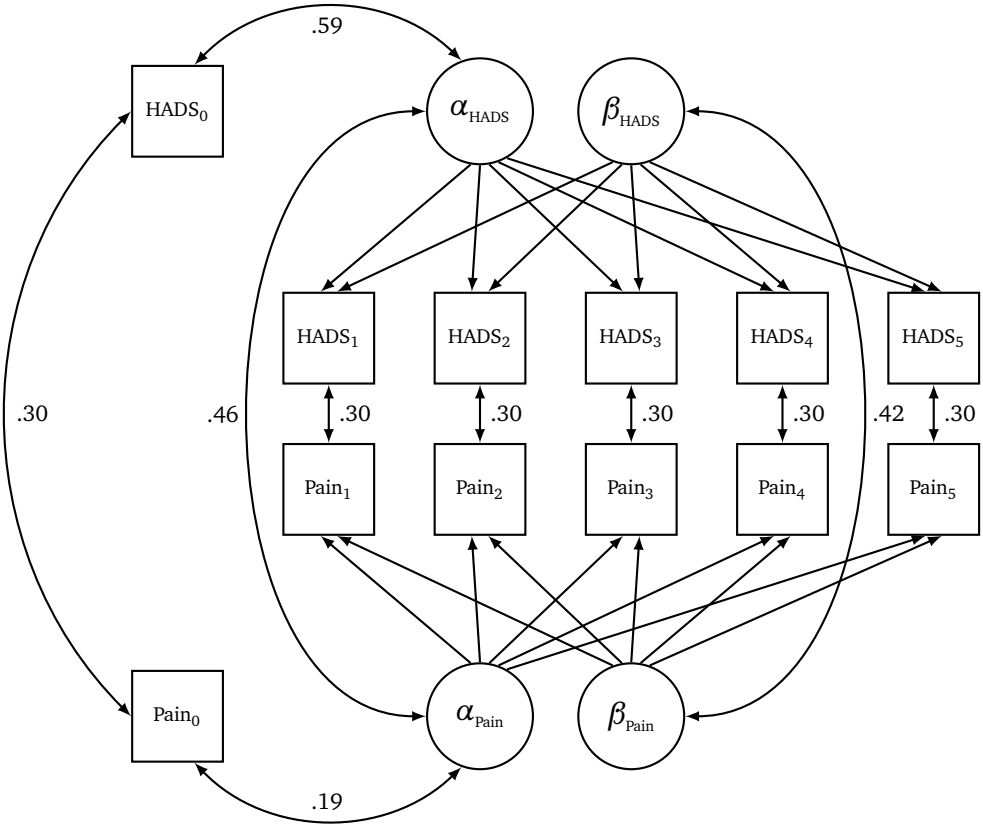


Figure 7.6: Unconditional autoregressive latent trajectory model for psychological distress and pain. Statistics are standardized parameters, non-significant paths are not shown

all small and non-significant.

In summary, the bivariate ALT model for distress and pain over 5-years in the ERAS cohort indicates that concurrent levels of pain and distress are highly related, as are longitudinal changes. The distress intercept factor was not related to the pain slope factor, and *vice versa* the pain intercept factor was not related to the distress slope factor, indicating that initial levels of one are not causally related to later changes in the other over one-year periods. The lack of causal association between the two is further supported by the lack of cross-lagged effects between the residualised values of pain and distress after accounting for the trajectory part of the model. This finding contrasts with those of previous research using autoregressive cross-lagged models (G. K. Brown, 1990; Schieir et al., 2009). It is likely the weak positive causal effects previously reported were due to the failure to account for the underlying trajectory.

Functional limitation and psychological distress The model building process for the bivariate ALT model for functional limitation and distress followed much the same process (Table 7.5). The best

fitting model prior to incorporating equality constraints was Model 5, which included AR paths only for HAQ. As with pain, fixing the slope factor variance to 0 (Model 7) or excluding the distress slope factor (Model 8) resulted in no significant loss of fit. This was true even after the inclusion of equality constraints. However, since the exclusion of the factor or its variance would result in the hypothesis under question being untestable they were retained within the model. The final model selected for the conditional model was Model 14. This included equality constraints for the time specific correlations, the AR paths for functional limitation, and the cross-lagged effects.

Figure 7.7 shows the standardized parameter estimates for model 14—again, non-significant paths are not displayed. As with the model for pain and distress the cross-lagged association were non-significant and moderate time specific correlations were observed ($r = .29$). There was a moderate autoregressive effect for functional limitation ($r = .28$), but not distress, after accounting for the underlying longitudinal trajectory. The correlations between the intercept factors for distress and functional limitation were again strong ($r = .44$), as were the correlations between the slope factors ($r = .37$). For functional limitation only, there was a weak, but significant, correlation between the intercept and slope factor ($r = .17$), suggesting that patients with higher levels of limitation at one-year tended to experience a faster decline in function.

To summarise the bivariate ALT model for distress and functional limitation, concurrent levels of distress and functional limitation and changes in distress and functional limitation are highly related. Similar to the model concerning pain, a lack of causal association between distress and disability is observed. It does not appear that either the initial level of distress or functional limitation is related to future changes in the other, or between the residuals. The autoregressive effect for HAQ disability indicates that, after controlling for the underlying rate of functional decline, worse functional limitation is predicted by having worse functional limitation one-year earlier. Since the underlying trajectory is likely to be related to progression of joint damage, this may be indicative that those with worse limitation due to other causes at one time-point are more likely to have worse functional limitation at later-time points, independent of their level of limitation at 1-year. Since no effect was observed for pain it seems unlikely that these other causes include disease flare.

7.3.3.5 Conditional bivariate autoregressive latent trajectory models

Predictors were added to the best fitting bivariate ALT models for psychological distress with pain and psychological distress with functional limitation—Model 14 for both. Distress, pain and functional limitation at the baseline assessment, the random intercepts (representing the level at one-year) and the

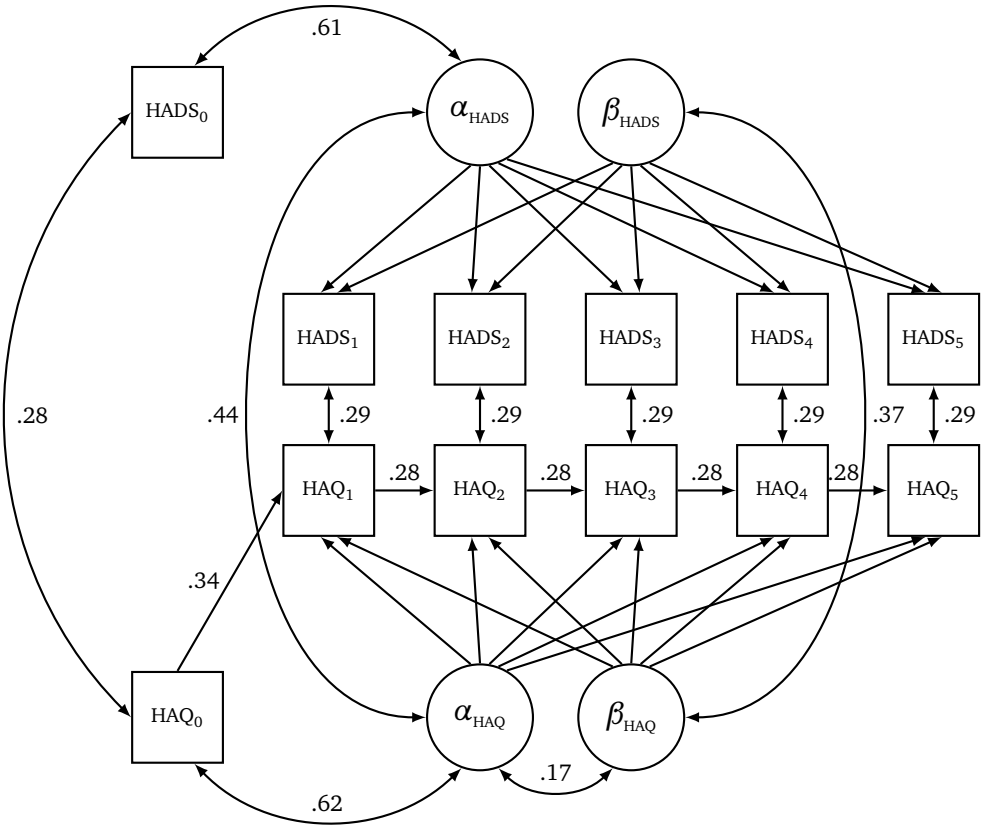


Figure 7.7: Unconditional autoregressive latent trajectory model for psychological distress and functional limitation. Statistics are standardized parameters, non-significant paths are not shown

random slopes (representing the rate of change) were each regressed on the predictor variables. Rather than incorporating the associations between distress, pain and functional limitation at the baseline assessment with the respective intercept and slope factors as correlations they were included as paths in the model. Including the associations as correlations or paths results in models that are equivalent (in terms of fit), although the model including paths leads to a more intuitive interpretation of intercept factors regressed on the predictors as relating to residualised change.

Convergence problems were experienced, mainly due to the small variance of the distress slope factor. Reinstating the autoregressive paths for distress for both models and constraining them to equality resolved the issue for both models—the estimated paths remained non-significant.

Table 7.6: Predictors of psychological distress

	Baseline		Intercept		Slope	
	β	SE	β	SE	β	SE
Age at onset	-0.07	0.04	**0.10**	**0.04**	0.04	0.09
Female	**0.08**	**0.04**	0.07	0.04	0.03	0.09
Low social class	**0.15**	**0.08**	0.02	0.08	-0.07	0.15
Low educational attainment	-0.07	0.07	-0.05	0.07	0.25	0.14
Smoker	0.07	0.04	0.03	0.04	0.14	0.09
Disease activity (baseline)	**0.20**	**0.09**	-0.06	0.10	0.17	0.21
Pain (baseline)	**0.35**	**0.04**	-0.03	0.05	0.19	0.11
HAQ disability (baseline)			**0.11**	**0.04**	**0.21**	**0.10**
HADT distress (baseline)			**0.60**	**0.05**	0.00	0.12
R^2	**0.17**		**0.39**		0.15	

Note. Parameters are standardised estimates, emboldened figures are significant ($p < .05$)

Table 7.7: Predictors of pain

	Baseline		Intercept		Slope	
	β	SE	β	SE	β	SE
Age at onset	0.06	0.04	0.05	0.05	0.14	0.11
Female	0.04	0.03	0.08	0.05	0.01	0.10
Low social class	0.04	0.06	0.09	0.08	0.01	0.14
Low educational attainment	-0.10	0.06	0.06	0.08	0.03	0.14
Smoker	0.07	0.04	0.05	0.05	-0.06	0.11
Disease activity (baseline)	**0.18**	**0.03**	0.00	0.05	0.10	0.10
HAQ disability (baseline)	**0.32**	**0.03**	0.04	0.05	0.00	0.09
Pain (baseline)			**0.19**	**0.06**	-0.03	0.13
HADT distress (baseline)			**0.20**	**0.06**	-0.02	0.16
R^2	**0.18**		**0.17**		0.04	

Note. Parameters are standardised estimates, emboldened figures are significant ($p < .05$)

Table 7.8: Predictors of functional limitation

	Baseline		Intercept		Slope	
	β	SE	β	SE	β	SE
Age at onset	**0.08**	**0.03**	**0.11**	**0.03**	0.08	0.08
Female	**0.12**	**0.03**	**0.11**	**0.03**	0.03	0.07
Low social class	-0.03	0.05	0.08	0.04	-0.09	0.09
Low educational attainment	**0.13**	**0.05**	0.05	0.04	0.15	0.09
Smoker	0.03	0.04	0.04	0.03	0.11	0.08
Disease activity (baseline)	**0.12**	**0.03**	0.00	0.04	0.01	0.07
Pain (baseline)	**0.32**	**0.03**	**-0.18**	**0.04**	-0.04	0.09
HAQ disability (baseline)			**0.62**	**0.03**	**0.24**	**0.08**
HADT distress (baseline)			**0.12**	**0.05**	0.16	0.12
R^2	**0.13**		**0.46**		**0.15**	

Note. Parameters are standardised estimates, emboldened figures are significant ($p < .05$)

Predictors of psychological distress Table 7.6 shows the standardised parameter estimates for the regression of psychological distress at the first time-point, the distress intercept factor, and the distress slope factor on the predictor variables.[8] At the baseline assessment occasion female sex, higher pain and greater disease activity were related to more symptoms of psychological distress. Only a modest amount of the variance in the initial level of distress was explained by the covariates.

Baseline psychological distress was the strongest predictor of the distress random intercept factor (i.e. 1-year psychological distress). Baseline functional limitation and age at onset were also predictive of the intercept factor. Just under 40% of the variance in the intercept was explained by the covariates.

The only baseline predictor of the change in distress between 1- and 5-years was functional limitation, which indicated the faster increase in psychological distress between 1 and 5-years for those with higher functional disability at baseline.

Predictors of pain Standardised parameter estimate for the regression of pain at the baseline assessment, the pain intercept factor, and the pain slope factor on the predictor variables are shown in Table 7.7. At the baseline assessment occasion, only functional limitation and disease activity at the same time were associated with pain. Little of the variance in pain scores at this time was explained by the covariates.

Pain and distress at the first time-point were significant but weak predictors of the random intercept for pain. Again, the model explained little of the variance in pain scores. None of the variables explained the rate of change in pain.

[8]The parameter estimates shown are from the conditional bivariate ALT model involving HAQ. Estimates from the model involving pain were similar and are not shown since they suggested no substantive difference in interpretation.

Predictors of functional limitation Cross-sectionally older age at onset, female sex, low educational attainment, higher pain and worse DAS score were significantly associated with functional limitation at the time of presentation to the rheumatologist (Table 7.8).

Functional limitation at the baseline assessment was the strongest predictor of one-year functional limitation. Older age at onset, female sex, and higher psychological distress at baseline were also significantly related to functional limitation at 1-year. The covariates explained around half the variance in the intercept factor. Unexpectedly baseline pain showed a significant negative effect. Further analysis revealed that it was not that those with a higher pain at baseline experienced lower 1-year functional limitation *per se*, but that those with higher baseline pain levels tended to experience a greater reduction in functional limitation between baseline and one-year than individuals with lower levels of pain but the same level of functional limitation at baseline (i.e. the negative relationship was conditional on baseline functioning).

Only baseline functional limitation was significantly related to the rate of progression in functional limitation. Those with worse functional disability at baseline tended to have a faster rate of progression.

7.4 Discussion

This chapter examined the synchronous relationship of psychological distress with pain and functional limitation in rheumatoid arthritis using ALT models. Regarding the objectives of the chapter, the analyses showed strong cross-sectional associations between psychological distress with pain and functional limitation, moderate associations between the rate of change in psychological distress with the rate of change in pain and functional limitation over the period 1 to 5-years following diagnosis. No cross-lagged effects between the variables were observed after accounting for the inter-individual differences in the rate of change. Moreover, no autoregressive effect for psychological distress or pain and only a relatively modest autoregressive effect was observed for functional limitation after accounting for the inter-individual trajectories.

The observation of strong cross-sectional correlations between psychological distress, pain and functional limitation was in line with the findings of previous research (G. K. Brown, Nicassio, & Wallston, 1989; Evers et al., 1997; Hawley & Wolfe, 1988; Schiaffino et al., 1991; Sharpe et al., 2001; Smedstad et al., 1997; Thyberg et al., 2009; Chaney et al., 2004; Demange et al., 2004; Nicassio & Wallston, 1992). Extending the findings of previous research (G. K. Brown, 1990; Schieir et al., 2009; Smedstad et al., 1997), the application of ALT models showed that rather than an autoregressive relationship it is more

appropriate to consider changes in psychological distress by considering the individual's underlying trajectory over a number of years. Whereas, the previous chapter showed that the majority of the change in psychological distress occurs early in the course of the disease, with stable levels observed from two to three-years after the initial diagnosis of the condition. This chapter extended these findings to show apparent stability in psychological distress from around one-year post diagnosis over a period of five years.

An important issue is whether the synchronous changes observed are driven by affect or the control of the disease. According to the Bonanno (2005) model, the change in distress observed in the first year of the disease is mainly the psychological response to a potentially traumatic event—namely, the diagnosis of RA. This is itself a manifestation of the individuals' coping response. However, it is perhaps more likely that the changes observed are due to changes in somatic symptoms due to the initiation of disease modifying therapy. The bivariate ALT model for distress and functional limitation showed that individuals with higher levels of limitation at the time of presentation to the rheumatologist were likely to experience greater decline in function, independent of demographic characteristics. Furthermore, individuals with higher levels of limitation at the time of presentation to the rheumatologist were also more likely to experience greater increases in psychological distress. This may suggest that it is the change in functional limitation—associated with worse initial disease status—that drives the change in distress. However, it may be that cognitive appraisals play an important role. Individuals with poorer function at baseline are likely to have heightened perceptions of the consequences of their RA (Moss-Morris et al., 2002) and when functioning begins to deteriorate again there understanding of the consequences may lead to greater distress. Chapter 3 identified Schiaffino and Revenson (1995), Schiaffino et al. (1998) and (Scharloo et al., 1999) as observing worse perceptions of consequences as predictive of later changes in distress in RA samples. Nevertheless the analysis in this chapter does suggest that the effect of functional limitation on distress is stronger than the reverse.

Similar to the findings of Chapter 6 low social class and disease activity were predictive of baseline distress. Age at onset was predictive of distress at one-year but not the baseline assessment. That older individuals have greater distress at one-year, controlling for initial distress, suggests that they are less likely to experience an improvement during the first years of the disease. In Chapter 6, it was observed that age at onset was related to the slope factor of the LCM modelling change over time using a reciprocal function. It would appear that this observation resulted from changes early in the course of the disease, that this functional form of time is particularly sensitive to. The greater distress at one year for older individuals may be due to the initiation of disease modifying treatment being less effective in older

individuals, or that they experience heightened perceptions of the consequences of the condition. That age at onset was predictive of functional limitation at one-year perhaps supports the former proposition.

A limitation of this analysis is that although no cross-lagged effects were observed between psychological distress with pain and functional limitation this does not mean that none existed. The duration between follow-up assessments was one-year. It is perhaps not surprising that after controlling for the underlying general trajectory no effects were observed between measurements taken at such intervals. Studies involving daily or weekly assessments perhaps provide a more natural way of examining cross-lagged effects. Several studies involving individuals with chronic pain conditions, including RA, suggest that at this interval cross-lagged effects may occur (Strand et al., 2006; Zautra et al., 2007; B. W. Smith & Zautra, 2008), although these studies do not account for the underlying trend.

In addition, in this situation the utility of the ALT model in general can be called into question. Only weak AR effects and no cross-lagged effects were observed. Thus, the findings of the ALT model offer little over estimating a bivariate LCM. However, the framework of building an ALT model provided a useful way of teasing out whether these effects do or do not exist. In situations where stronger AR processes and cross-lagged effects are likely, the ALT model provides an approach for distinguishing between the two processes (e.g. Simons-Morton & Chen, 2006).

An extension of the analyses in the chapter would be to consider autoregressive latent trajectory mixture models. That is, combining an ALT model with a GMM. It would be a relatively straightforward programming modification to consider multiple latent trajectory classes within the ALT model. However, this would be computationally highly demanding and add extra-complexity to models that may already be considered over parameterized. A simpler alternative would be to model a bivariate growth mixture model incorporating an autocorrelated error structure.

In summary, this chapter has shown that changes in psychological distress in rheumatoid arthritis occur synchronously with, and are perhaps mainly driven by, changes in somatic features of the condition. Other factors, particularly psychosocial ones, are likely to play a part in the relationship between disease and distress in RA. This will be assessed in the following chapter.

Chapter 8

The role of illness perceptions

8.1 Introduction

The previous two chapters have shown that levels of the psychological distress in RA are highly variable following distinct non-linear patterns after diagnosis and that change in distress co-varies with change in physical well-being. Specifically the rate of change in self-reported psychological distress correlated in the order of .4 with changes in pain and functional limitation. No clear causal association was observed. That is, it did not appear that depression caused increased disability, or alternatively that disability caused increased distress, or that there was some pattern of causality akin to a 'vicious cycle'—at least over assessment periods one-year apart. Rather it would appear that increased distress was related with increased disability at the concurrent time. Although this rather simplifies the likely mechanism, in reality, it is likely that the inflammation caused by the disease leads to pain and stiffness which impacts on functional ability and leads to increased levels of distress (Katon, 2003). Distress may also be associated with increased symptom perception and through behavioural and physiological mechanisms lead to disease exacerbation and worse physical outcomes, either directly through disease or via the development of further comorbidity such as cardiovascular disease (Katon, 2003).

Psychological and social factors are likely to act as mediating or moderating factors in the relationship between disease and psychological well-being in RA. Hale, Treharne, and Kitas (2007, p.904) state that, in RA, there is "often a difference between objective clinical and radiographic evidence of musculoskeletal disease activity or severity and the experience of pain, other symptoms and functional ability reported by the patient". Chapter 3 systematically reviewed the published literature investigating the role of psychosocial variables in longitudinal studies of psychological well-being. Although some support has been found for a wide range of different factors, there is particular evidence for the role of

illness perceptions and coping. The contribution of illness perceptions and coping is the focus of the Self Regulation Model (SRM) of illness cognitions and behaviour developed by Leventhal and colleagues (Leventhal, Weinman, Leventhal, & Phillips, 2007; Leventhal et al., 1992, 1980, 1984). This chapter will build on the findings of the existing literature reviewed in Chapter 3 to assess whether illness perceptions and coping impact on changes in psychological distress. Specifically, this chapter will examine whether distinct patterns of illness perceptions are associated with changes in psychological and physical well-being and whether they these individual illness perceptions act as mediators or moderators of disease severity on psychological well-being. Prior to outlining the specific aims and objectives of this chapter the SRM and the literature concerning the study of the SRM in RA is introduced.

8.1.1 Illness perceptions

8.1.1.1 The Self Regulation Model of illness representations

The SRM was introduced in section 2.2.3.2 (in particular see Figure 2.4) and the evidence for an association between illness perceptions and changes in psychological well-being was reviewed in Chapter 3. The SRM and the role of illness perceptions in RA are now reintroduced.

Briefly, the SRM is a self-regulatory framework, which posits that an individuals' illness representation informs there coping response to illness related threats (Leventhal et al., 1984). The specific content of illness representations are termed *illness perceptions* (identity, timeline, consequences, control/cure and causes), which have been described as "an organized set of beliefs regarding how the illness affects our body, its likely impact on life activities and experiences, whether it can be cured and so on" (A. A. Kaptein & Weinman, 2004, p.85).

There is a considerable body of evidence examining the role of illness perceptions in RA. As well as the four studies included in the systematic review presented in Chapter 3 (Schiaffino & Revenson, 1995; Schiaffino et al., 1998; Scharloo et al., 1999; Sharpe et al., 2001), there are numerous other studies examining the cross-sectional relationship between illness perceptions and psychological and physical well-being (H. Murphy, Dickens, Creed, & Bernstein, 1999; Groarke, Curtis, Coughlan, & Gsel, 2005; Graves, Scott, Lempp, & Weinman, 2009; Carlisle, John, Fife-Schaw, & Lloyd, 2005; Treharne, 2004). The cross-sectional studies indicate a moderate association between the illness perceptions of identity, consequences and controllability with both psychological and physical well-being (H. Murphy et al., 1999; Groarke et al., 2005; Graves et al., 2009; Carlisle et al., 2005). The longitudinal studies reported mixed findings but provided evidence for the role of perceptions relating to identity, consequences,

timeline, and cause and change in psychological distress.

In two studies of the same cohort of 63 RA patients, Schiaffino and colleagues (Schiaffino & Revenson, 1995; Schiaffino et al., 1998) found that, controlling for baseline depression, higher perceptions of the curability and stronger causal perceptions of personal responsibility (internal attributions) for their RA were related to increased depression 4- and 18-months later. Furthermore, interaction effects were observed such that individuals with negative perceptions of the consequences of their illness and high functional disability had increased levels of depression four-months later (Schiaffino et al., 1998).

In a separate study of 71 Dutch RA patients, Scharloo et al. (1999) observed that perceptions of serious consequences, identity, and chronic timeline predicted worse psychological distress one-year later, controlling for baseline levels. Furthermore, perceptions of consequences and identity predicted increased levels of fatigue at follow-up, while identity also predicted higher pain at follow-up. None of the perceptions was related to changes in functional disability. Similarly, a small study of just 22 RA patients recruited within 2-years of disease onset and assessed 6 times over a 21-month period revealed that—controlling for the initial levels of distress, disability, pain and pain coping—higher perceptions of consequences were associated with higher levels of distress at later assessments (Sharpe et al., 2001).

Further to these studies, in his doctoral dissertation Treharne (2004) assessed the longitudinal association between selected psychosocial variables and both psychological and physical well-being in 134 RA patients.[1] Amongst the psychosocial variables, only the illness perception of consequences was considered. Controlling for baseline well-being and sociodemographic characteristics, perceptions of consequences were not found to be associated with psychological well-being (assessed by depression, anxiety or life satisfaction) or physical well-being (assessed by functional disability or pain) assessed six or 12-months later. Furthermore, self-efficacy, which was previously noted as being conceptually close to the perception of personal control was not found to be associated with any of these outcomes either. Further tests for moderation with either psychological distress and psychological well-being were also negative.

These studies are all limited by small sample size, meaning that statistical power was only sufficient to detect large effects. For example, for even the most basic assessment of the bivariate correlation between an illness perception and psychological well-being none of the four published studies would have had sufficient power to detect correlations smaller than $\rho_{Pearson} = .33$ not adjusting for multiple testing ($1 - \beta = .80$; $\alpha = .05$). Furthermore, the studies generally considered illness perceptions in separate analyses even though a considerable overlap in the constructs is indicated by the strength

[1] Selected findings reported in the dissertation are reported in Treharne et al. (2007) but do not consider illness perceptions.

of the inter-correlations. This is perhaps understandable considering the low statistical power of the studies.

Recently, two studies of illness perceptions in other conditions have sought to identify common patterns of illness perceptions using cluster analytic methods (Hobro, Weinman, & Hankins, 2004; Miglioretti, Mazzini, Oggioni, Testa, & Monaco, 2008). Such an approach may have extended utility, as virtually all research considers the impact of individual illness perceptions rather than evaluating groups of inter-related perceptions (i.e. 'representations'). Hobro et al. (2004) identified two groups, which they labelled 'adaptors' and 'non-adaptors' in a sample of 130 chronic pain patients. Similar groups were also observed by Miglioretti et al. (2008) in 74 patients with motor neuron disease. Whether distinct patterns of illness perceptions are present in RA, and whether such patterns relate to clinical and psychological outcomes has yet to be considered.

8.1.2 The present study

The study presented in this chapter is a longitudinal examination of the role of illness perceptions on future psychological well-being in RA in a cohort of patients mainly with established disease. It balances the more statistically involved studies of the ERAS cohort of the previous chapters to provide an insight into the health psychology of changes in well-being in RA. The ERAS cohort consists of a wealth of prospectively collected clinical data but a dearth of information concerning psychosocial factors. The initial aim was to introduce assessments of psychosocial factors (illness perceptions, coping, and social support) into an existing multi-centre RA inception cohort, the Early RA Network, to which over 1000 patients receiving a recent diagnosis of RA attending 22 centres were recruited between 2004 and 2008. However, funding issues lead to a dramatic reduction in new cases being recruited to the study and bureaucratic issues meant that obtaining approvals in a timely fashion were unfeasible. As a result, it was decided to set up a smaller scale longitudinal study of patients with established disease recruited from rheumatology clinics at local hospitals in Hertfordshire.

The aim of this study was to assess whether (i) illness perceptions are related to changes in psychological and physical well-being, including an assessment of positive psychological well-being, and (ii) whether this effect is mediated by coping strategies. As well as individual perceptions predicting change in psychological well-being it was hypothesised that distinct patterns of illness perceptions would exist, relating to the 'adaptive' and 'non-adaptive' representations of RA.

8.2 Methods

8.2.1 Participants & procedure

The sample were individuals with a diagnosis of rheumatoid arthritis currently taking at least one disease modifying anti-rheumatic drug (DMARD) mainly recruited whilst attending outpatient appointments at rheumatology clinics in six hospitals in Hertfordshire, England.[2] Patients were excluded if they were under 18-years of age or were not responsible for the management of their own medications. Of the 248 eligible patients approached, 189 (76%) agreed to participate and returned completed questionnaires.

To boost numbers of recently diagnosed individuals, postal invitations were sent to 161 patients attending the clinics and receiving a diagnosis of RA in the previous 24-months that had not attended an appointment within the 3-month recruitment period. Of these 38 (24%) returned completed questionnaires.

Follow-up questionnaires were sent by post after a period of 3-months to patients receiving a diagnosis of RA within the past 12-months and to all patients after a period of 6-months. Reminders were sent to those not returning completed follow-up questionnaires after 4-weeks. Details of the numbers of participants returning questionnaires are provided in Figure 8.1.

At the 6-month assessment, 171 patients returned completed questionnaires (75.3%), although one was excluded due to the returned questionnaire not being sufficiently complete. Of those that did not return the follow-up questionnaire the reason was known for 3 (1 died, 2 moved). Patients who returned completed questionnaires tended to be younger, in paid employment and had higher levels of positive outlook at baseline (all $p < .05$) compared to those that did not.

The study was conducted in collaboration with Miss Lyndsay Hughes, who was investigating the role of illness perceptions on medication adherence. Approval was granted by the Hertfordshire committee of the NHS National Research Ethics Service (Reference no: 09/H0311/102).

8.2.2 Measures

8.2.2.1 Illness perceptions

The Revised Illness Perception Questionnaire (IPQ-R; Moss-Morris et al., 2002) tailored to RA was employed to assess patients' cognitive representation of their RA. The IPQ-R measures illness perceptions relating to the symptoms (identity, 14-items), timeline (chronic, 6-items, & cyclical, 4-items), conse-

[2]Barnet Hospital, Chase Farm Hospital, Hemel Hempstead General Hospital, Lister Hospital (Stevenage), Potters Bar Community Hospital, St Albans City Hospital.

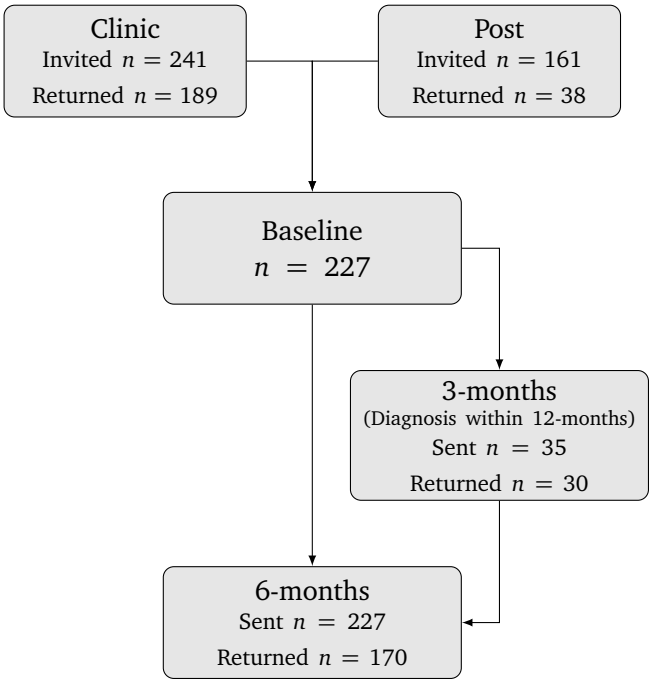


Figure 8.1: Recruitment flow chart

quences (consequences, 6-items), and controllability (personal, 6-items, & treatment, 5-items) of RA as well as the extent to which they have a coherent understanding of their condition (coherence, 6-items). To reduce respondent burden, and in line with similar studies using RA cohorts (e.g. Moss-Morris et al., 2002), the 18-item causal perceptions scale was not used. Furthermore, the emotional responses to the illness (6-items) were not included in the analysis due to the overlap with psychological well-being.

In the current sample the internal consistency for the majority of the sub-scales was acceptable ($\alpha_{\text{Identity}} = .83$; $\alpha_{\text{Time-line chronic}} = .85$; $\alpha_{\text{Time-line cyclical}} = .76$; $\alpha_{\text{Consequences}} = .84$; $\alpha_{\text{Personal Control}} = .81$; $\alpha_{\text{Coherance}} = .92$), although it was low for the treatment control sub-scale ($\alpha_{\text{Treatment Control}} = .63$).[3]

A confirmatory factor analytic model was used to test the construct validity of the IPQ-R against the expected structure. Robust weighted least squares estimation was used to account for the binary "yes"/"no" response format for the identity items and the ordinal response format for all other items. Model fit was not particularly good ($\chi^2(94)$=319.5; RMSEA = .103; CFI = .907; TLI = .927). All items loaded significantly onto their respective sub-scale. For the treatment control sub-scale the standardised factor loadings were smaller than for the other sub-scales, as would be expected based on the values of Chronbach's α. Inspection of modification indices revealed that the source of misfit was partially due to two of the treatment control items—*'There is very little that can be done to improve my RA*' and *'The negative effects of my RA can be prevented (avoided) by my treatment'*—also loading onto the coherence

[3]There has been much recent discussion regarding the limitations of Chronbach's α as a measure of reliability (e.g. Sijtsma, 2009). Despite these issues it is reported here as an indicator of the likely lower bound of reliability.

sub-scale. This perhaps indicates a lack of understanding with regard to the disease modifying treatments used in RA. In addition, there was some indication that the identity sub-scale should be split into symptoms experienced and attributed to RA that were either i) typical of RA (i.e. pain, stiff joints, swollen joints, tiredness), or ii) not typical of RA (i.e. sore throat, lost appetite, sickness, breathlessness, stomach cramps). To allow for greater comparability with other studies the standard scoring method for the identity sub-scale was implemented. Factor scores for the CFA model without any modifications were estimated for use in the analysis. These were on the z-score metric with a mean of 0 and a standard deviation of 1.

8.2.2.2 Psychological well-being

The Depression, Anxiety and Positive Outlook Scale (DAPOS; Pincus, C. Williams, Vogel, & Field, 2004) is designed to measure symptoms pertaining to the named constructs in chronic pain populations. The DAPOS sub-scales include items that measure the affective component of the constructs and exclude any items relating to somatic problems. Specifically, Pincus et al., 2004 selected 11 items from the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1978) and the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) that did not exhibit high correlations with pain and discriminated well across the latent factors identified by an exploratory factor analysis. Each of the items is scored using a Likert scale response format (ranging from 'almost never' to 'almost all the time'). Three items—concerning cheerfulness, enjoyment and looking forward to things—form the positive outlook scale which assesses positive affect. These were originally reverse scored items included in the HADS depression sub-scale.[4]

The DAPOS has previously been shown to have good construct validity and test-retest reliability (Pincus, et al., 2008). In the current sample internal reliability for the three scales was acceptable ($\alpha_{\text{Depression}} = .866$; $\alpha_{\text{Anxiety}} = .878$; $\alpha_{\text{Positive outlook}} = .813$).

The construct validity of the DAPOS was assessed using confirmatory factor analysis (robust WLS estimation). The proposed 3-factor model showed levels of fit that were outside acceptable limits ($\chi^2(9)$=178.2; RMSEA = .290; CFI = .907; TLI = .907). The correlation between the anxiety and depression sub-scales was high at .87, indicating that they likely measure the same latent construct. The model was therefore respecified with all anxiety and depression items loading onto a single general distress factor. Fit was more agreeable for this model, although the RMSEA was still outside acceptable

[4] A recent, paper has indicated better fit to the two-factor model by accounting for the positively worded items using a methods factor (Schönberger & Ponsford, 2010)

limits ($\chi^2(14)$=68.6; RMSEA = .132; CFI = .970; TLI = .981). In addition, following from the results of Chapter 5, a bifactor model for the anxiety and depression factor was considered. This model provided better fit to the data ($\chi^2(14)$=39.4; RMSEA = .090; CFI = .986; TLI = .991) but the factor loadings for the items on the anxiety and depression factors were small and preliminary analysis revealed no correlation between the anxiety and depression group-factors with demographic or clinical variables. Resultantly, the factor scores for the 2-factor model were included in the analysis.

8.2.2.3 Coping

The Brief Cope was used to assess coping (Carver, 1997). This 10-item questionnaire assess 5 types of coping style: active, instrumental, planning, acceptance and denial. The factorial validity of the instrument was assessed using confirmatory factor analysis with parameter estimated using the robust WLS approach. The fit of the expected model was good ($\chi^2(13) = 20.8$; RMSEA = .052; CFI = .993; TLI = .993) and modification indices suggested no adjustments to the model were necessary. Hence, the factor scores for the model as is were used in the analysis.

8.2.2.4 Functional disability

Functional disability was measured using the Health Assessment Questionnaire (HAQ) disability index. As was previously described, the HAQ assesses rheumatic patients' functional limitation during the past week across eight common activities: dressing, arising, eating, walking, hygiene, reach, grip, and common activities (Kirwan & Reeback, 1986). Scores range between 0 and 3 with higher values indicating greater disability. Scores are weighted if patients require help or aid to perform a particular activity. Generally, scores greater than 1 indicate that an individual has moderate disability, and above 2 severe disability, although specific cut-offs have not been defined.

8.2.2.5 Pain

Health-related quality of life was assessed using the EQ5D (Rabin, Oemar, Oppe, Janssen, & Herdman, 2011). The total score was not used in the analysis since assessments of psychological distress and functional limitation are already covered by the DAPOS and the HAQ. However, the pain question from the EQ5D was used. This question asks respondents to rate whether *today* they *"have [no–slight–moderate–severe–extreme] pain or discomfort"*. Although scored on an ordinal scale, responses were approximately normally distributed. Therefore it was treated as a continuous variable in the analysis.

8.2.2.6 Demographic information

As well as date of birth and sex, participants were also asked to report their highest level of eduction and their current employment status. For the analysis education was dichotomised to indicate those that had achieved a University degree.

8.2.2.7 Clinical information

Clinical information, including medication and disease duration, was collected from the patient's medical notes. The Disease Activity Score-28 (DAS28; Prevoo et al., 1995) is a combined index that incorporates assessments of inflammation (either Erythrocyte Sedimentation Rate [ESR] or C-reactive Protein [CRP]), physician assessments of the tenderness and swelling of 28 joints (in hands, feet and wrist), and self-reported general disease severity on a 100mm visual analogue scale (VAS).[5] DAS28 has been extensively validated and is used almost universally in clinical trials (Riel & Schumacher, 2001). Scores range between 0 and around 10. Generally, scores over 5 indicate severe disease and less than 3 low disease activity.[6] In addition, patients were asked to report whether they considered their RA to currently be 'active' or 'in remission'.

8.2.3 Statistical analysis

8.2.3.1 Latent profile analysis

Latent profile analysis (LPA) is one form of a larger class of models commonly referred to as *generalized latent variable models* (see Chapter 4 for greater exposition). Similar to cluster analysis, LPA aims to group individuals with similar patterns into discrete groups (latent classes) represented by a categorical latent variable. For the analysis, the IPQ-R sub-scales of identity, timeline chronic, timeline cyclical, consequences, personal control, treatment control, and coherence were included. The estimated factor scores from the model described above were used in the analysis and can be interpreted as z-score units allowing easy comparison across variables (i.e. mean of zero and a standard deviation of one).

LPA models with 1 through 5 latent classes were considered. Within class covariances between the illness perceptions were unconstrained. The best fitting model was identified using standard model comparison techniques that have been shown to perform well in simulation studies (Nylund et al., 2007; Tofighi & Enders, 2006): Bayesian Information Criterion (BIC), consistent Akaike Information Crite-

[5] The original version of the DAS28 used in ERAS is based on a larger number of joints and does not include the VAS.

[6] A DAS28 score of less than 2.6, opposed to 1.6 for the original DAS, corresponds to the American Rheumatology Association preliminary criteria for clinical remission (Fransen et al., 2004).

rion (CAIC) and the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT). Entropy, a summary measure of classification quality, is also reported.

8.2.3.2 Missing data

As was already indicated the majority of missing data in the analysis was due to non-returned questionnaires at the 6-month assessment. The vast majority of covariates were complete except for the two physiological markers of inflammation, ESR and CRP, as well as the composite measures of disease activity, DAS28. These variables were only available if a blood test was performed at the time of the visit and the results recorded in the patient's medical notes. They were missing for ESR in 134 (59%), CRP in 104 (45%), and DAS28 in 52 (23%) at the baseline assessment. The amount of missing data for other variables at baseline was negligible, ranging between 0 and 6 (3%) for the other clinical and demographic variables used in the analysis.

With regard to individual items within the questionnaires assessing illness perceptions, coping and psychological well-being missing responses were more common. For the DAPOS missing item responses ranged between 6 (3%) and 12 (6%), for the IPQ-R between 1 (.5%) and 17 (8%), and for the Cope between 4 (2%) and 7 (3%). Across the majority of participants only a few items was missing for each scale. For the DAPOS 212 (93%) had either no or one missing response, out of a total of 11-items, and for the IPQ-R 215 had three or less missing responses out of a total 52-items, and for the Cope 220 (97%) had either one or no missing responses.

Missing responses within scales were imputed using the Stata `ice` routine which performs multiple imputation by chained equations (Royston, 2004, 2007; van Buuren et al., 1999). Due to the ordinal response format of most items, and to avoid out of range predictions, ordinal logistic regression models were used to impute missing responses for all items. The imputation analysis also included age and sex. Only one imputed dataset was generated. Since the proportion of missing item responses was low and the items being combined this is unlikely to result in downwardly biasing the estimated variance (Allison, 2002).

The largest cause of missing data was the non-return of questionnaires at the 6-month assessment (57, 25%). Ten multiply imputed data sets were generated using `ice`. All items used in the regression analyses were included in the imputation models along with other relevant variables that may have influenced missingness. This was to ensure that the validity of the *missing at random assumption* stretched as widely as possible. For the one individual known to have died missing responses at the 6-month assessment were not imputed. Hence all longitudinal analyses using multiply imputed data were based

Table 8.1: Sample demographic and clinical characteristics ($N = 227$)

	N	Mean	SD	Min	Max
Age	224	57.7	15.0	19	89
Sex	227				
Male		55	24%		
Female		172	76%		
Education	222				
High School		110	50%		
College		61	27%		
University		32	14%		
Postgraduate		19	9%		
Working	227				
No		131	58%		
Yes		96	42%		
Disease duration (years)	222	12.6	10.8	0.5	54
Disease status	226				
Remission		73	32%		
Active		153	68%		
Biologic therapy	223				
No		146	65%		
Yes		77	35%		
Disease activity score	175	3.6	1.5	0	8.08
HAQ disability	227	1.1	0.8	0	2.88
Pain	225	2.1	0.6	0	5

on 226 individuals.

Sensitivity analysis was performed comparing the results from the multiply imputed data, and combined using the Stata `mim` package using Rubin's rule (Little & Rubin, 1987; Carlin, Galati, & Royston, 2008), with the results of a complete case analysis. The findings from the complete case analysis are given in Appendix E.

8.3 Results

8.3.1 Sample

Using the data without missing values imputed. The demographic profile of the sample was as expected for a hospital based study and was comparable to that of the ERAS cohort (Table 8.1). The mean age at the self-reported time of disease onset for the sample was 45.1 years (SD = 15.5), indicating that the sample was younger compared to the ERAS cohort. Furthermore, there were slightly more females than expected (76% vs. 66% for ERAS).

8.3.2 Cross-sectional associations

Table 8.2 displays the inter-correlations between illness perceptions, coping, demographic, clinical variables and psychological well-being measured at the baseline assessment.

A high correlation was observed between perceptions of treatment and personal control of the condition ($r = .66$). Both control perceptions correlated moderately and negatively with consequences and coherence, indicating that individuals with increased beliefs of the seriousness of their condition and whom reported worse understanding of the condition also reported having lower beliefs about the controllability of the condition. Identity, which refers to the symptoms experienced, correlated positively and highly with the perceptions of the consequences of the condition ($r = .69$) and moderately with perceptions of the cyclicality of the condition ($r = .40$). Furthermore, perceptions of chronicity correlated moderately with perceptions of the cyclicality of the condition ($r = .43$) and consequences ($r = .34$).

At baseline, distress and positive outlook showed a moderate negative correlation ($r = -.47$). Neither correlated particularly highly with HAQ disability ($r_{\text{Distress}} = .18; r_{\text{Positive outlook}} = -.06$) or pain ($r_{\text{Distress}} = .27; r_{\text{Positive outlook}} = -.20$). This is somewhat surprising given the strength of the associations reported for the HADS total scores and HAQ disability and pain in the previous chapter. The correlation between HAQ disability and pain was moderate ($r = .50$)

Illness perceptions showed weak to moderate associations with psychological and physical well-being, with correlations ranging between $r = -.37$ and .56. The SRM predicts that illness perceptions should influence coping so stronger associations would be expected. Furthermore, coping showed only weak cross-sectional associations with psychological distress ($r = -.20$ to .29) or positive outlook ($r = -.14$ to .26). Consequently the rest of this chapter will focus on the direct effect of illness perceptions on psychological well-being since the magnitude of the associations does not support a mediational process.

Moderate positive associations were observed between perceptions of identity, consequences and coherence with psychological distress. A moderate negative association was observed between perceptions of treatment control with distress, but only a small negative correlation was observed with perceptions of personal control. Positive outlook exhibited relatively low correlations with the difference illness perceptions that were in the opposite direction to those observed with distress. The highest correlation was observed for treatment control ($r = .27$), which suggested a tenuous but plausible link between the level of positive outlook and perceptions of treatment control. Furthermore, higher levels of HAQ disability and pain at baseline were associated with higher perceptions of illness identity as well as higher perceptions of the consequences of the condition.

Table 8.2: Pairwise correlations for study variables at the baseline assessment

	Illness perceptions							Coping					Demographic				Clinical					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1. Identity	1.00																					
2. Timeline chronic	.12	1.00																				
3. timeline cyclical	.40	.17	1.00																			
4. Consequences	.69	.43	.34	1.00																		
5. Personal control	-.18	-.05	-.09	-.41	1.00																	
6. Treatment control	-.30	-.25	-.10	-.51	.66	1.00																
7. Coherence	.05	-.18	.29	.10	-.34	-.55	1.00															
8. Active	.11	.06	.02	.07	.22	.24	-.18	1.00														
9. Instrumental	.21	.02	.11	.19	.19	.15	-.11	.69	1.00													
10. Planning	.20	.06	.09	.18	.23	.16	-.08	.84	.87	1.00												
11. Acceptance	-.02	.14	-.09	.04	.19	.25	-.29	.69	.36	.52	1.00											
12. Denial	.19	-.02	.21	.15	.05	-.10	.24	.13	.19	.39	-.34	1.00										
13. Age	-.20	-.02	-.10	-.06	-.10	-.01	-.05	.04	-.06	-.01	.16	-.08	1.00									
14. Female*	.15	.12	.17	.23	-.05	-.05	.02	.07	.04	.11	.12	.02	-.19	1.00								
15. Education*	-.03	-.16	.01	-.13	.18	.26	-.15	.13	.14	.14	.00	.03	-.41	.12	1.00							
16. Working*	.06	.05	-.06	-.07	.03	-.03	-.01	-.08	-.05	-.09	-.15	-.05	-.65	-.10	.40	1.00						
17. ln(Diagnosis)	-.10	.28	-.04	.17	-.07	-.12	-.11	-.07	-.05	-.09	.16	-.23	.26	.13	-.18	-.29	1.00					
18. HAQ disability	.42	.12	.10	.56	-.30	-.32	.05	.03	.07	.09	.13	-.01	.19	.26	-.25	-.39	.24	1.00				
19. EQ5D pain	.53	.12	.17	.54	-.34	-.37	.12	.12	.13	.14	.08	.06	-.05	.03	-.10	.00	.13	.50	1.00			
20. Disease activity score	.38	.04	.10	.39	-.28	-.35	.14	-.03	.02	.00	-.09	.05	-.11	.16	-.05	-.14	-.02	.43	.57	1.00		
21. Biological treatment*	.19	.24	.05	.29	-.04	-.01	-.26	.03	.08	.06	.10	-.02	-.23	.26	.04	-.06	.29	.12	.05	.16	1.00	
22. General distress	.35	.05	.15	.36	-.19	-.35	.38	-.13	.07	.06	-.28	.34	-.29	.17	.02	.15	-.19	.18	.27	.24	-.02	1.00
23. Positive outlook	-.19	-.04	-.11	-.24	.11	.26	-.21	.21	.07	.08	.28	-.19	.06	-.02	.04	-.08	.12	-.06	-.20	-.11	.11	-.47

*Polyserial or tetrachoric correlation as binary variable

8.3.2.1 Discrete patterns of illness perceptions

Since moderate correlations were observed between the illness perceptions, indicating possible overlapping clusters of perception, LPA was implemented to assess whether illness perceptions fell into discrete patterns. LPA models with 1 through 5 latent classes were considered. Within class covariances between the illness perceptions were unconstrained.

Unconditional model Table 8.3 shows the model fit statistics for the latent profile models for the 1- through 5-class solutions. Of the information theoretic statistics both the consistent AIC and the BIC provided evidence for the 2-class model providing the optimal solution. The AIC continued to reduce with 6-classes but has been shown previously to over select the number of classes in mixture models (Nylund et al., 2007; Tofighi & Enders, 2006). Furthermore, it is not consistent with relatively small sample sizes, particularly when the ratio of the sample size to the number of free parameters is low (Tofighi & Enders, 2006), and so should not be used to base model selection decisions on in this instance. As a further test of the appropriate number of classes we can use the LMR likelihood ratio test, which compares the model with K classes to one with $K-1$ classes. For the models with 3 or more classes the test is non-significant ($p > .05$) indicating that the extraction of more than 2-classes provides no significant improvement model fit.

The means and 95% confidence intervals for the 2-class solution are shown in Figures 8.2. The different patterns for the classes were characterized by differences in perceptions of the chronicity, consequences and coherence of the condition. Specifically, the second class ($n = 81$, 36%) consisted of individuals with greater perceptions of chronicity and consequences of RA, and lower perceived understanding of their condition. In line with previous research (Hobro et al., 2004; Miglioretti et al., 2008), this class is henceforth referred to as 'non-adapters' and the remaining class 'adapters'.

Table 8.3: Model fit for unconditional LPA of illness perception ($N = 227$)

	1	2	3	4	5
Params.	29	59	89	119	149
LL	-1824.3	-1708.5	-1649.6	-1595.2*	-1531.0*
AIC	3706.6	3535.0	3477.3	3428.3	3360.1
CAIC	3834.9	3796.1	3871.0	3955.0	4019.3
BIC	3805.9	3737.1	3782.1	3835.9	3870.4
Entropy	.	.912	.899	.923	.927
LMR-LRT p-value	.	0.0001	0.36	0.2342	0.133

*Best log-likelihood not replicated over 100 optimizations of an initial set of 1000 random sets of starting values

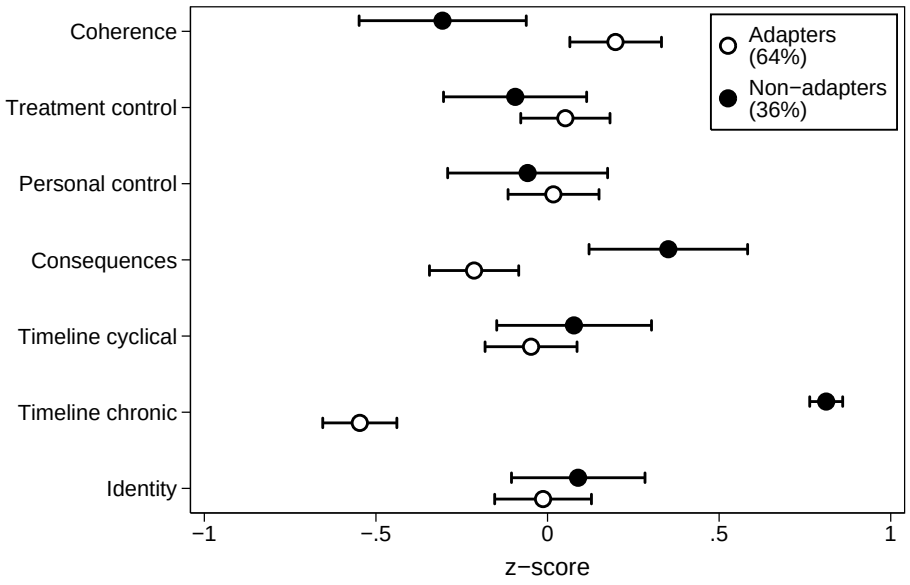


Figure 8.2: Estimated means and 95% CIs of illness perceptions for the unconditional 2-class solution

The 3-class model split the largest class from the previous model into two. Although no significant difference was observed for the illness perceptions of these two classes, the difference appeared to be characterised by difference in the perception of the chronicity of the condition since it was for this perception that magnitude of the difference in means was largest. The other class consisting of individuals with greater perceptions of the chronicity and coherence of their condition remained stable. Thus 2-classes was selected for the remainder of the analysis.

Predictors of discrete patterns of illness perception For the 2-class model, latent class membership was regressed onto selected covariates using a logistic regression model. The inclusion of covariates as predictors of class membership did not alter the class profiles. The class means across the illness perceptions were almost identical and the proportion of the sample in each class were almost identical. The resultant logistic regression estimates averaged over the 10 multiply imputed datasets are presented in Table 8.4. The parameter estimates for the complete case analysis (excluding ESR) were similar although the standard errors were increased (see Appendix E).

The strongest predictor of class membership was disease duration, a one-unit increase in the natural logarithm of disease duration was associated with a two-fold increase in the odds of belonging to the 'non-adapters' class. Being in paid employment was also significantly related to membership of this, relating to a 2.5 times increase in the odds. Inflammation, as indexed by natural logarithm of ESR, was

Table 8.4: Logistic regression (odds ratios) for class membership with higher perceptions of consequences, chronicity and lower coherence based on 10 multiply imputed datasets

	OR	SE	*z*	*p*	95% CI	
Age	0.99	0.02	-0.64	0.521	0.96	1.02
Sex	1.15	0.41	0.34	0.731	0.50	2.64
Education	0.62	0.43	-1.12	0.265	0.26	1.46
Working	2.45	0.42	2.11	0.035	1.05	5.73
ln(Diagnosis)	2.12	0.24	3.20	0.001	1.32	3.39
HAQ disability	1.42	0.26	1.93	0.054	0.99	2.02
EQ5D pain	0.85	0.32	-0.53	0.597	0.45	1.59
DAS28	1.17	0.15	1.05	0.296	0.87	1.57
ln(ESR)	0.61	0.21	-2.33	0.020	0.40	0.93
Biologic treatment	1.58	0.53	1.38	0.169	0.82	3.04
Active Disease	1.19	0.42	0.49	0.622	0.60	2.37
Distress	1.03	0.25	0.12	0.901	0.63	1.69
Positive outlook	1.26	0.25	0.95	0.342	0.77	2.07

related to a reduction in the odds of membership of the second class of around 39% per one-unit increase in the natural logarithm of ESR. Conversely, there was a borderline significant association between HAQ disabilty and membership of the non-adapter class, relating to a 42% increase in the odds of membership of this class for each one unit increase in HAQ disability, or to put this on a standard deviation metric, a 31% increase in the odds of membership of the second class for a one standard deviation (SD = .76) increase in HAQ disability.

In summary, it would appear that two distinct patterns of illness perceptions characterize this sample of RA patients. The smallest class, accounting for just over one-third of the sample, reported significantly higher perceptions of the chronicity of the condition and its perceived impact on their lives, furthermore, less understanding of the condition was also reported. Individuals with this pattern of illness perceptions were more likely to have greater experience of the condition, be in paid employment and have lower markers of inflammation compared to the result of the sample. Although there was some indication of greater functional disability. The predictive validity of these distinct patterns in relation to changes in psychological and physical well-being will be examined later in the chapter.

8.3.3 Longitudinal associations

I now move on to the main focus of this chapter the longitudinal association between illness perceptions and psychological well-being. This section will consider whether illness perceptions account for heterogeneity in 6-month change scores. In light of the findings of Chapter 7, the role of illness perceptions in changes in physical well-being will also be considered. Prior to these detailed analyses I will first

consider whether changes in psychological well-being were observed during the period of follow-up.

8.3.3.1 Change in psychological well-being

At the sample level, psychological well-being changed little between the baseline and 6-month assessments. The mean change in psychological distress was just .01 (SD = .60), which was not statistically significantly different from zero ($t(165) = 0.18$; $p = .854$). Furthermore, the mean change for positive outlook was also small, -.07 (SD = .77), and non-significant ($t(165) = -1.21$; $p = .229$). Although, at the sample level, changes were relatively small, the size of the standard deviations for the changes scores indicates substantial variability in changes across individuals.

It is important to remember here that the scaling of time is somewhat arbitrary since the disease duration at the baseline assessment was wide. Regressing distress at the baseline assessment on the natural logarithm of the time since diagnosis indicated a significant reduction in distress levels across the range of disease duration for the sample. Specifically, distress decreased by -.15 standard deviations (95% CI:-.26,-.04) for every one-unit increase in the natural logarithm of disease duration. Since this suggests greater change early in the course of the disease it provides support for the nonlinear pattern observed in Chapter 6.

Latent curve model To further examine changes early in the course of the disease at the individual level, a linear latent curve model was fitted to the psychological distress data for the 34 individuals with a diagnosis within 12-months and who were assessed over three-time points (baseline, and then 3- and 6-months after the baseline assessment). Confirming the above findings, the value of the slope factor, representing the total expected change over 6-months, for the distress model was small and non-significant, .02 (95% CI: -0.02, 0.06). This indicates that for this sub-sample there was no change in symptoms of distress over the period. Furthermore, the standard deviation of the latent slope factor was non-significantly different from zero indicating no heterogeneity in the slopes ($\sigma = .02$; SE = .09). It is important to remember that power will be low given the small sample size.

Similarly, for positive outlook the slope factor was small and non-significant, .01 (95% CI: -.05, .08), indicating no change over the period for the early disease sub-sample. Again the variance of the slope factor was small and non-significant.

These findings are in contrast to analyses reported in the immediately preceding section, and also to the findings of Chapter 3, both of which suggested that a reduction in distress with substantial variability in changes should be observed. This latter finding is somewhat more surprising but may be due to the

small size of the sample used for this analysis. It may also be that since *all* individuals in the sample were taking DMARDs at baseline, as opposed to the ERAS study where none had, that the reduction in distress associated with the initiation of disease modifying therapy had already occurred.

8.3.3.2 Illness perceptions as predictors of future psychological well-being

Despite the indications of the latent curve models, the standard deviation of the 6-month change scores for distress and positive outlook suggest substantial variability. The ability of illness perceptions to predict future psychological well-being was examined using a hierarchical linear regression modelling approach. Four models were estimated for each of the illness perceptions assessed in the study. The first model, 'M1', simply regressed the assessment of psychological well-being—either the distress factor score or the positive outlook factor score—at 6-months on the illness perception at the baseline assessment. The second model, 'M2', adjusted for the baseline status on the measure of psychological well-being. The third model, 'M3', additionally adjusted for the demographic variables age, sex, education and work status. The final model, 'M4', adjusted for level of disease severity at baseline as indicated by HAQ disability, the EQ5D pain item, Disease Activity Score, ESR, self-reported disease status, disease duration and whether biologic treatment was being taken.

Due to the large number of models assessed and the resulting difficulty in presenting the results in an easily interpretable format the standardised regression coefficients for the illness perceptions are presented graphically for each of the models. Tables are presented that include all variables entered in the fourth model, but also including all illness perceptions (rather than considering them separately as in the figures). All results presented are based on the combined estimates across the 10 multiply imputed datasets. Estimates from the complete case analysis were similar unless otherwise stated and are given in Appendix E.

Psychological distress Considering first psychological distress, the unadjusted analyses indicated that the illness perceptions of identity, consequences, cyclical timeline, treatment control and coherence assessed at baseline were related to the levels on this construct at the 6-month assessment (Figure 8.3). In addition, perceptions of personal control had a borderline significant relationship ($p = .051$). After controlling for the initial level of psychological distress the effect for cyclical timeline, treatment control and coherence was nullified. This suggests that the observed crude effect was due to residual confounding as a result of the cross-sectional association with distress. Specifically, individuals with higher beliefs regarding the cyclicality of RA, lower perceptions of the ability of their treatment to control

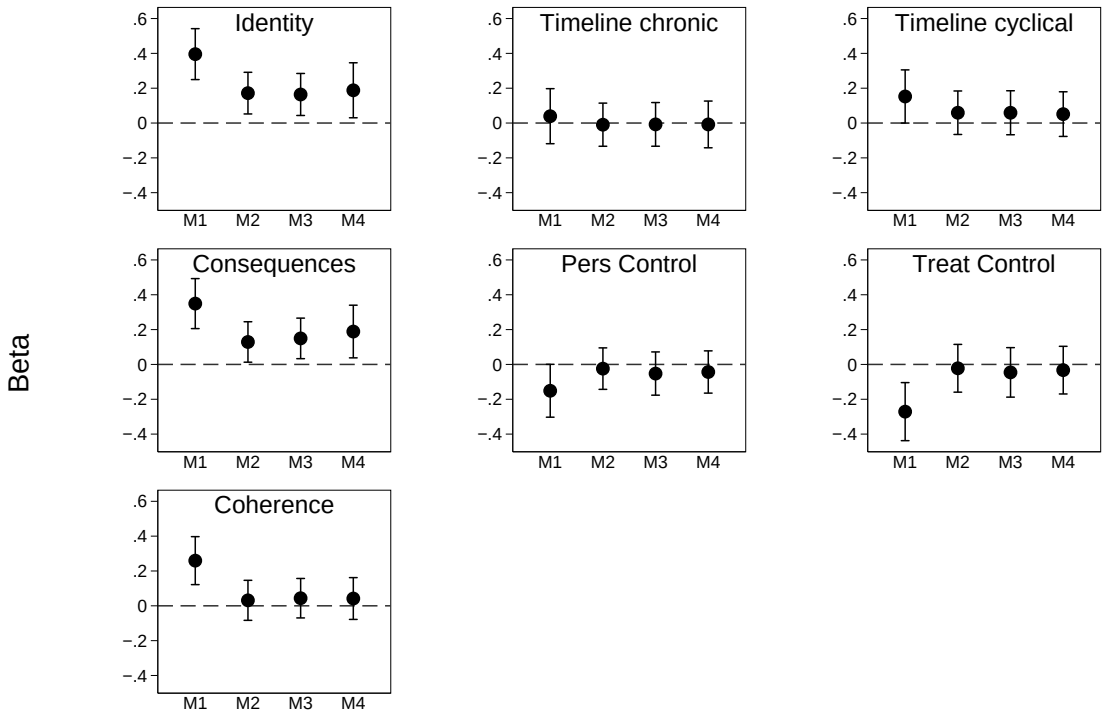


Figure 8.3: Standardised parameter estimates for psychological distress at 6-months regressed on illness perception with varying levels of adjustment (M1 = unadjusted; M2 = baseline distress; M3 = + demographics; M4 = + disease status)

the condition and less understanding of their condition appear likely to have worse psychological distress at follow-up simply because they are cross-sectionally related. The direction of causality is not clear, but it would appear that these factors do not lead to changes in distress over time. Further adjustment for demographic and clinical characteristics did not effect the parameter estimates, which were all non-significant and close to zero

The parameters for identity and consequences were reduced but remained significant after controlling for baseline distress. Both effect size estimates were of similar magnitude, indicating that a one standard deviation increase in perceptions of identity and consequences related to, on average, around a 19% or 14% of a standard deviation increase in distress, respectively. Controlling for demographic confounders did not further attenuate the associations, both remained statistically significant and even increased slightly in magnitude. Additionally controlling for disease status also slightly increased the magnitude of the association for both identity and consequences with the parameter estimates remaining statistically significantly different from zero.

Illness perceptions relating to the perceived chronicity of the condition (timeline chronic) were not related to future psychological distress in the crude analysis or any of the adjusted models. After adjust-

Table 8.5: Standardised parameter estimates averaged over 10 multiply imputed datasets for psychological distress at 6-months regressed on a combined model of illness perceptions adjusted for multiple confounders all assessed at baseline

	β	t	p	95% CI	
Identity	0.20	2.08	0.039	0.01	0.40
timeline chronic	0.03	0.33	0.739	-0.13	0.18
timeline cyclical	-0.09	-1.34	0.183	-0.23	0.04
Consequences	0.08	0.73	0.466	-0.14	0.30
Personal control	-0.10	-1.29	0.200	-0.24	0.05
Treatment control	0.15	1.51	0.133	-0.05	0.34
Illness coherence	0.10	1.32	0.190	-0.05	0.26
Age	0.00	-0.86	0.395	-0.02	0.01
Female sex*	0.02	0.18	0.855	-0.22	0.26
Education*	0.13	1.03	0.308	-0.14	0.40
Working*	0.06	0.51	0.610	-0.19	0.31
ln(Diagnosis)	-0.04	-0.77	0.444	-0.15	0.07
HAQ disability	-0.02	-0.28	0.783	-0.18	0.14
EQ5D pain	0.13	1.21	0.230	-0.09	0.35
DAS28	-0.07	-1.65	0.106	-0.17	0.02
ln(ESR)	0.02	0.22	0.831	-0.15	0.19
Biologic treatment*	-0.04	-0.32	0.750	-0.31	0.23
Active Disease*	-0.05	-0.45	0.653	-0.28	0.18
Distress	0.60	8.58	0.000	0.46	0.75
Positive outlook	-0.15	-2.19	0.036	-0.29	-0.01

*Unstandardised parameter estimates b reported for dichotomous variables

ment all parameter estimates were non-significant and close to zero.

Entering all of the illness perceptions into a combined model along with all confounding variables revealed identity to be the only illness perception significantly related to future psychological distress (Table 8.5). The reduction of the effect for consequences to non-significance is likely because of the overlap of the construct with the perceptions of identity. That is, individuals attributing greater numbers of symptoms to their condition also tend to report greater perceptions of the seriousness of the condition.

As was observed in the previous chapter there was a strong autoregressive effect for distress. This accounted for the majority of the variance explained by the model. Also predictive of future distress was positive outlook. The effect related to a .15 standard deviation lower residualised change in psychological distress at the 6-month follow-up for a one standard deviation higher level of positive outlook at baseline.

It is worthwhile noting that power to detect a significant effect of any of the illness perceptions or other predictors would be reduced due to the strong autoregressive effect observed for distress.[7]

[7]Post-hoc power calculations indicate that after controlling for baseline distress predictors in the model would have to account for at least an additional 2% of the variance to acheieve power of 80% (based on $n = 170; \alpha = .05$).

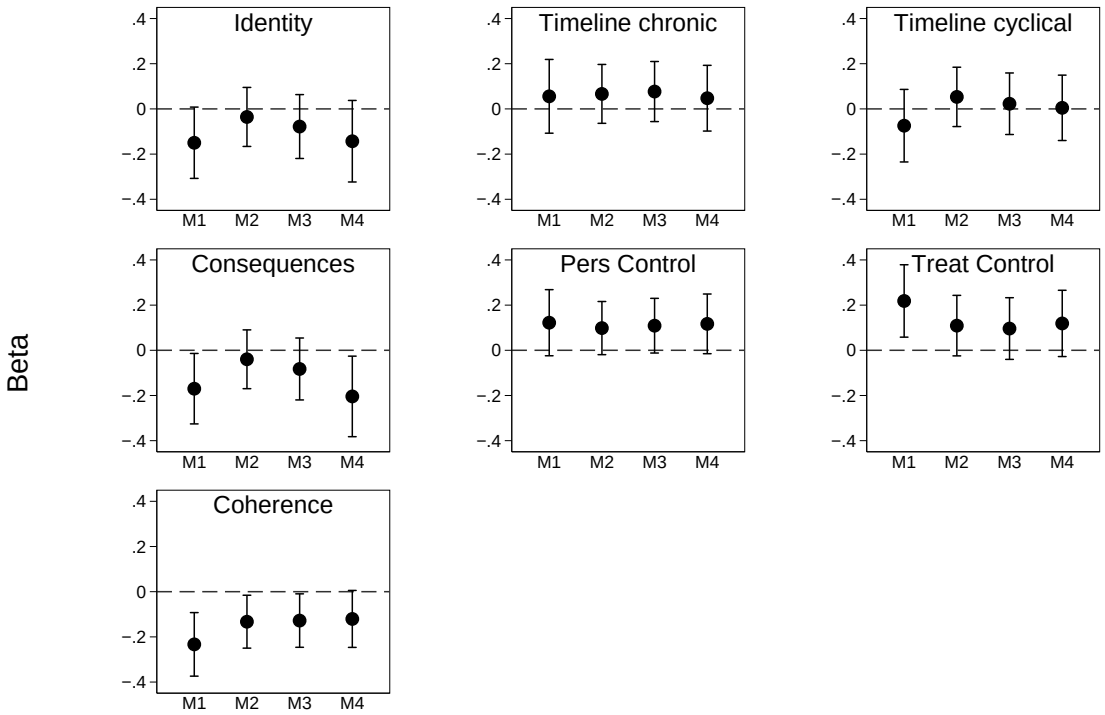


Figure 8.4: Standardised parameter estimates for positive outlook at 6-months regressed on illness perception with varying levels of adjustment (M1 = unadjusted; M2 = baseline positive outlook; M3 = + demographics; M4 = + disease status)

Further analysis, assessing for possible moderating effects of baseline distress or functional disability on the effect of illness perceptions on distress at the 6-month assessment were all non-significant indicating no moderation.

Positive outlook Turning to positive outlook, standardised parameter estimates for varying levels of adjustment are displayed in Figure E.2. The unadjusted estimates indicate perceptions of treatment and personal control, identity, coherence and consequences as significant predictors of future positive outlook. After controlling for the initial level of positive outlook the size of the association for each was attenuated, remaining significant only for coherence.

For identity and consequences the further adjustment for demographic and then clinical variables increased the magnitude of the parameter estimates, although statistical significance was not achieved. In contrast the estimates for coherence were further attenuated after adjustment for demographic and clinical characteristics and were non-significant ($p = .058$) after controlling for both demographic and clinical variables.

The parameter estimates with regard to chronic and cyclical timeline were small and non-significant for all levels of adjustment.

Table 8.6: Standardised parameter estimates averaged over 10 multiply imputed datasets for positive outlook at 6-months regressed on a combined model of illness perceptions adjusted for multiple confounder's all assessed at baseline

	β	t	p	95% CI	
Identity	0.03	0.28	0.783	-0.21	0.27
timeline chronic	0.04	0.45	0.651	-0.14	0.23
timeline cyclical	0.12	1.49	0.142	-0.04	0.27
Consequences	-0.19	-1.58	0.120	-0.43	0.05
Personal control	0.07	0.94	0.347	-0.08	0.22
Treatment control	-0.08	-0.70	0.485	-0.30	0.14
Illness coherence	-0.10	-1.21	0.229	-0.26	0.06
Age	0.00	-0.58	0.565	-0.01	0.01
Female sex*	0.28	1.99	0.052	-0.01	0.56
Education*	0.12	0.81	0.423	-0.18	0.41
Working*	-0.01	-0.06	0.956	-0.28	0.27
ln(Diagnosis)	-0.03	-0.42	0.675	-0.17	0.11
HAQ disability	0.19	1.96	0.054	-0.01	0.39
EQ5D pain	-0.14	-1.11	0.269	-0.40	0.12
DAS28	-0.03	-0.56	0.581	-0.14	0.08
ln(ESR)	0.13	1.56	0.130	-0.04	0.29
Biologic treatment*	0.17	1.33	0.188	-0.09	0.44
Active Disease*	-0.02	-0.12	0.905	-0.28	0.25
Distress	-0.18	-2.32	0.023	-0.33	-0.03
Positive outlook	0.49	7.64	0.000	0.37	0.62

*Unstandardised parameter estimates b reported for dichotomous variables

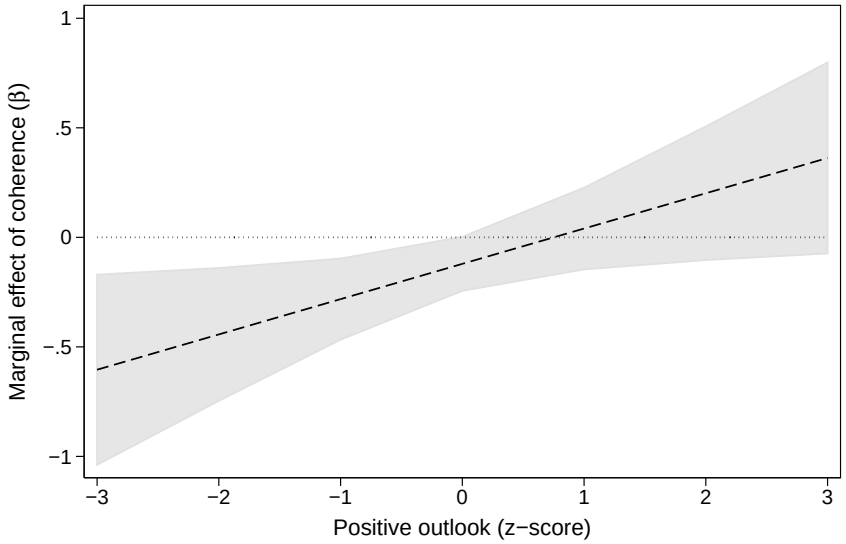


Figure 8.5: Marginal effect of coherence on positive outlook at 6-months by baseline positive outlook

The model including all illness perceptions as predictors of future positive outlook whilst simultaneously adjusting for baseline positive outlook and psychological distress, as well as demographic and clinical variables was estimated (Table 8.6). The majority of the variance explained was accounted for by baseline positive outlook, for which there was a large autoregressive effect. None of the illness perceptions was observed to significantly predict positive outlook assessed 6-months later, although the effect size observed was similar for consequences compared to consequences model four shown in Figure E.2.

Of the control variables, distress at baseline was also a significant predictor of later positive outlook. Indicating that, controlling for earlier positive outlook, a one standard deviation higher level of distress at baseline was associated with a 18% reduction in positive outlook 6-months later. Sex was a borderline significant predictor, relating to around a 28% of a standard deviation higher residualised change in positive outlook for females. The estimate of HAQ disability was also borderline significant, worse disease severity was related to an increase in positive outlook at 6-months. It is likely that this effect is an artefact due to regression to the mean since those with worse disease at baseline would have had lower positive outlook at baseline. However, it must be emphasised that the effect was not significant and this suggestion is therefore rather tenuous.

Possible moderation of the effect of illness perceptions at baseline by positive outlook or functional disability on positive outlook at the 6-month assessment was considered. The analyses indicated a significant interaction between positive outlook and coherence. Figure 8.5 plots standardised parameter estimate β for coherence on 6-month positive outlook across values of positive outlook at baseline.

This indicates that coherence has a significant negative association with future positive outlook only for patients with levels of positive outlook below the mean value for the sample. This finding can be interpreted as individuals with less of an understanding of their condition experience lower positive outlook at 6-months only when there initial level of positive outlook was low, suggesting a possible vicious cycle.

At this point a caveat is warranted since the analysis was conducted in a post-hoc manner and the risk of a false positive finding is high. Nevertheless this suggests an interesting and plausible relationship that warrants further attention.

8.3.3.3 Illness perceptions as predictors of future physical well-being

Further analysis was undertaken to examine whether illness perceptions were predictive of pain and functional limitation at the 6-month assessment. A similar procedure was used to the assessment of illness perceptions as predictors of future psychological well-being. Initially, the level of physical well-being at 6-months was regressed separately on each of the illness perceptions without adjusting for potential confounder's (M1). Then the level of physical well-being was included at the second step (M2). At the third step demographic variables were adjusted for (M3: age, sex, education and work status). Finally, estimates were adjusted for clinical confounder's as well as the baseline levels of psychological well-being (M4: disease status, Disease Activity Score, ESR, disease duration, biologic treatment, psychological distress, positive outlook and the alternate measure of physical well-being)

Functional limitation Figure 8.6 shows that without adjusting for baseline functional limitation or possible confounding variables HAQ disability at 6-months was significantly associated with earlier perceptions of identity, consequences, timeline chronic, and perceptions of both personal and treatment control. However, adjusting for baseline HAQ disability reduced the effect to non-significance for all illness perceptions. Parameter estimates were stable and remained non-significant with additional levels of adjustment.

The correlation between between HAQ disability scores at both assessments was extremely high ($r = .91$), indicating that 83% of the variance in HAQ disability at follow-up was explained by the baseline level. As a result any analyses considering HAQ disability controlling would have low power, so it is not suprising that no significant effect was observed.

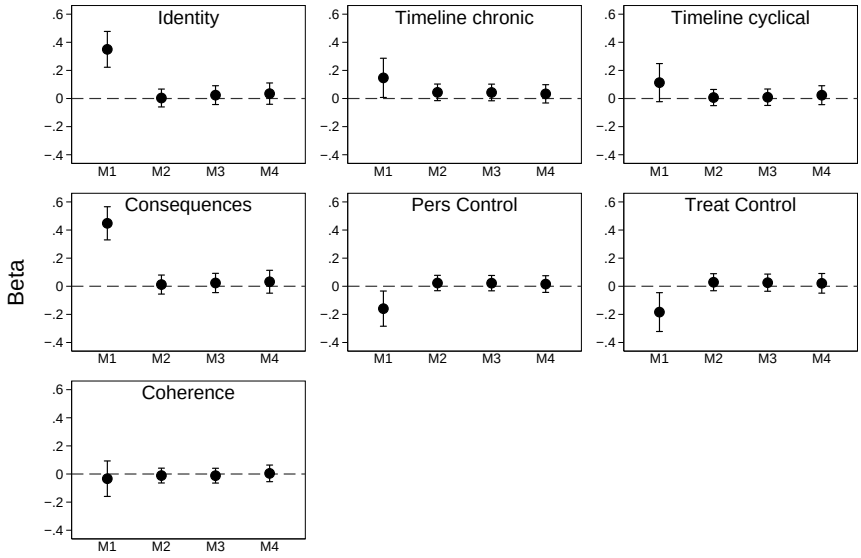


Figure 8.6: Standardised parameter estimates for HAQ disability at 6-months regressed on illness perceptions with varying levels of adjustment (M1 = unadjusted; M2 = baseline positive outlook; M3 = + demographics; M4 = + disease status)

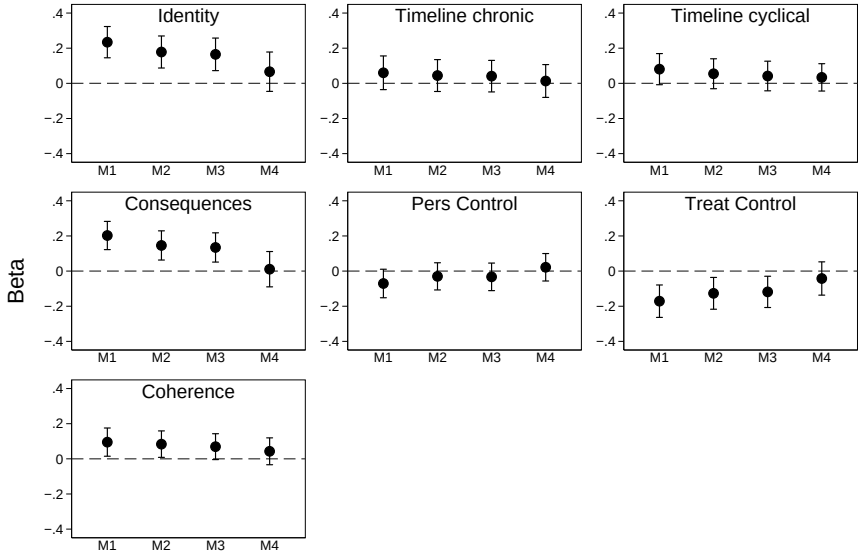


Figure 8.7: Standardised parameter estimates for EQ5D pain question at 6-months regressed on illness perceptions with varying levels of adjustment (M1 = unadjusted; M2 = baseline positive outlook; M3 = + demographics; M4 = + disease status)

Table 8.7: Membership of the non-adapter class as a predictor of 6-month psychological and physical well-being (multiply imputed data).

	Crude					Adjusted				
	b	*t*	*p*	95% CI		*b*	*t*	*p*	95% CI	
Distress	0.05	0.36	0.719	-0.20	0.30	0.00	-0.03	0.975	-0.19	0.18
Positive outlook	0.12	0.89	0.376	-0.15	0.40	0.10	0.85	0.398	-0.14	0.34
HAQ disability	0.25	2.01	0.046	0.00	0.49	0.01	0.21	0.838	-0.09	0.11
EQ5D pain	0.10	1.20	0.232	-0.07	0.27	-0.01	-0.15	0.878	-0.16	0.14

Pain The illness perceptions of identity, consequences, coherence, timeline cyclical and treatment control were associated with pain at 6-months in the unadjusted models (Figure 8.7). Controlling for pain at baseline the effects were attenuated but remained significant for all except timeline cyclical. Further controlling for demographic variables, only coherence was non-significant. However, controlling for clinical characteristics and baseline psychological status the effects of identity, consequences and treatment control were reduced to non-significance. Further analysis indicated that the reduction in the effect was mainly accounted for by the inclusion of HAQ disability.

8.3.3.4 Distinct patterns of illness perceptions as predictors of future psychological and physical well-being

Membership of the non-adapter class derived from the 2-class latent profile analysis was entered into separate regression models as predictors of future psychological and physical well-being (Table 8.7). Initially the class indicator variable was entered into a crude model that incorporated no other variables. The adjusted model included the variables included in model 4 of the above models, including the baseline status on the outcome variable as well as demographic and clinical variables.

In the crude analysis membership of the class with higher perceptions of consequences, chronicity and coherence was significantly related only to HAQ disability 6-months later, but not distress, positive outlook or pain. The effect was relatively small, relating to an increase of .25 HAQ units for this class. Following adjustment for potential confounding variable none of the associations between class membership and well-being at 6-months was significant.

No substantive difference was observed in comparison to the complete case analysis (see Appendix E) other than the crude association between membership of the non-adapter class and higher HAQ disability being reduced to non-significance as a result of the reduced power ($p = .086$)

8.4 Discussion

The aim of this chapter was to examine the role of illness perceptions in the relationship between disease and psychological well-being in RA. Perceptions concerning the attribution of symptoms to the condition, their illness identity, and the perceived personal consequences of the condition were related to changes in psychological distress after controlling for demographic and clinical characteristics. Furthermore, there was some indication that the reported level of understanding of their condition, coherence, was related to future positive outlook.

Two distinct patterns of illness perceptions were observed. These appeared to be differentiated by disease duration and activity. Specifically individuals with longer disease duration and lower physiological markers of inflammation tended to have higher perceptions of the chronicity of their condition and consequences of the condition. These individuals perhaps have more realistic representations, which is further supported by the concurrent higher reports of the perceived understanding of their condition.

This is the first attempt to identify distinct patterns of illness perceptions in RA. Two studies in other chronic physical conditions have identified patterns that have been termed 'adapters' and 'non-adapters' using cluster analytic methods (Hobro et al., 2004; Miglioretti et al., 2008). The same labels were used for the 2-classes derived in this chapter. Unlike the two previous studies no association was observed between the clusters and psychological well-being. It is likely that, along with psychological distress, illness perceptions change rapidly early in the course of the disease and distinct patterns at that stage in the course of RA may therefore differ from the patterns identified here. Furthermore, clusters identified at such a time may have better predictive validity. Unfortunately this study has not been able to address this issue.

The findings of the study regarding illness perceptions corroborate those of previous cross-sectional studies in RA, supporting the utility of the SRM in rheumatology research. In particular, the illness perceptions of identity, consequences and controllability were found to be related to concurrent levels of distress and disability (H. Murphy et al., 1999; Carlisle et al., 2005; Groarke et al., 2005; Graves et al., 2009). However, there were some notable differences regarding coping. This study observed no correlation between coping with illness perceptions or distress although such associations have previously been reported (Uhlig et al., 2000; Treharne et al., 2007; Evers et al., 1997; G. K. Brown, Nicassio, & Wallston, 1989; Groarke et al., 2005). Moreover, Carlisle et al. (2005) observed a 'mediational' role of avoidant coping on the effects of identity and consequences on both psychological distress and disability. Ignoring that the study was cross-sectional and a mediational conclusion is somewhat tenuous, the present study

observed no association between coping with either illness perceptions or distress so evidence for such a relationship is lacking. Differences in the findings reported in this chapter and those of previous studies may stem from the tools used to assess coping. The analysis in this chapter used the Brief Cope (Carver, 1997), which was not used by other studies. The Brief Cope does not assess of avoidant coping, which has been indicated by two of the previous studies as being related to worse psychological well-being both cross-sectionally and longitudinally (Carlisle et al., 2005; Evers et al., 1997). Furthermore, in line with the conclusions of a recent systematic review of coping, it may be that flexibility in the selection of appropriate coping strategies rather the tendency to use particular strategies is important (Vriezekolk et al., 2011).

Previous studies examining longitudinal effects of illness perceptions on psychological well-being have been limited by small sample sizes. This is further compounded by the reduced statistical power resulting from the strong autoregressive effect of well-being at one time point on the next. This study has used a larger sample size, and has used statistical techniques to avoid the loss of power as a result of missing data at follow up. This will have helped to maintain statistical power for the analysis and explains the commensurate but stronger findings observed for this study. In line with the findings of Scharloo et al. (1999) and Sharpe et al. (2001) perceptions of identity and consequences were related to a residualised change in distress. However, Schiaffino and Revenson (1995) observed an interaction between perceptions of consequences and functional limitation. This was not observed in the current study. However, a moderating effect *was* observed for illness coherence and positive outlook.

It is of note, that other studies have also failed to find an association between illness perceptions and changes in disability (Scharloo et al., 1999; Treharne, 2004). As with this study it appears that the lack of effect likely stems from the stability of disability assessed by the HAQ in individuals with established disease. As a result, it is not clear whether illness perceptions are really not related to changes in functional limitation or whether there simply is not enough heterogeneity in change in HAQ scores over 6-months to be able to tell. Other measures, that are more sensitive to change, may allow for a more reliable analysis.

To date, only the unpublished work of Treharne (2004) has investigated the role of illness perceptions on positive psychological well-being. This found no association between perceptions of consequences and residualised change in life satisfaction, however no other illness perceptions were considered. This study has revealed the individuals level of understanding to be an independent predictor of future positive outlook.

The study has several limitations. A major limitation was to not assess causal perceptions. The

literature revealed that causal perceptions may have had a longitudinal impact on well-being (Scharloo et al., 1999). However, it was decided that in order to reduce respondent burden the already long illness perceptions questionnaire needed to be shortened, and it was the 18-item cause sub-scale that was excluded. It is unfortunate but ultimately unavoidable that in trying to balance the detail and breadth of information collected with the burden on the respondent that some important data may not be collected. Although there exists a brief eight-item (as opposed to 64-item) version of the illness perception questionnaire (Broadbent, Petrie, Main, & Weinman, 2006) it is likely to suffer from reduced reliability as only single items are used to assess each illness perception.

A further limitation of this study in common with the wider research in this area is the measurement of illness-identity. Illness-identity refers to the label given to the condition and the attribution of specific somatic symptoms to the condition. This is assessed by a count of the number of symptoms experienced and the number attributed to the condition. In practice, however, whether these symptoms can realistically be attributed to the condition is ignored. In section 8.2.2.1 it was noted that these symptoms appeared to be multi-dimensional. The comparison of RA to non-RA symptoms as a predictor of psychological and physical well-being could be assessed. Furthermore other measures such as the ratio of all symptoms experienced to those attributed to their RA could also be used. A detailed examination of illness identity was beyond the scope of the current chapter but should be the focus of future research.

Some concern must be given to the DAPOS. This is a relatively new measure and more standard assessments would have provided findings that have greater generalisibility. As has already been stated the need to limit the burden on respondents sometimes means the brevity of the assessment tool on balance is more important. The DAPOS as an eleven-item instrument was selected on this basis. Correlations between distress with both pain and functional limitation were lower than expected. It may be that by by removing items that related to pain as well as distress an important component of distress has been removed. Furthermore, with regard to the DAPOS positive outlook scale, the extent to which scores on the scale reflect current levels of positive outlook or dispositional optimism is not clear. The authors of the scale state that they believe it to measure *positive affect* (Pincus et al., 2004), suggesting that they believe the tool to measure a state based component. However, that the label of the sub-scale is 'positive outlook' surely suggests that there is some overlap with trait optimism. Despite these concerns the findings of this study emphasise the need for considering positive psychological well-being as well as psychological distress, that has been promoted elsewhere (Seligman & Csikszentmihalyi, 2000). It seems that although the two are closely related they function independently and have different determinants and longitudinal effects.

A further important point for discussion concerning the DAPOS is the relatively low correlations observed for psychological distress with pain and functional limitation. The previous chapter highlighted the strength of these associations. However in the current analyses the association was very small. The DAPOS was designed to measure, without criterion contamination, depression and anxiety. This was achieved by excluding any items from the HADS and BDI that were observed to cross-load onto a (forced) somatic factor. It seems that this approach may have excluded important features of distress. Depression and anxiety share many symptoms with rheumatoid arthritis and the consideration of whether these symptoms are attributable to the physical or psychological condition may not be important.

The findings of the current study indicate that interventions to change illness perceptions are unlikely to have an effect on individuals with established disease. Although illness perceptions were observed to be related to psychological well-being it would seem that higher perceptions of consequences are likely to correspond with a more realistic view of RA. There may be some support for educational interventions to improve understanding of the condition, since this may improve positive well-being. Previous studies in other conditions have shown interventions targeted at illness perceptions following a myocardial infarction have resulted in improvements in psychological and physical well-being (Petrie et al., 1996). For the most likely chance of success it seems appropriate to recommend intervention research be guided towards study of individuals with recent onset RA.

To summarise, illness perceptions play an important, albeit small, role in the relationship between disease and psychological well-being over time in patients with established disease. Cross-sectional associations are stronger suggesting considerable interplay between the constructs over shorter periods of time. Coping on the other hand was not found to be related to illness perceptions or psychological well-being.

Chapter 9

General discussion

9.1 Overview of the discussion

This chapter summarizes the findings of the four empirical chapters concerning the measurement of and changes in psychological distress in the ERAS cohort, and the findings of the longitudinal association between illness perceptions and coping in a separate cohort. The empirical findings are discussed in the context of the original aims and objectives described in section 3.5.3. This is followed by a general discussion of the strengths and limitations of the methods and data used in this dissertation, in relation to the use of observational data (to draw causal conclusions) and the latent variable approach to longitudinal modelling. Finally the implications of the findings of this dissertation with regard to the clinical management of individuals with RA and future research concerning RA, and more broadly studies of well-being in chronic physical illness, are considered.

9.2 Overview of the aims and objectives

The systematic review, Chapter 3, identified a considerable body of literature concerning the study of longitudinal changes in psychological well-being over the course of the disease in individuals with RA. Although the body of literature was large, much of the research was based on small to medium sized samples. Several larger studies were conducted with follow-up over several years (e.g. those within the EURIDISS consortium) but often did not apply advanced longitudinal data analysis methods that are currently available. For example, analytical methods sometimes made use of data collected at two time points where more were available. The main limitation, however, was the lack of large longitudinal studies following individuals from soon after the onset of the disease, and furthermore, using appropriate

analytical methods to examine the heterogeneity of changes in psychological well-being at the individual level.

A theoretical model was presented in Figure 3.3 that drew upon the frameworks concerning the disablement process in RA (Verbrugge & Jette, 1994; Escalante & del Rincon, 2002), the relationship between psychological distress and physical illness (Katon, 2003), and the role of psychosocial factors in the pathway between disease to psychological and physical outcomes (Leventhal et al., 1980, 1984). This model described the relationship between psychological and physical well-being as a complex dynamic system. Cross-sectionally, strong associations were indicated between psychological distress and somatic symptoms. These were expected to persist longitudinally. The model indicated distress as being influenced by somatic symptoms, which mediated the impact of the underlying disease activity. It was expected that distress and somatic symptoms at an earlier time would have direct effects on future psychological well-being, also these longitudinal effects were expected be mediated or moderated by other factors. For example, it was expected that coping strategies would moderate these effects and illness cognitions would mediate them.

Based on the systematic review and the theoretical model three objectives were presented: (i) To describe patterns of change in psychological well-being during the RA disease course; (ii) to quantify the association between psychological well-being and somatic symptoms; and (iii) to investigate the impact of illness cognitions and coping on psychological well-being. The remainder of this section describes the empirical findings of this dissertation and discusses the extent to which each of these objectives has been met. Prior to addressing each objective the findings of Chapter 5 concerning the the measurement of psychological distress in ERAS cohort is described.

9.2.1 The measurement of psychological distress in RA

The first empirical chapter, Chapter 5, did not directly address the main aims of the dissertation but provided a detailed examination of the assessment of psychological distress using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Evidence for a bifactor structure, consisting of a general psychological distress factor that explained 69% of the common variance in item responses was found. This factor structure was replicated in samples of patients with end stage renal disease and cancer. Furthermore, the factor structure of the HADS in RA was found to be non-invariant over time. Although only sum-scores of the individual scales were available for most individuals in the ERAS cohort, the findings of this chapter suggested that the use of the HADS total score as an indicator of general distress that incorporated some of the components specific to depression (anhedonia) and anxiety (autonomic

arousal) was appropriate. This supported the earlier findings of studies using IRT methods (e.g. Pallant & Tennant, 2007) that had recommended the HADS total score as a measure of general psychological distress, since the general factor saturation of the test was high.

The findings of a bifactor structure is at odds with the conclusions of the most recent review of the construct validity of the HADS, which described a factor structure consisting of three lower order factors as providing the most acceptable fit (Martin, 2005). However, to my knowledge, this is the first study to consider a bifactor structure in relation to the HADS. The bifactor structure provides a more acceptable empirical explanation of the item covariance structure than previous research and may be viewed as providing a conceptual interpretation that reconciles the ambiguous findings of previous studies using different methods. Furthermore, the observation of a bifactor structure is commensurate with current thinking on the factorial structure of psychological distress and mood disorders in general (T. A. Brown et al., 1998; Krueger & Finger, 2001; Krueger et al., 2005; Watson, 2005; Mineka et al., 1998) and findings of psychometric studies of other measures of psychological distress (Simms et al., 2008; Crawford & Henry, 2003; Steer et al., 1999).

Pincus et al. (1996) raised concerns with the potential biasing influence of somatic symptoms of RA on HADS items. Although evidence for item bias was observed for item D8 *"I feel slowed down"* as a function of disease activity and for item D14 *"I can enjoy a good book or radio or TV programme"* by gender the impact of this bias was found to have little effect on the estimated association with clinical and demographic factors.

Caution must be taken when attempting to separate out the influence of somatic symptoms on the measurement of psychological distress. The experience of somatic symptoms due to both physical and psychological influences are perhaps inextricably linked. Attempts to remove the influence of somatic symptoms from the assessment of psychological distress may result in excluding a central component of distress—that is to say 'throwing the baby out with the bathwater' (C. A. Smith, Wallston, & Dwyer, 1995, p.64). For example, the DAPOS (Pincus et al., 2004) used in Chapter 8 was designed as a measure of distress that excluded symptoms related to pain. However, this was perhaps done with too much zeal since the resulting estimates of distress and pain observed in the chapter were lower than expected leading to concern that an important component of the strong psychosomatic impact of RA was being missed by the measure.

It is perhaps more appropriate to focus attention on tools that allow for the discrimination of the different features of psychological distress. For example, in a study of the factor structure of the BDI-II in patients with renal disease Chilcot et al. (2011, see Appendix A) it was shown that it is possible

to separate out the cognitive and somatic symptoms of depression from a general distress factor. This method has the advantage of retaining more information while also allowing for the examination of the influences of separate features of distress on future disease outcomes, such as mortality (Roest et al., 2011).

9.2.2 Changes in psychological well-being during the RA disease course

With respect to the first objective. The pooled analysis of changes in distress in early RA samples reported by published studies suggested a decline in distress early in the course of the disease (see section 3.3). The findings from Chapter 6 supported these findings. At the group level distress did reduce over the first few years after disease onset and remained stable thereafter. Specifically, latent curve modelling (LCM) indicated that levels of distress reduced during the early course of the disease, remaining stable after around 2-years. Further analysis examining the heterogeneity in changes in distress over time, using a grwoth mixture modelling approach (GMM), revealed four distinct distress trajectories: resilient, chronic distress, delayed distress and recovered. Interestingly, changes in distress were related to self-reported somatic symptoms but not serological markers of disease activity. This was the first study to apply this technique in an RA cohort, and complimented recent studies in cardiovascular disease and breast cancer (Helgeson et al., 2004; Lam et al., 2009; K. I. Kaptein et al., 2006). This supports the generalisability of the results to other rheumatological conditions and to chronic physical illnesses in general (Stanton et al., 2007).

These findings support the assertion of Bonanno (2005), that greater changes are expected early on in the disease course. This is commensurate with the view that chronic physical illnesses can be defined as a stressful life-event that is characterised by recurrent stressful situations associated with the symptoms of the condition (De Ridder et al., 1998; Moos & Schaeffer, 1984; Zautra, 1996).

It is presumed that the changes in psychological distress observed reflect two processes. Firstly, that individuals' psychological adjustment to living with a chronic physical illness and the day to day management of their symptoms (Stanton et al., 2007); and secondly, the improved control of symptoms as a direct result of reduced disease activity through the use of disease modifying therapy. No direct causal inferences can be made with regard to these two processes based on the findings reported in this dissertation. However, there was clear evidence that distress was strongly related to the experience of somatic symptoms, including pain and functional limitation, but not to physiological markers of inflammation (ESR & CRP) or the physicians count of the number of swollen joints (Section 6.3.4). This suggests that psychological factors, such as illness perceptions, play an important mediating role. In addition, the

different patterns of change exhibited by the four groups derived from the GMM analysis were related to changes in somatic symptoms, which supports the second postulation since disease modifying therapy was typically initiated between the baseline and 1-year assessments.

The methods used in Chapter 6 assumes that changes in distress follow a smooth trajectory. This conflicts with the understanding that RA is a condition with a flaring-remitting course. As a result the residuals from the distress trajectories reflect not only random variation in levels of distress, but also systematic variation in distress as a result of disease flares. This was supported by the improved fit of models allowing correlated disturbances across time points. The issues of systematic variation from the trajectories was addressed more directly in Chapter 7.

9.2.3 Association between psychological distress and somatic symptoms

Chapter 7 extended the findings of the preceding chapter to consider whether changes in distress were related to changes in physical well-being. Analysis, using autoregressive latent trajectory (ALT) models to jointly model changes in physical function and pain with changes in psychological distress revealed strong cross-sectional and longitudinal associations. It would appear that changes in psychological distress are largely related to the deterioration in function associated with the progressive nature of the condition. To my knowledge this is the first study to employ this type of strategy to examine the link between distress and somatic symptoms in any chronic physical illness.

These findings extend those of previous studies using autoregressive models by showing the importance of considering the underlying trajectories of distress, pain and function that may be related to disease course. Previous research reported only relatively weak longitudinal relations between distress and somatic symptoms (G. K. Brown, 1990; Smedstad et al., 1997), despite the expected association (Escalante & del Rincon, 2002; Katon, 2003; Leventhal et al., 1984). Correlations between changes in distress with changes in symptoms of pain and functional limitation were high (Section 7.3.3). Thus, it would appear that a trait rather than state approach that takes account of the underlying progression of the disease is important.

Expanding on this last point it is important to remember that, as well as accounting for the underlying trajectory of disease progression ALT models allow modelling of the causal relations between the residuals of the latent trajectories (Bollen & Curran, 2004). This enables the model to capture the fluctuations in somatic symptoms and thus distress due to disease flares. Strong cross-sectional links between the residuals to the trajectory were observed, as would be expected, however cross-lagged causal effects between distress with pain and function were not. This is perhaps not surprising since observations were

at yearly intervals. The application of this method to studies using prospective daily diary methods may be useful (Strand et al., 2006).

9.2.4 Impact of illness cognitions and coping on psychological well-being

The fourth empirical chapter presented a study of the role of illness related cognitions and coping in changes in psychological and physical well-being over time. Data were from a smaller sample of 227 individuals with RA attending outpatient clinics at six hospitals in Hertfordshire, and were collected prospectively over 6-months. Coping was not found to be related to illness perceptions or psychological or physical well-being. However, analysis revealed two groupings of patients with similar patterns of illness related cognitions—that is closer to the concept of an "illness representation"—that were labelled *adapters* and *non-adapters* in line with previous research (Hobro et al., 2004). The individual illness perceptions of identity (the symptoms attributed to the condition) and consequences (the perceived seriousness of the condition) were related to changes in distress, whereas coherence (the reported level of understanding of the condition) was related to changes in positive well-being. No moderating factors were observed.

Theoretically illness perceptions are mediators in the pathway from the stressors that arise due to the impairments and limitations caused by condition to the psychological well-being. To a certain extent this was supported by the data although mediation was not explicitly considered in the models.

This third objective was only partially met by the findings of the thesis. This was due to the limitations of the study presented in Chapter 8 and also more widely to the robustness of the theory underpinning the impact of illness cognitions and coping on psychological well-being. The dynamic process whereby psychosocial factors impact on psychological well-being was not adequately captured by the longitudinal study which only included two time-points and involved patients with wide variation in disease duration. Although a third time point was collected for those with recent RA onset the numbers were too few for any sensible analysis. As was previously stated the original aims was to incorporate the assessments into the data collected by the Early RA Network. Had this been successful the information gleaned may have been useful in driving forward understanding in this area. Nevertheless the findings of this thesis have provided some useful information regarding the role of illness perceptions, particularly their clustering in certain groups. With respect to coping, I will again cite the recent review of coping in RA Vriezekolk et al. (2011, .6): the "flexible use of a variety of coping strategies across situations that may be beneficial for adjustment to a chronic disease, perhaps especially in RA with its fluctuating and often unpredictable disease course".

9.3 Strengths and limitations

The extent to which the studies presented in this dissertation meet the overall aims and objectives has been discussed. It is now important to note some of the main strengths and limitations of these studies. The main strength of this study is the use of sophisticated analytical framework applied to a large prospective observational study of individuals with RA recruited at the time of diagnosis (ERAS). This has enabled research undertaken within these studies to make a major contribution to the large body of research concerning this topic that should drive forward research in this field. However, despite the impact of the findings presented in this dissertation on research in this area it is important to note some of the limitations with regard to observational studies in general, and specifically the ERAS cohort. Furthermore, limitations of the latent variable modelling approach for the analysis of longitudinal data are discussed.

9.3.1 Strengths and limitations of observational studies

Causal conclusions may be most strongly drawn from experimental studies (Shadish, Cook, & Campbell, 2002). With observational studies, the likelihood of confounding effects due to unmeasured variables is high. Nevertheless, the Oxford Centre for Evidence Based Medicine still ranks the evidence from prospective observational studies higher than those from randomised controlled trials in terms of prognostic models. In the presence of natural experiments within observation studies, sophisticated matching and instrumentation techniques may be employed to statistically control for the effects of residual confounding (Morgan & Winship, 2007). In this study no such statistical matching methods were employed. As such causal conclusions can only be tentatively extrapolated from the findings reported here. The danger of drawing causal conclusions from observational studies alone has been highlighted in the research concerning the the effects of hormone replacement therapy on coronary heart disease risk (Hernán et al., 2008).

As was highlighted in the discussion of chapter 7, the causal association between psychological and physical well-being is complex. The relationship is almost certainly bidirectional, with psychological status as likely to influence somatic symptoms as the reverse (Katon, 2003). In RA we can be fairly confident that the introduction of disease modifying treatment that reduces somatic symptoms early in the course of the disease accounts for a large portion of the change early in psychological distress at that time.[1] The use of sophisticated matching techniques to more confidently make causal assertions are

[1]Findings from experimental studies support this bidirectional association. For example, psychological treatments have been found to impact on somatic symptoms (Zautra et al., 2007; Dixon et al., 2007) and disease-modifying therapies have

moot as the results would neither confirm nor falsify the expected bidirectional relationship—since it is assumed to be bidirectional. They would however indicate whether the strength of the direction was larger in one way or the other, highlighting where intervention would be mot likely to have an effect on both.

A further limitation of virtually all observational studies, particularly those with long-follow up is missing data. Although missing data was common in the ERAS study, particularly for the HADS, the nature of follow up in ERAS were data was collected as part of annual review which formed part of the standard treatment meant that loss to follow-up was small. The use of full-information maximum likelihood and multiple imputation allowed for all available data to be included in the data under the MAR assumption. NMAR sensitivity analysis in Chapter 6 did not reveal the dropout mechanism to be non-ignorable providing support for the validity of the results in this dissertation.

9.3.1.1 Strengths and limitations of ERAS

The strength of the ERAS cohort include the large sample size recruited from multiple centres, with long and frequent follow-up in a naturalistic setting and low levels of dropout means that confidence in the ERAS data and its external validity is high—at least to other RA patients in the UK. Longitudinal analyses of this traditional 'pre-biologic' cohort provide valuable information on natural disease course, outcomes and prognostic factors in RA. There are however a number of important limitations of the ERAS cohort that should be noted.

There is a possibility of bias in this type of hospital-based observational study due to the failure to include patients who go into remission early and therefore do not attend hospital (i.e. left censoring). As such the ERAS cohort must be seen as a cohort of individuals with RA that is more established and severe than individuals with more generalised forms of inflammatory arthritis recruited to primary-care or community based studies. These studies, most notably the Norfolk Arthritis Register (Symmons et al., 1994), includes a large number of individuals with a milder undifferentiated condition, many of whom progress to a diagnosis of RA. However, there a number of logistical limitations of such studies. The main limitation is the difficulty with which diagnosis of RA can be confirmed in population or primary care based cohorts.

It is important to remember that the problem of confirming diagnosis is present in ERAS as well, although to a lesser extent. Nevertheless, all individuals do undoubtedly have some form of inflammatory arthritis and since the focus is on the relationship between psychological and physical well-being

been shown to impact of psychological well-being (NICE, 2009b).

that relates to the symptoms experienced by all with such conditions, the effect on the overall findings is likely to be small.

A further limitation of primary care based studies, and a strength of ERAS, is considerable attention devoted to ensuring the comparability of assessments across centres. Ensuring that assessments are performed uniformly across centres reduces the impact of centre effects on model estimates. In studies with larger numbers of centres this becomes more difficult, although to some extent the larger number of centres offsets the bias that is introduced. In this dissertation little attention was paid to the nested nature of the data within different centres—both the ERAS data and the cohort in Chapter 8. This is particularly an issue for the analyses in Chapters 6 and 7 since only participants from three centres were used and over half attended the Winchester centre. However, the characteristics of patients included in the analysed sample were on the whole very similar to those in the full ERAS sample.

Despite these limitations, the ERAS cohort along with other early RA cohorts have provided much useful information with regard to the natural but treated history of the disease (Young et al., 2011; Young, 2009). Comparisons across cohorts will allow for the validation of findings, but also the assessment of age, period and cohort effects.

9.3.2 Strengths and limitations of the latent variable modeling approach

Chapter 4 provided an overview of the latent variable modelling framework used in this dissertation, with particular reference to the application of latent variable modelling approaches to the analysis of longitudinal data. There has been considerable debate concerning the utility of latent variable modelling, for cross-sectional as well as longitudinal data. The main criticism has been the usefulness of the structural model, the path analytic component of a latent variable model, as a mathematical tool for drawing causal conclusions from observational data, under certain theoretical assumptions (c.f. Freedman, 1987; Pearl, 2009). This is an important issue with latent variable modelling in general, however the main concern here is not of the causal interpretation of the models but rather the usefulness of the longitudinal models applied to describe longitudinal processes.

Some specific concerns have been raised regarding the application of latent variable modelling to describe longitudinal trajectories. Specifically, Mulaik (2009, p.281) states that latent variable models attempt to model longitudinal data 'in ways where the mathematics seems to outrun the science of what is represented by these models. To what extent do these models correspond to reality?' The issue is that as increasingly advanced statistical methods are developed, and their application becomes easier through wider access to software, it becomes increasingly easy to generate models that have little

theoretical grounding and resultantly provide empirical estimates that are of no real value—sometimes referred to as the 'rubbish-in rubbish-out' principle. Voelkle (2008) provides a cautionary example of this principle in the context of ALT models. In a simulation study it was shown that misspecification of the trajectory component of the model resulted in extreme bias to the estimates of the autoregressive part of the model. To avoid such a problem great care was taken in Chapter 7 to ensure that models were correctly specified.

Further criticism of the latent variable modelling approach, this time in relation to GMM, has been provided by Bauer and Curran (2003). They suggest that the presence of non-normal data may result in the multiple trajectory classes appearing optimal even when only one group exists in the population. Bauer (2007) went on to describe several other problems with GMM that result from its apparent sensitivity to various assumptions that are made. I would agree with the several rejoinders written in respect to the first paper (Cudeck & Henly, 2003; B. Muthén, 2003; Rindskopf, 2003), which are best summarised by Cudeck and Henly (2003, p.378): "A realistic perspective is that although a healthy skepticism to complex statistical results is appropriate, there are no true models to discover ... The purpose of a mathematical model is to summarize data, to formalize the dynamics of a behavioral process, and to make predictions. All of this is scientifically valuable and can be accomplished with a carefully developed model, even though the model is false".

There is always the concern that the complexity of the statistical techniques applied, and a failure to understand their assumptions, may result in the development of models with no real scientific value. The diligent researcher must ensure the validity of their findings not simply by confirming that findings hold across different situations (e.g. patient groups, research designs etc.) but also that models generated provide realistic results from which the findings might generalise to the real world. As has been previously noted, the novel findings presented in this dissertation should be interpreted in a tentative manner since future research is needed to confirm them.

Also in relation to model complexity, the principle of Occam's razor *lex parsimoniae* suggests selecting the the simplest model when a number of models fit the data equally well (i.e. the one that makes the least assumptions). Information criterion such as the AIC and BIC penalise for model complexity and so it is this principle that they embrace—and to some extent so does the RMSEA (Mulaik, 2009). As long as, theoretically grounded, competing models are compared, with assumptions that are made explicit it should not be too difficult to examine there predictive ability. Furthermore, simpler models are more generalisable than more complex ones, and thus more easily falsifiable (Popper, 2002).

In conclusion, the potential risks of misinterpreting the findings of complex latent variable mod-

elling approaches to longitudinal data are clearly outweighed by the potential benefits of extending the understanding of the complex processes they seek to describe. As is always the case, it is essential to ensure that model estimates are reasonable and that sensitivity analysis is performed to ensure models developed are robust.

9.4 Clinical implications

From the perspective of the rheumatologist, who is usually the health professional with the ultimate responsibility for the clinical management of an individual with RA, the findings of this dissertation have some important implications. The strong association between psychological distress and the somatic symptoms of the condition is congruent with current guideline for treating to a low disease activity target (Kiely et al., 2009; Smolen et al., 2010). Achieving low disease activity is likely to have an indirect effect on psychological well-being and more generally quality of life. Furthermore, since psychological well-being is more likely to be amenable to change early in the course of the disease it is individuals in this group that should be of most concern to health professionals. Again this is in-line with current treatment guidelines in RA that emphasise the importance of timely treatment (NICE, 2009b).

Treatment with effective but expensive biologic therapies is reserved for those with established active disease that have failed to respond adequately to conventional disease modifying drugs (NICE, 2009b). Treatment decision are largely based on disease activity, as indicated by the DAS or DAS28, and it is therefore important to understand the relationship between DAS and inflammatory disease activity, as well as potential effects of confounding factors. DAS is based on a physiological marker of inflammation (either ESR or CRP); physician assessed tenderness and swelling of joints mainly of the hands, wrists and feet; and a patient reported global disease activity VAS. It has, however, been noted that the largest contribution to the overall score is based on the tender joint count a marker of pain (Fransen et al., 2004). Although joint tenderness and self-reported disease activity increase alongside inflammatory disease activity, they may also be increased by changes in pain processing such as central sensitisation, or by comorbidities. Patients without RA who have fibromyalgia or central sensitisation report high disease activity and joint tenderness, generating high DAS28 scores despite low swollen joint count and acute phase response, scores that may be comparable to those of people with active RA (Leeb, Andel, Sautner, Nothnagl, & Rintelen, 2004). Evidence of central sensitisation and joint inflammation may coincide, thereby confounding interpretation of DAS28 in people with RA (Leffler, Kosek, Lerndal, Nordmark, & Hansson, 2002). People with concurrent RA and fibromyalgia report increased pain (Dhir, Lawrence,

Aggarwal, & Misra, 2009) and show higher DAS28 scores (Ranzolin et al., 2009) than those with RA alone, perhaps indicating that central sensitisation or painful co-morbidity influences the scoring.

Assessment of psychological distress in routinely during annual review would provide greater information with regard to the factors modulating pain. For those with persistently high levels of distress who report high disease activity and joint tenderness, but low swollen joint count and acute phase response, other measures may be considered prior to, or instead of, disease modifying and biologic therapies. These include psychological interventions as well as pain control and remedial therapies. Such measures could reduce problems associated with drug safety and DMARD monitoring, and for biologics, costs. Intervention targeted at psychological well-being may also be effective at improving somatic symptoms, which are the main concern for the patient (Heiberg & Kvien, 2002; Hewlett et al., 2005).

Psychosocial interventions—including cognitive-behavioural, patient education and self-management—have a twofold role. Firstly, interventions that improve psychological functioning are likely to indirectly improve somatic symptoms and physical functioning (Katon, 2003; Leventhal et al., 1992). Secondly, psychosocial interventions that, for example, improve a patients' understanding of their condition and for greater self-management may reduce the need for medication, and if not, is likely to improve acceptability of and adherence to treatment regimes, thereby indirectly improving disease activity and thus somatic symptoms (Petrie et al., 1996; DiMatteo et al., 2000). Furthermore, in RA cognitive behavioural interventions have been indicated as having physiological effects, reducing levels of cortisol or IL-6 (Zautra et al., 2008; de Brouwer, 2011), and meta-analyses have shown that combined multimodal cognitive with exercise therapy may be more effective than either alone (Dixon et al., 2007).

A key finding of Chapter 6 was that the majority of individuals were resilient to the effects of their RA, experiencing little or no disruption in psychological well-being following disease onset. A smaller number experienced long-term adjustment problems. It may be possible to select patients in need of psychosocial interventions in addition to standard disease-modifying treatments. Examples include those with persistently high levels of distress, especially those where the response following initiation of disease-modifying therapy is limited. The increased use of psychological measures, such as the HADS, that are not currently used routinely may help to tailor patient care. Broader measures of health related quality of life, such as the SF36, may be preferable since they incorporate assessments of psychological distress, physical function, fatigue and pain—the psychological and physical dimensions most affected by RA (Hewlett et al., 2005)—and other factors such as illness cognitions and social support. Evers, Kraaimaat, Riel, and Jong (2002) provide an example of an effective tailored treatment approach. Patients received cognitive-behavioural therapy focusing on fatigue, negative mood, social relationships, or

pain and functional disability depending on individual psychosocial risk profiles, based on assessments of psychological distress, illness cognitions of helplessness and acceptance, passive coping and social functioning.

Increasing availability of biologic therapies is likely to lead to increasing rates of remission in RA and thus reducing psychological distress associated with the pain, disability and deformity caused by the disease. However, improving access to psychological therapies remains a concern to health providers (National Audit Office, 2009; NICE, 2009a). An evidence-based approach suggests that failing to incorporate assessment and assistance with psychological needs of the patient is likely to reduce the effectiveness of medicines that have proved so efficacious in clinical trials.

9.5 Directions for future research

The most salient finding of the dissertation for future research is the importance of using large cohorts of patients recruited as close to symptom onset as possible to examine how RA progresses with time. Although several large RA inception cohorts exist few collect even basic information of psychological well-being (Young, 2009). At the very least assessment of psychological distress, or more broadly health related quality of life should be undertaken. Although, ideally other psychosocial factors should also be recorded, including social support and illness perceptions.

The findings of much of the current literature concerning psychosocial factors is limited by the evidence being based on small samples, generally with wide variation in disease duration. Furthermore, much of the research into psychosocial factor in RA has considered risk factors for poor long-term physical and psychological well-being. Research into resilience factors, that is factors associated with successful adaption, is more limited. The resilience approach focuses on identifying characteristics of the person that permit successful adaptation. Since such a large proportion of those with RA do not experience long-term adjustment problems, greater focus on resilience factors is clearly needed. Research in other areas has found factors such as self-esteem, self-efficacy, social support, extroversion, and a sense of purpose (Stanton et al., 2007; Evers, Zautra, & K., 2011). Furthermore, it is also important that risk and resilience factors are considered in combination rather than in isolation, as has previously been typical, since both have separate but related influences on adaptive capacity (Evers et al., 2011).

As well as clinical cohorts there is an increasing need to consider RA patients in the wider context of chronic physical illness in general. As larger population studies are initiated and linkage to hospital records becomes more widely available it becomes more feasible to perform nested case-control studies

to compare groups of individuals with different conditions. This will allow for the assessment of whether similar distress trajectories exist in these studies and, furthermore, will allow for the examination of the influence of earlier psychological well-being on the development and progression of chronic physical illnesses. Birth cohorts have shown the importance of life-course influences on later health (Barker, Osmond, Golding, Kuh, & Wadsworth, 1989; Kuh & Ben-Shlomo, 2004). As such studies mature it becomes possible to examine such effects on specific diseases like RA.

9.6 Final conclusions

RA is a chronic progressive condition associated with an insidious decline in function. The somatic symptoms of the condition, such as pain and fatigue, are associated with increased levels of psychological distress. Across the course of the disease psychological well-being is relatively stable for the population. However, it does appear to be increased early in the course of the disease, prior to the initiation of disease modifying therapy. Early identification and treatment of RA is imperative not only to slow or even halt the progression of the disease but also so that the individual may maintain their health related quality of life. This early treatment is currently focused on pharmaceutical interventions. However, the further inclusion of a psychosomatic approach based on the biopsychosocial model (Engel, 1980) involving the skills of a wide range of health professional, such as nurses, physiotherapists, occupational therapists and psychologists is likely to improve outcomes for the patient.

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