MASTER THESIS

Psychology of Safety & Health

Rheumatoid Arthritis [RA]: More than an Inflammatory Disorder? A Systematic Review

by

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PREFACE

This master thesis is the final project for receiving the degree of Master of Science in Health and Safety Psychology at the University of Twente, Enschede (NL).

Writing this report started with some delay according to my college course because I experienced troubles finding a research topic which was of really interest for me. With regard to a good friend, who was shortly before starting my thesis diagnosed with a rheumatic disease, my interest was sparked in this field of research. In this connection I would like to thank him for inspiring me and sending him my best wishes for getting well soon.

The collaboration with my two supervisors ran comfortable and in a familiar ambience. Therefore, I would like to thank them and for their adjuvant advice, their support, encouragement and patience regarding postponing of appointments.

My warmest acknowledgements direct to my parents and boyfriend for always supporting me and having a sympathetic ear. You have always stuck by me and encouraged me by being proud of me regardless of what I've planned and done.

My special thanks also go to Gerti, not only as a fellow student but also as a good friend, being side by side on good and bad days during the whole college which we have conducted together.

Finally, I declare in lieu of oath, that I wrote this thesis and performed the associated research myself, only using literature cited in this volume.

Enschede, April 2010

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LIST OF ABBREVIATIONS

RA	Rheumatoid Arthritis
CFS	Chronic Fatigue Syndrome
HADS	Hospital Anxiety & Depression Scale
CES-D	Centre for Epidemiological Studies Depression Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
FSS	Fatigue Severity Scale
VAS	Visual Analog Scale
Psy+	Sample group with current/lifetime affective disorder
Psy-	Sample group without current/lifetime affective disorder
AD	Affective Disorder
MD	Major Depression
GAD	General Anxiety Disorder
AIMS (2)	Arthritis Impact Measurement Scale
DMARD	Disease Modifying Anti-rheumatic Drugs
TPB	Theory of Planned Behavior
PBC	Perceived Behavior Control
GHQ	General Health Questionnaire

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Rheumatoid Arthritis (RA): More than an Inflammatory Disorder? – A Systematic Review

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ABSTRACT

Rheumatoid arthritis is a chronic inflammatory disorder which affects the joints by destroying body tissues. Thereby, pain and fatigue are very common and often reported symptoms. But rheumatoid arthritis is not only connected to devastating bodily ailment but also to restrictive mental problems. The aim of this study was to analyze the progress of pain and fatigue in rheumatoid arthritis and the overall relation with problematic moods (depression/anxiety), psychosocial resources (social support, self-efficacy) and burdens (social distress, problematic social support). The design which is utilized is a Cochrane Systematic Review. A broad search of literature which report on the relations in demand is applied in four electronic databases. The methodological quality of the included studies was assessed and data extracted, based on pain and fatigue as primary outcomes, depression and anxiety as secondary outcomes and social burdens/resources were extracted as third outcomes. The results of 7 adequate articles for fatigue, 13 for fatigue and pain and 23 for pain summarized partly opposing results. Through the different studies, pain and fatigue seemed to fluctuate in different directions over a period of 10 years. Most of the studies show considerable relations of pain/fatigue with anxiety and depression. Partly, that mood influenced pain/fatigue, partly that pain/fatigue led to mood problems. Some papers failed to confirm any relation. The psychosocial resources/burdens were all related to pain/fatigue: self-efficacy and the amount of social support negatively and social distress and problematic social support positively. Further, social distress mediated positively and self-efficacy mediated negatively the relation between problematic moods and pain/fatigue. These data suggest on the one hand a need for further high qualitative research for describing the progress of pain and fatigue as well as the causality between pain, fatigue, mood problems and psychosocial resources/burdens on the field of rheumatoid arthritis but on the other hand also that psychological aspects, as tutoring in self-management and support in mood problems, should play a greater role in treating RA.

Keywords: Systematic review, rheumatoid arthritis, pain, fatigue, depression, anxiety, social stress, self-efficacy, social support, problematic social support

Reumatoïde Artritis (RA): Meer dan een Onsteking? – een Systematische Review

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SAMENVATTING

Reumatoïde artritis is een chronische ontstekingsziekte die de gewrichten aantast. Maar, pijn en vermoeidheid zijn ook veel vermelde symptomen bij reumatoïde artritis, die niet alleen geassocieerd zijn met ernstige lichamelijke klachten maar ook met enorme mentale problemen. Het doel van deze studie was het analyseren van het verloop van pijn en vermoeidheid bij reumatoïde artritis en de relatie met problematische stemmingen (depressie/anst), psychosociale resources (sociale steun, zelfvertrouwen) en beperkingen (sociale stress, problematische sociale steun). Het gebruikte design voor deze studie is een systematische review volgens Cochrane. Een breed literatuuronderzoek van de desbetreffende relaties werd uitgevoerd in vier elektronische databases. De methodologische kwaliteit van de gevonden artikelen werd gewaardeerd en de data geëxtraheerd baserend op pijn en vermoeidheid als primaire, depressie en angst als secundaire uitkomstmaat en sociale resources/beperkingen als derde uitkomstmaat. De resultaten van 7 geschikte artikelen over vermoeidheid, 13 over pijn en vermoeidheid en 23 over pijn, leverden gedeeltelijk divergente uitkomstmaten op. In de verschillende artikelen leken pijn en vermoeidheid in verschillende directies te fluctueren over een tijdsbestek tot 10 jaren. De meeste studies lieten aanzienlijke relaties tussen pijn/vermoeidheid en angst en depressie zien; voor een deel dat stemmingen pijn/vermoeidheid kunnen bepalen, voor een ander deel dat pijn/vermoeidheid invloed op stemmingsproblemen hebben. Slechts enkele artikelen konden een dergelijke relatie niet bevestigen. De psychosociale resources/beperkingen waren allen gerelateerd aan pijn/vermoeidheid: zelfvertrouwen en de hoeveelheid aan sociale steun negatief en sociale stress en problematische sociale steun positief. Bovendien was sociale stress een positieve mediator op de relatie tussen problematische stemmingen en pijn/vermoeidheid en zelfvertrouwen een negatieve. Deze data wijzen aan de ene kant op een behoefte aan verder kwalitatief hoogwaardige onderzoeken op het gebied van reumatoïde artritis voor het bepalen van de voortgang van pijn en vermoeidheid maar ook voor causaliteit tussen pijn, vermoeidheid, stemmingsproblemen en psychosociale resources/beperkingen. Aan de andere kant werd duidelijk dat psychologische aspecten, zoals training in zelf-management en steun bij stemmingsproblemen een grotere rol in de behandeling van reumatoïde artitis zouden moeten innemen.

Trefwoorden: Systematische review, reumatoïde artritis, pijn, vermoedheid, depressie, angst, sociale stress, zelfvertrouwen, sociale steun, problematische sociale steun

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder which affects the joints and is associated with swelling, stiffness and pain. Advanced disease stages can lead to substantial loss of functioning and mobility. RA is an autoimmune disease, whereby the body's immune system attacks its own tissues. The triggers for the onset of RA are only speculated, but it is expected that a genetic liability to the disorder, several viruses and bacteria (e.g. Epstein-Barr-Virus and Mycobacterium tuberculosis; Miehle, et.al, 2000), disruption of the immunological tolerance as well as the psychological condition by further weakening the immune system of people concerned could play a major role (Breitenberger, 2008). As the causes for RA are still unknown, cures have not been discovered yet as well. All treatments and therapies which are applied so far are intended largely to reduce symptoms and delay the progress of the disease (Newman & Fitzpatrick, 1995). The onset of RA arises usually between the age of 30 and 50, but may also occur at any other age. Women are three times more affected by it than men and people who are less educated and with fewer socioeconomic resources experience more problems emerging of RA. About 1% of the whole world population is attacked by rheumatoid arthritis (Majithia & Geraci, 2007) whereof about 790,000 people in the Netherlands are affected (Reumafonds, 2009).

The Progression of Rheumatoid Arthritis

Rheumatoid arthritis begins with the inflammation of the synovial membrane of the joints, especially in the small ones of the fingers and feet and is mostly bilateral. The inflammatory cells, if in inappropriate large amount, destroy body tissue. The synovial fluid accumulates and the joints swell in time and thicken into a pannus (abnormal tissue). Over time the pannus erodes the joint's cartilage and, possibly, scar tissue will be formed, connecting bone ends. Later this scar tissue can ossify wherewith the joints get immobilized and deformed. The surrounding structures of the inflammatory joints, as tendon sheaths, bursas and origins of muscles are often involved supporting joint deformations as well. These strains are generally irreversible (Marieb, et.al, 2006). In seldom cases the vertebral column, vasculatures and several organs as skin, heart and lungs are also inflamed by RA. The disease gets diagnosed by several methods: ultrasound and MRI (magnetic resonance imagery)

which detects inflammation marks in the joints and the surrounding structures; radiograph and MRI which detects meanderings in cartilage and bones. The progress of RA differs clearly from person to person. It goes from an interminable mild devolution, over consecutive periods of active illness and phases free of complaints, to a very progressive illness, which rapidly grand joint damages and loss of functioning. Although the disease pattern is very individual, over time all people concerned have restricting joint movement and extreme pain in common. About 90% of the people with RA suffer from irreparable joint damages and loss of function. However, only pain can be decreased and the progress of joint damages and loss of function narrowed down. This is achieved by several treatments as drugs, physiotherapy, occupational therapy and adjuvants as orthoses/prostheses (Bijlsma, et.al, 2004).

RA affects not only the body but also impacts the mental condition. Therewith, people concerned fend mostly for themselves because physicians still rarely go into mental discomfort, such as great complaints of fatigue, loss of appetite and energy, stress and social isolation (Belza et.al, 1993; Hewlett, et.al, 2005). Through these multifaceted non-physical symptoms related to rheumatoid arthritis, the disease impairs all areas of life and thus the quality of life: The destruction of joints leads to pain and immobilizing which further reduces several activities as walking, playing around with children and personal hygiene to a minimum. Moreover, the related pain leads to frustration and feelings of losing control of the own situation. Also, fatigue occurs and people aggrieved draw back more and more which can consequently result in restrictions in social lives. These restrictions can assume broad proportions in people's life. It can impair the leisure activities with friends, occupation as the people concerned cannot further fulfill their common workload and the ability to comply social roles which also form restrictions for other family members (Stenström, et.al, 1992; Hewlett, et.al, 2005; Kuhlow, 2007).

Pain and fatigue are the two most common and most frequent reported symptoms in rheumatoid arthritis and are strongly associated with people's allover quality of life (Stone et.al, 1997). Consecutively, these components get enlarged in separate paragraphs.

Pain in Rheumatoid Arthritis

Pain is the first main factor in this review and is an ailment with serious impact on people's lives. In rheumatoid arthritis, the pain enters aggrieved people's lives as constant companion. In rest periods, the joints are swollen, sensitive to pressure and warm and mostly underlie the so-called morning stiffness. The latter complicates people's movement abilities, especially in the morning. Once the joint structures are partly damaged, the pain also appears during exercising and becomes chronic. This sensation constrains people's activities painfully and the affected joints get conserved by avoiding everyday activities as far as possible. But a relieving posture could in turn lead to disease-unrelated hardening of the joints or to other joints being overly strained, resulting in perceiving more pain. Although pain severity was perceived very individually in several studies, it is generally greater experienced by women than by men (differences up to 72%; Cooper & Dennison, 1998; Affleck, 1999). Through the permanent presence of pain, it can become the central focus of people with RA. Therefore, the available efforts get predominantly addressed to pain relief and pain coping rather than to family, friends, occupation, health and/or personal encouragement. Thus, the personal and social functioning gets impaired (McCracken & Yang, 2006). Patients end in a vicious circle wherein they invest in methods of decreasing pain for a better quality of life which simultaneously leads to accretive social isolation and hence, heightened attention on pain. However, supportive relationships could be especially beneficial for the experience of symptoms, whereby not all interactions with close social network members are helpful; non-supportive interactions, as a sort help which is not intended by the recipient could further stress people concerned (Revenson, 1991). This would worsen health condition and end ultimately in a more miserable quality of life and severe pain sensation (Revenson, 1991). Psychosocial factors which also play a role in RA as depression and stress can hardly be separated from pain because of similar characteristics (i.e. worse sleep, sparse activities; Covic, Adamson & Hough, 2000). Thus, comorbidity as well as a condition of augmented psychological discomfort according to RA can be on hand in people concerned. In case of comorbidity, if pain is the central focus in the life of people with RA other things can lose in value and could further lead to a depression (Skevington, 1986). Also states of anxiety are often associated with RA as people concerned feel overstrained with the constrictions accompanying the disease, i.e. the extreme chronic pain,

the emergence of movement limitations and uncertainty over the further progress (Bradley, 1984 & Chandarana, 1987 in VanDyke, 2004). According to the relation between pain and mood, there are also gender differences. Men seem to evidence a greater "carry-over" effect of intensifying pain on negative moods (i.e. depression) than women who possibly utilize more pain coping strategies for emotional regulation (Affleck, 1999). Severity of pain is in case of RA mostly ascribed to the degree of inflammation, the progress of joint damages and deviations (Newman & Matzko, 2007) and although these symptoms could be improved by treatments wherewith also pain should temporarily relief, it could nevertheless be present to a high level. This could be attributed to an automating and high sensibility of nerve impulses. If "pain neurons" (nociceptors) fire the same pain impulse over a period of time to the brain, its metabolism can change and the warning signal gets assigned to the brain onward (Scholz & Woolf, 2007). In RA, additional inflammation mediators can be released, which deliver the inflammation reaction also to surrounding neural structures and, thus, increase the irritability of the nociceptors (Zimmermann, 2004). Through this hypersensitivity, the threshold for pain decreases and also makes innocuous and comfortable stimuli, as warmth and gently touching, painfully (Leffler et.al, 2002; Baenkler, et.al, 2007). Moreover fear of perceiving pain and certain cognitive factors could intensify pain sensations through elevating attention on it (Taal, 1993; Grossarth-Maticek, 1999), i.e. low self-efficacy over the own ability to bring up the needed effort for reducing pain. A set of studies could also detect further psychosocial factors being related to pain in RA: catastrophizing (Keefe, 1989), mental well-being (Kojima, 2009), social stress (Zautra & Parrish, 2007), anxiety and life-satisfaction (Treharne, 2007) and neuroticism (Affleck, 1992; Hamilton, 2005).

Fatigue in Rheumatoid Arthritis

Beside pain, chronic fatigue is the second main factor in this review. It is also a very life-impairing factor in rheumatoid arthritis (Silman, 2001). In several studies of RA, more than 80% of the samples told to experience fatigue to a certain degree (Belza, et.al, 1993; Wolfe, et.al, 1996; Pollard, et.al, 2006) and interferes with physical and mental processes (Piper, 1989). The form of fatigue which is the main topic in the current thesis refers exclusively to

fatigue of rheumatoid arthritis. Before amplifying it, an established other form of fatigue gets described to prevent that fatigue in RA from getting mixed up with it: the chronic fatigue syndrome (CFS).

CFS is a self-contained chronic illness, characterized by paralyzing exhaustion without any advance after resting, plus a specific combination of further symptoms as headache, sore throat and worse sleep, pain in joints and muscles and problems with concentrating as well as a sustained worsening of fatigue after struggle (Butcher, 2007). But the physical symptoms cannot be explained by acute illnesses of the concerned structures. It is assumed that CFS is a heterogeneous disorder, possibly caused by already cured injuries and/or inflammations whereby the immune system left chronically active and broaden to the nervous system (Englebienne & Meirleir, 2002).

Fatigue in RA is also described as a sustained form of exhaustion with no enhancement after sleeping but does not fall in the same category as CFS. Particularly different, are the physical constraints conducting fatigue in RA, as worse sleep and pain in joints and muscles can be related to the inflammations caused by the underlying disease. Several qualitative studies (Hewlett, et.al, 2005; Repping-Wuts, et.al, 2007) have asked people with RA to evaluate multiple causes for fatigue in RA. Partially, it is believed that fatigue results from the inflammatory cells in the body and thus from the excessive activity of the immune system. Others credit fatigue with the drugs they have to take or with disturbed and non-restorative sleep. Another factor which people concerned ascribe to fatigue is the increasing energy effort expended to perform normal despite injured joints. While there is only little known about the general etiology of fatigue and a unified international definition also lacks (Swain, 2000), research on predicting factors for fatigue in RA found that physical as well as psychosocial factors are dispose for the degree of fatigue. These factors are for instance pain intensity (Belza, et.al, 1993; Huyser et.al, 1998), degree of physical disability (Mancuso, 2006), worse sleep quality (Belza, et.al, 1993; Wolfe, et.al, 1996), general health (Repping-Wuts, et.al, 2007), the presence of depressive (Fifield, et.al, 1998; Pollard, et.al, 2006; Huyser, et.al, 2007) and anxiety symptoms (Mancuso, et.al, 2006), the degree of self-efficacy (Riemsma, et.al, 2000; Treharne, et.al, 2008) and social support (Huyser, et.al, 2007). In addition to the latter, not only the *amount* of social relations is negatively related to RA, also the *character* of them has an effect on the illness progression.

Thus, good social support is particularly important for coping with symptoms as fatigue, pain and emotions in rheumatoid arthritis (Krol, et.al, 1993), whereby accretive social isolation and problematic social support worsen the experience of disease symptoms (Morrison & Bennet, 2006; Riemsma, et.al, 2000). In this connection it has to elaborate insistently that problematic social support, i.e. the provider's action (unasked advise) is well intended but not desired by the recipient (Mancuso, et al. 2006) and is not comparable to social stress, in which for instance someone who provides a great deal of social support (i.e. the partner) may also be a source of significant social stress (i.e. a serious illness). But social stress is also not implicitly inversely related to social support. It rather forms an additional psychosocial construct.

As individual as the possible *accounts* for fatigue, qualitative studies could also note that the *experience* of it differs from person to person (Nikolaus et.al, 2009). The emerging emotions, resulting consequences and the management of fatigue get variably experienced by different age-groups and gender. Some of the found differences could be related to the amount of daily roles that people concerned have to fulfil. Those people, especially women, with multiple daily roles, as parenting, housekeeping, occupation, etc. experience more fatigue because of striving for sufficient gratification of all roles and simultaneous exercising rest periods (Belza, et.al, 1993).

Studies about Pain and Fatigue in Rheumatoid Arthritis

There is still proportionally little agreement about nearly all topics according to RA; the character and progress of pain and fatigue in RA itself as well as their relations with problematic moods and several resources/burdens, as personal and network characteristics. Thus, many studies were targeted on clarifying these relations with partly still opposing results. For example, Fifield (2001) and Jump (2004) detected heightened fatigue reports in people with past episodes of affective disorders as depression and anxiety. Dickens (2002) found that there is no direct attribution between pain and affective problems. On the other hand, in a study of Smedstad (1996), RA symptoms were of great impact for psychiatric illnesses but mediated also between inflammation and stress. Similarly, Covic (2006) found that the degree of fatigue as well as pain can predict depression. Contrary to the results of

Covic (2006), Huyser (1998) could only confirm an interrelation between RA-fatigue and -pain and problematic moods. Zautra (2007) could detect that a past episode of depression could have the effect that pain at baseline was higher than in people without a depression history. Further in this study, social distress had a strengthening effect on this relation. Other studies wherein psychosocial factors had impact on the relation between RA symptomatic and mood problems were of Covic (2003) who detected that helplessness not only affect depression but also increases pain perception and mediate the relation between depression and pain and Chaney (2004) who found that internal attributions as helplessness enforce pain perception and depression. Also, Frantom (2006) could relate several psychosocial factors as stress and self-efficacy directly to pain.

Motivation for this Study

While the results of the studies according to the field of rheumatoid arthritis are discordant, several topics of the disease are nevertheless of great prominence to fully understand. The temporal nature of pain and fatigue in rheumatoid arthritis varies from person to person and is, thus, important to conceive because information about the variability and levels of pain and fatigue throughout the disease could be useful for a more precise characterization and understanding of it. Hence, subgroups of people with RA could be formed whereupon treatment needs could be matched more individually with decreasing the immense life impact through the symptoms. Furthermore, understanding the interrelation between RA symptoms and psychological mood problems (depression and anxiety) would be crucial because they seem to be the most common related mood problems in RA. Therefore, information about the strength of relation and causal directions could be utilized for shifting the treatment focus on substantial pathways. This could prevent people with RA experiencing unneeded worse conditions of the disease by itself and comorbidity. Appreciating the affective modality and effective strength of several psychosocial factors on pain and fatigue as well as their mediating effect on the relation between pain and fatigue and problematic moods would also compose a precious contribution in treating RA. Several confounders or covariates as stress, self-efficacy and social support are gently manageable through improving person's self-management. As combined with pharmaceuticals for the

biological markers of RA, disease conditions and the relation between them and psychological problems could be treated more effectively than only medical treatments of the main symptoms. Moreover, this combined therapy could evoke fewer side effects because of lower doses of drugs. A fully understanding of the disease could also provide room for research on developing new therapy models exactly catered to rheumatoid arthritis.

This Systematic Review

According to the great importance of conceiving the progress of pain and fatigue and the proportion of associations with subclinical mood problems and psychosocial resources/burdens, a systematic review of the literature has been performed. Specifically, this review aimed at clarifying the following questions: 1) How does the intensity of pain and fatigue change over the course of rheumatoid arthritis and when is it highest? 2) Are RA-pain and -fatigue associated with dysphoric mood as well as anxiety? 3) How are the effects of psychosocial resources/burden on pain and fatigue in RA? 4) Are there psychosocial resources/burdens which mediate the relation between the disease symptoms and problematic moods? For an overview of the questions, the relations in demand are illustrated in figure 1.

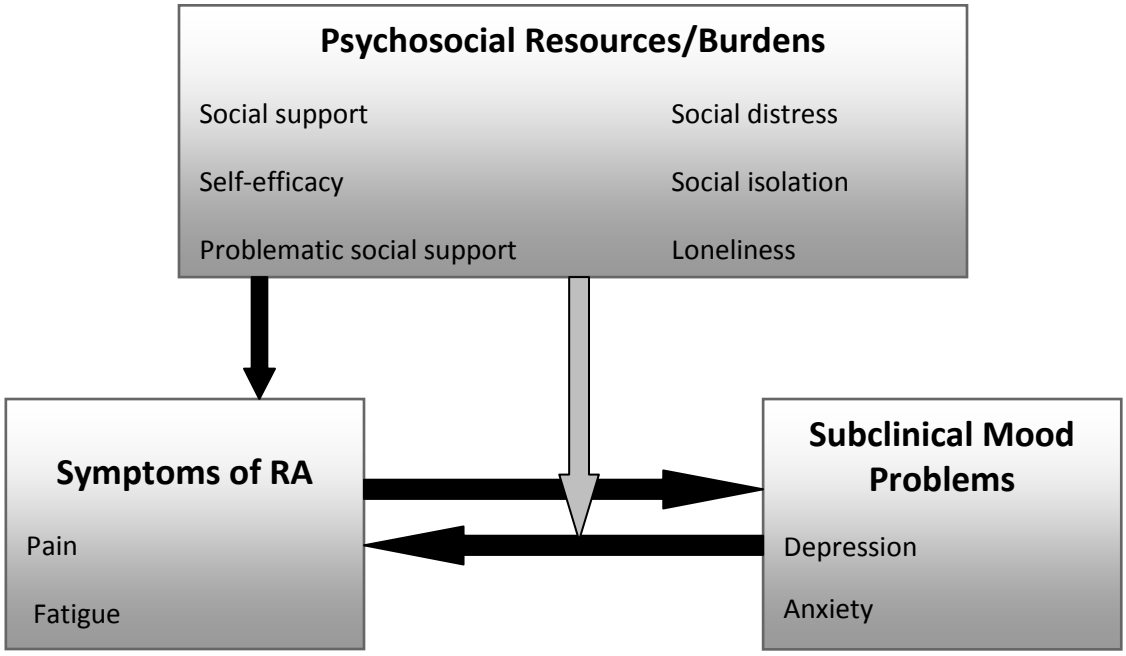


Figure 1: Conceptual model of relations between demanded variables

METHODS

Search Strategy

According to pain and fatigue in rheumatoid arthritis and their possible relations with psychosocial resources/burdens and subclinical mood problems, a systematic search was performed in four electronic databases: PsychINFO (all years), Web of Science (all years), Scopus (all years) and MedLine (all years) in the period from October till November 2009. The databases were searched for English-language studies using the following terms: “rheumatoid arthritis” or “RA” and “pain” and/or “fatigue” and “depression” or “anxiety” or “social distress” or “social support” or “loneliness” or “social isolation” all excluding “fibromyalgia”. Fibromyalgia is especially excluded because it is, beside RA, the most frequent studied matter. Furthermore, the reference lists of included studies were examined for additional potentially eligible studies.

Selection of Studies

The following criteria guided the inclusion of studies in the systematic review:

- Pain and/or fatigue exclusive to rheumatoid arthritis
- At least one further variable in demand related to pain/fatigue in RA
- Samples of all ages & illness duration
- Both cross-sectional and longitudinal studies
- Both studies with and without comparison group (healthy people)
- Published and unpublished (e.g. dissertations) studies

Studies were excluded in accordance with the following criteria:

- Referring to other forms of arthritis than rheumatoid arthritis
- Missing a relation between pain/fatigue and variables in demand
- Case studies (considering the potential of generalization)
- Pilot studies (considering a very small sample)

Quality Assessment

The methodological quality of included studies was assessed according to several criteria: the study design, the study length, using a comparison group, the sample size, consistency of monitoring (same measuring for all subjects) and the substantiation of drop-outs, if present. These criteria based on the validated Jadad Scale (Jadad, et.al, 1996), the Cochrane Handbook (Higgins & Green, 2008) and self-formulated criteria. Details of defining the quality criteria are displayed in table 1. Each study was assigned a score whereas the quality of them was assessed as high when 4 or more criteria were met, medium when 3 criteria were met, and low when 2 or less criteria were met. Appendix B summarised the quality of the included studies.

Table 1: Criteria of the methodological quality

A	Longitudinal study: Measuring over a longer time period for detecting changes in variables	1
	Cross-sectional study: Measuring at one single point	0
B	Studies with several but at least one follow-up measuring for detecting later effects between the variables	1
	Studies without any follow-up measuring	0
C	Sample is divided in people with RA and healthy people for having a baseline for comparison	1
	Sample consists only of people with RA (if in longitudinal study, this has no prevalence)	0
D	Sample size is in due proportion to the amount of measured variables for minimizing false-positive-/false negative-effects	1
	Sample size is too small for the amount of measured variables, false-positive-/false-negative-effects are feasibly	0
E	Studies use the same measurements in all subjects for the ability of comparing them	1
	Studies use different measurements among the groups	0
F	Studies execute a drop-out analysis, or there were no drop-outs, for characterizing drop-outs and comparing them with sample	1
	Studies do not substantiate their drop-outs	0

Data Extraction

Due to the great variability of measured variables, this review is not used for synthesizing all outcomes. The results get rather discussed conform the expressed questions of this review and the topics of the included studies. The primary outcomes of this review were pain and fatigue in rheumatoid arthritis. Problematic mood as depression and anxiety formed the secondary outcomes. Self-efficacy, social support, problematic social support and social distress were also recorded outcomes in the context of the primary and secondary outcomes.

RESULTS

Initially 632 articles about fatigue were retrieved from the databases (PsycINFO 133, Scopus 157, Web of Science 124, MedLine 218) and 63.019 articles about pain (PsycINFO 54.500, Scopus 3.147, Web of Science 1.996, MedLine 3.370). After screening titles and abstracts and removal of duplicates, 50 studies were identified as potentially eligible for inclusion in this review. Full-text versions of these papers were obtained and 13 articles were excluded for the following reasons: no pain or fatigue included or handled as dependent variable (Barlow, 2002; Cooper, 2000; Creed, 1990; Kerr, 2004; Krol, 1993; Revenson, 1991; Skevington, 1986; Suurmeijer, 2001; Treharne, 2005; VanDyke, 2004; Wright, 1996), other psychosocial resources/burdens than demanded (Covic, 2000), sample examined other than rheumatoid arthritis patients (Margetic, 2005). Furthermore, reference lists of the included studies were examined and added 5 dedicated papers. Overall, 43 articles were included in this systematic review (7 about fatigue, 13 about pain and fatigue and 23 about pain in rheumatoid arthritis). For fatigue, there were 3 longitudinal studies with comparison group (CG), 3 cross-sectionals and 1 longitudinal without CG. For pain and fatigue there were 1 cross-sectional and 4 longitudinals with CG and 5 cross-sectionals and 3 longitudinals without CG included and for pain, there were 2 reviews, 7 cross-sectionals and 9 longitudinals without CG and 3 longitudinals and 2 cross-sectionals with CG.

Characteristics of included Studies

The characteristics of the included studies are summarized in appendix A. In general, participants were predominantly female adults with a mean age between 50 and 60. Only 2 studies included equal numbers of males and females, 1 study included exclusively males and 4 studies evaluated only females. The evidence bases were generally of medium (12 studies) up to high (21 studies) methodological quality. Only 8 papers denoted low quality and two were reviews. The quality deficiencies of several studies were primarily due to the design and small sample sizes compared to the amount of measured variables (detailed information in appendix B). In all studies the attrition rate was not higher than 20% and did not differ substantially from the sample. However, five studies (2 about pain and fatigue and 3 about pain) failed to report on drop-outs and their characteristics. Of the 7 papers about

fatigue, 6 measured also depression, 5 anxiety, 2 self-efficacy, 2 social distress and 3 social support. Of the 23 articles about pain, 20 quantified depression, 8 anxiety, 1 self-efficacy, 5 social distress, 5 social support and 2 affect. In the articles of both pain and fatigue, 12 gauged depression, 4 anxiety, 1 self-efficacy, 1 social distress and 2 social support. Aside from 2 studies which gathered data via structured interviews, all others utilized paper and pencil self-report questionnaires. All instruments had good psychometric properties, except for the Hospital Anxiety and Depression Scale (HADS). This scale seems to have found subjects more depressed than other scales, as for instance the Centre for Epidemiological Studies- Depression Scale (CES-D; Dickens, 2002). This conclusion was drawn from a comparison of eleven studies using different instruments for measuring depression. Three of the included studies utilized the HADS and detected considerably higher depression scores than the rest of the studies utilizing other scales measuring depressive mood. Dickens (2002) has precluded that this effect could be ascribed to sample characteristics. Sharpe (2001) and Pincus (1996) have also found a lower base rate for identification of depressed mood by utilizing the HADS. Additionally to the subjective reports, 14 studies also applied inflammation markers (3 in exclusively fatigue studies, 6 in pain studies and 5 in studies about both topics). The measures of depression and anxiety were mainly only quantified via the instruments. Merely 5 studies measured it on the basis of DSM III-IV criteria.

How pain and fatigue change over the course of RA and when is it highest?

This review comprised only two studies which dealt with the changes of fatigue over the course of RA (Mancuso, 2006; Treharne, 2008). Both trials stretched over one year. Mancuso (2006) made use of 122 people with RA and the same amount of healthy subjects for completing the Fatigue-Severity Scale (FSS) at baseline and one-year follow-up. The author gave no information about the duration people were already affected by RA. On the results, it struck first that the RA-group had significant higher scores (M= 4.2) at the FSS than the healthy controls (M= 3.4). Second, in the one-year follow-up, it was discovered that fatigue improved very slightly in patients (M= 4.1) as well as in controls (M= 3.2). Treharne (2008) examined 154 subjects with RA. Thereof one-third had RA for less than six months, one-third had RA for 1-7 years and the last-third had RA for more than seven years. Fatigue was rated

on a visual analog scale (VAS) at baseline and one-year follow-up. The mean results show that fatigue remained relatively stable from baseline (47.4 mm) to follow-up (46.8 mm). But in detail, 51 subjects decreased slightly in fatigue (44.7 mm), 61 increased considerably (53.5 mm) and only two subjects remained stable. Unfortunately, these directional changes of fatigue were not controlled for the duration of RA so that it could not be concluded that subjects with specific disease durations possessed an appointed progress direction.

The course of pain over the progress of RA is slightly better researched. This review involved seven studies dealing with this topic. Eberhardt (1993) examined 89 subjects who were affected by RA for one year. Pain was scored on a VAS at baseline and thereafter annually up to two years. Pain was detected to be moderate and decreased from baseline (M= 1.3) to two-year follow-up (M= 0.9). Frantom (2006) examined pain experience in 41 participants with about 12 years of RA. The sample underwent currently an antidepressant trial and was furthermore split into two groups, in which 21 subjects had a history of mood problems (PSY+) and 20 had not (PSY-). Pain was measured via the PPI (Present Pain Intensity Scale), AIMS pain scale and a VAS. Data was gathered four times in both groups: at baseline, after three, six and 15 months. The pain experience differed significantly between the groups. While the composite pain scores for the PSY- group indicated a significant improvement in pain level from baseline to 15-months follow-up ($p= .0001$), no significant change was found for the PSY+ group. Evers (2003) studied pain in 78 subjects with RA for less than one year. The trial stretched over 5 years, with measurements at time of diagnosis, after three and five years. Pain was detected via the IRGL scale (Impact of Rheumatic Diseases on Health and Lifestyle) at each time of measurement. The outcome was that pain significantly decreased within five years after diagnosis ($F_{(3,75)}= 9.6$, $p< .01$) with most improvement in the first year of the disease. But it cannot be excluded that this effect could be ascribed at least partly to beneficial effects of medication.

Odegard (2007) examined pain in 149 subjects with two years of RA. Pain was scored via VAS and the AIMS (Arthritis Impact Measurement Scale) at baseline and after one, two, five and ten years. Both scales, VAS and AIMS, demonstrated a strong stability of pain over time. At all measuring points during the 10-year follow-up, 30-35% of participants had moderate up to high VAS pain scores (≥40 mm). Brown (1990) made use of 234 subjects with RA since three years for studying pain. The utilized measurement instruments were a pain VAS and the subscale of the AIMS and were conducted at baseline and thereafter semi-

annually up to three years. Over this time period, pain fluctuated from M= 14.07 at baseline over M= 13.53 at 1.5 year follow-up back to M= 14.05 at 3 year-follow-up. Therewith, moderate pain improved temporary but expired at the initially level at trial end. In the study of Covic (2003), 257 participants with RA for a time of 13 years completed the pain subscale of the AIMS quarterly over a period of one year. The results spoke for moderate pain throughout the sample which decreased non-significantly over time (Means from baseline up to one year 4.55 and 4.47 respectively). Last but not least, Nicassio (1992) determined 242 subjects with RA for about three years. Pain was gauged via the subscale of the AIMS and was conducted two times over a period of two years. The trial resulted in the conclusion that pain remained reasonably stable over time (Means for pain at baseline up to two-year follow-up 13.52 and 14.08 respectively) but with an increasing trend.

Conclusion: For an overview of the results, see table 2. The change of fatigue over the years with rheumatoid arthritis seemed to be under-researched. The two studies, included here, stretched over one year and examined subjects with a disease duration of 0 - >7 years. Both studies had good methodological quality but came to awkward interpretable results. The interpretation of the results based on means whereupon fatigue seemed to remain relatively stable over the time period of one year with a decreasing tendency. But by unraveling the data (Treharne, 2008) it became obvious that each subject reacted very different with a more increasing drift. The studies about the course of pain over the years with RA came to different results and were also based primarily on means. Three studies reasoned, independently from disease duration and the length of trials, an improvement in pain sensation, experiencing pain highest in the beginning of the disease. Thereof, two studies (Frantom, 2006; Evers, 2003), with good methodological quality recorded a relatively small sample and utilized an intervention. Evers (2003) treated directly on pain reduction so that the progression of pain could be partly attributed to this

Table 2: Overview progression of fatigue and pain over the course of RA

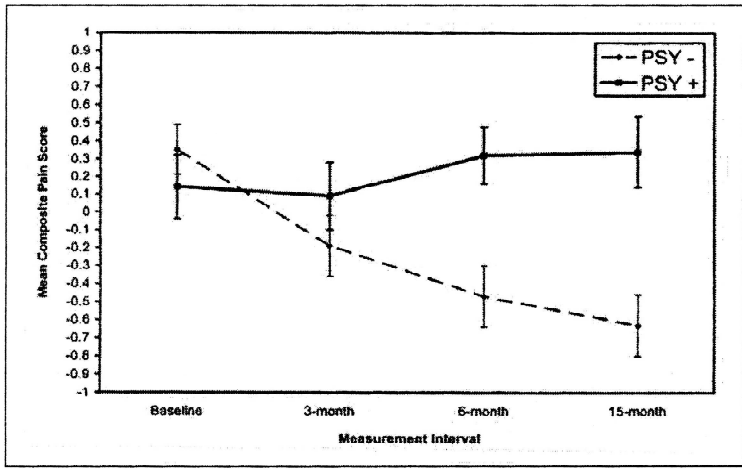
		Stable	Increase	Decrease
Fatigue	Mancuso (2006)			✓
	Treharne (2008)		✓	
Pain	Eberhardt (1993)			✓
	Frantom (2006)			✓
	Evers (2003)			✓
	Odegard (2007)	✓		
	Nicassio (1992)	✓	✓	
	Brown (1990)	✓		
	Covic (2003)	✓		

intervention. Frantom (2006) treated with antidepressant drugs, so that in this case an intervention effect would be improbably. Brown (1990) found fluctuating pain sensation and the rest of the other studies came to the conclusion that pain remained stable over time, independently from disease and trial duration. All of them had good methodological quality.

Are RA-pain and fatigue associated with dysphoric mood as well as anxiety?

Several studies have investigated the relation between pain and fatigue in RA and problematic moods, as anxiety and depression, but with inconsistent results. In this review 36 studies were included for answering this question. In advance, it is consecutively spoken from "current/lifetime AD" or "Psy+" when reviewing the studies about the effect of current (last few weeks) and/or lifetime (anytime in the past but not in the last few weeks) affective disorders (AD) as a major depression (MD) and general anxiety disorder (GAD) unless it is more specified. The study of Fifield (2001) shows that fatigue increased significantly in people with RA and current/lifetime AD (PSY+; 15% MD, 4% GAD) while people with RA in the control group, who do not have current/lifetime AD (PSY-) reported considerably less fatigue. The PSY+ group reported 10% more fatigue than the PSY- control group and this was still stable over the study time of seven years. Furthermore, Jump (2004) also found a positive relation between RA affected persons with current/lifetime AD (GAD & MD) and fatigue (M= 34.31) comparing to RA controls without current/lifetime AD, which experienced less fatigue (M= 28.77). Frantom (2006) found, that current/lifetime depression also has an effect on reported pain in RA. Here, the PSY+ group experienced significantly greater pain than the PSY- group over a time of 15 months (see figure 2). Some years earlier, Fifield (1998) studied the difference in

Figure 2: Pain experience in people with and without current/lifetime depression (Frantom, 2006)



experiencing pain and fatigue in RA-affected subjects and specified three groups according to the time and frequency of an AD: at least one past episode of depression, only currently higher depression scores without a previous episode and subjects who had both, one or more depressive episodes in the past and currently higher depression scores. It was found that the latter RA-concerned persons with at least one past depressive episode and also current depression, reported the highest pain and fatigue (M= 62 for pain; M= 68 for fatigue), followed by subjects who denoted only currently heightened depression scores (M= 51 for pain; M= 65 for fatigue). At least one past episode of depression without current indications of depressive mood show the least but still significant affect on pain and fatigue (M=35 for pain; M= 46 for fatigue). Zautra & Parrish (2007) examined the impact of departed depression episodes exclusively on pain. It was differentiated between people without any past depressive episodes, people with one past depressive episode and people with more than one past episode of depression. It was found that in case of one past episode of depression, pain gets experienced higher (M= 48) than among people without any past episodes (M= 45). Furthermore, the more past episodes of depression, the more severe became the pain (M= 55) and higher scores of current depression also added more pain (Pain: $F_{(1,133)}$= 31.32, p< .01).

Brown (1990) reported the conversely relation between pain and depression and reasoned that the more past/current pain episodes and intensive pain were experienced, the severity of current depression increased. Data was gathered six-monthly over a period of three years (seven waves, inclusive baseline). During the first three waves of the study (ranging over 1 ½ years) the data did not support any causality between pain and depression. However, data gathered at waves five through seven (ranging over 3 years) strongly suggested a predominantly causal influence of pain predicting depression (R^2= .65, p= .05). This direction was also indicated by Chaney (2004) who detected a strong connection between pain and depression. The study spanned over one year with two times of measuring. Results suggested a causal relation between pain and depression in that pain experience in RA increases the liability to depressive mood (r= .56, p= .001 at time 1 and r= 53, p= .01 at time 2).

Moreover, some investigators found a strong interrelation between fatigue and depression (r= .51, Huyser, 1998) and fatigue, depression and anxiety (r= .523 for anxiety, r=

.501 for depression, Wolfe, 1996). Despite the significant correlation between anxiety and fatigue, in multivariate analyses only depression explained 44% of the variance, beside sleep problems and pain. In addition, other examiners could also found an interrelation between pain, fatigue and depression (Broderick, 2008; Rupp, 2004). Rupp (2004) detected a moderate to strong relation between pain and fatigue (r= .468) and between fatigue and depression (r= .440 for low depression; r= .576 for high depression scores). Broderick (2008) found in 105 subjects, who were examined daily for 30 days that pain and fatigue could be partly related to depression. Several subjects (10%) increased in depression (6.0 points) and several others (20%) decreased in depression over time (7.2 points). Depression was measured utilizing the BDI-II. Pain and fatigue were reported to decrease over the trial duration, but without giving data for checking this. In turn, other investigators examined and found such a relation for pain and depression. Covic (2003) detected a beta value of .55 from pain to depression over a time of 12 months. Sharpe (2001) examined depression, pain and disability over a period of 21 months, gathering data six times. It could be determined an adjusted R^2 value for a set of predictors (depression scores of earlier measurement points, disability and pain) from over .70 (p=.008) at 15 and 21 months follow-up measures which accounted for variance in current depression. In this model, previous depression scores amount to 43% of the variance and disability and pain accounted for more than 10% respectively. Furthermore, positive correlations between pain and depression were supported by the results of Orengo (2001; pain and depression explained together 54% of variance in peoples' functioning), Kojima (2009; depression explained 36% of variance in pain) and Dickens (2002). Also Zautra & Smith (2001) detected through a cross-sectional study that the level of depression scores predicted strongly for pain (beta value of 9.3). Some other studies could identify the reverse effect that pain and fatigue were strong long-lasting predictors for depression (discriminant loading of pain= .55 and fatigue= .57, Covic, 2006; Wolfe & Michaud, 2009). Belza (1995) found likewise a positive relation between depression and fatigue, even though the relation in this study was not only found for fatigue in rheumatoid arthritis (r= .47) but also for healthy control subjects (r= .46). However, controls, without RA experienced considerably less fatigue (M= 26-29) than RA-affected ones (M= 15-17 at a range from 1-50).

Smedstad (1995), Tamiya (2000), Vaeroy (2004) and Creed (1990) found a positive relation between pain, depression and anxiety. In a regression analysis, Smedstad (1995) has found a value of 31% for depression and 33% for anxiety explaining the variance in pain. Tamiya (2000) found 30% of the variance in pain explained by anxiety and 17% explained by depression but linked pain more with the degree of inflammation. Unfortunately, Vaeroy (2004) presented the correlations between pain and depression, and pain and anxiety resulted from regression analysis only via scatter-plots, so that details of data could not be reported. Therefore, a clear description of the results is not possible. Nevertheless, the results were considerably significant (p= .03 for anxiety, p= .04 for depression). Creed (1990) studied in his review ten papers about anxiety and depression in RA and concluded that depression is significantly associated with increasing pain. Smith & Zautra (2008) determined a relation only between pain and anxiety. Anxiety accounted for about 15% of the explainable variance in pain and was therefore the strongest predictor in this study.

Several other studies could not confirm the association of fatigue and mood problems (Mancuso, 2006; Treharne, 2008). Data of Mancuso (2006) did not suggest an association between fatigue and depression but between fatigue and anxiety (r= .38). Treharne (2008) investigated the relation of fatigue with depression, but could also not confirm it. Belza (1993) found that fatigue and pain are more gender- and disease-related but not associated with depression or anxiety. In this regard, a set of further studies has detected similar outcomes. Odegard (2007) has examined pain, depression and anxiety in 149 subjects over a time of ten years. It was concluded, that pain increased 0.33 units for each rising unit in anxiety. But depression was completely unrelated to pain. Therefore, depression had a strong interrelation with anxiety (β= 0.46 - 0.65). Smedstad (1996) has investigated pain, fatigue, anxiety and depression cross-sectional in 238 subjects with RA and 116 subjects without RA. It was reported that depression and anxiety were significantly higher in people with RA than in healthy subjects (mean difference between groups in anxiety and depression 1.4 and 1.1 respectively) whereas patients completed two mood scales (general health questionnaire (GHQ), AIMS) and control only the GHQ. Pain and fatigue were significantly worse rated by people with RA (mean difference between groups 1.6 for pain and 0.6 for fatigue) than in controls. If controlling anxiety and depression for pain and fatigue, the differences between the groups were not anymore significant at a level

of 5%. Thus, Smedstad (1996) concluded that the four variables were not related to each other. Another study (Stone, 1997) has also researched pain, fatigue, depression and anxiety in a number of subjects (N= 35) with RA over a period of seven days. Due to ordinary least squares (OLS) regressions, it was concluded that pain, fatigue, anxiety and depression could indeed be all present in rheumatoid arthritis, but that the disease symptoms in demand could utterly not be related to the explored mood problems. This declaration could not be checked due to absence of data information in the paper. Other studies show that in cross-sectional appraisals the most predicting factors for fatigue and pain were respectively pain and fatigue. Riemsma (1998) found that fatigue got increased by pain (R^2= .27). Furthermore, fatigue correlated with the affect scale of the AIMS2 which measured anxiety and depression (r= .45; p< .001). Pollard (2006) detected results in the oppositional direction that pain was predicted by fatigue (R^2= .50). Additionally, the relation between pain and fatigue got mildly moderated by depression (Pollard, 2006). Evers (2003) found that pain in RA mostly got predicted by pain over a time of three up to five years.

Conclusion: For an overview of the results, see table 3. The results were highly variable and pain was considerably more studied in RA than fatigue. Also, depressive mood was twice as much (33 times) examined in the included studies than anxiety (17 times). The most papers could confirm a relation between pain and/or fatigue and mood. In detail, 17 studies could determine mood as predicting value for pain/fatigue (with ordinarily 40% of variance explained by mood) whereof 10 studies met high methodological quality, four achieved medial quality, only two scheduled low quality and one paper was a review. Furthermore, four studies (three high qualitative and one medial qualitative paper) detected pain as predictor for mood. Additionally, six studies could confirm a positive relation between pain/fatigue and problematic moods. Thereof three denoted high, two met medial and only one met low methodological quality. The most frequently denoted quality limitations were a cross-sectional design, the lack of follow-ups and control groups. Despite high frequency of good confirming researches, there are nevertheless a few meaningful contradicting papers. Two high qualitative (5-6 quality points) studies about fatigue detected no relation between depression and fatigue, thereof one also between anxiety and fatigue. One high qualitative paper on pain could also only identify a relation between pain and anxiety, but not with depression. Three researches about pain and fatigue also found no

relation to mood. Thereof, two studies denoted low methodological quality (2 points, with failures in design, control group, sample size and follow-ups), one show medium (3 points, with lack of longitudinal design, follow-ups and consistency in measurements) and one met high quality (5 points). Moreover, three other studies excluded mood absolutely as predicting value and detected pain and fatigue as main impact on each other, one of them with high quality. Concerning the averaged 40% of variance in pain/fatigue which were explained by mood, it could be obviously concluded that RA symptoms are predicted by mood. But concerning to the also high conflicting results of good qualitative studies and the imbalance of studies available about depression and anxiety and pain and fatigue, it is not possible to draw an unambiguous conclusion about these relations within RA.

Table 3: Overview association between mood and symptoms of RA

		Pain	Fatigue	Depression	Anxiety
Fatigue	Fifield, 2001	/	/	+	+
	Jump, 2004	/	/	+	+
	Huyser, 1998	/	/	+	-
	Wolfe, 1996	/	/	+	+
	Mancuso, 2006	/	/	-	-
	Treharne, 2008	/	/	-	/
Pain & Fatigue	Broderick, 2008	/	/	+ p/f	/
	Belza, 1993	/	/	-	-
	Covic, 2006	/	/	+ p/f	/
	Fifield, 1998	/	/	+ p/f	/
	Pollard, 2006	+ f	/	+ p/f	-
	Belza, 1995	/	/	+ f	/
	Rupp, 2004	/	/	+ f	/
	Wolfe & Michaud, 2009	/	/	+ p/f	/
	Smedstad, 1996	+ p	+ f	-	-
	Stone, 1997	-	-	-	-
	Riemsma, 1998	/	+ p	+ f	+f
Pain	Brown, 1990	/	/	+	/
	Chaney, 2004	/	/	+	/
	Covic, 2003	/	/	+	/
	Frantom, 2006	/	/	+	/
	Nicassio, 1992	/	/	-	/
	Orengo, 2001	/	/	+	/
	Kojima, 2009	/	/	+	/
	Smedstad, 1995	/	/	+	+
	Dickens, 2002	/	/	+	/
	Creed, 1990	/	/	+	+
	Sharpe, 2001	/	/	+	-
	Tamiya, 2000	/	/	+	+
	Vaeroy, 2004	/	/	+	+
	Odegard, 2007	/	/	-	+
	Smith & Zautra, 2001	/	/	-	+
	Zautra & Parrish, 2007	/	/	+	/
	Zautra & Smith, 2001	/	/	+	/

/ = not studied + = relation - = no relation p/f= found for pain/fatigue f= found for fatigue

How is the effect of psychosocial resources/burdens on pain and fatigue in RA

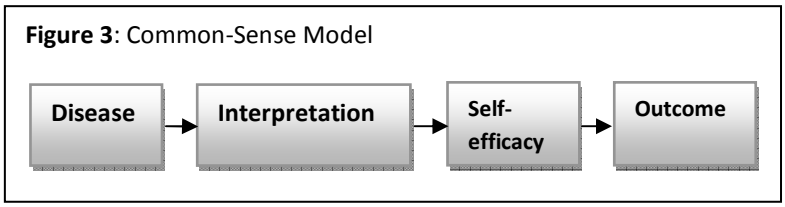
Psychosocial resources/burdens were in a set of studies associated with respectively strengthened or weakened pain/fatigue perceptions in rheumatoid arthritis. In order to answer this question, thirteen articles were found.

The amount and quality of social support is an important factor in the experience of chronic pain and fatigue in RA (Mancuso, 2008). Mancuso (2008) found that less social support (r= .24 at baseline, r= .33 longitudinal) and more social stress (r= .39 at baseline, r= .34 longitudinal) led to more fatigue. This effect was not only confirmed in people with rheumatoid arthritis but also in controls. However, in controls the effect was not as powerful as in people with RA (mean scores respectively 3.2 and 4.2). Huyser (1998) also came to the result that a lack of current social support (r= -.32, p= .05) and furthermore an increase in current social stress (r= .49, p= .002) enhanced the degree of fatigue in RA. These outcomes confirmed the finding of Belza, ten years before (1989). At this time it was already stated that social support can act as energy enhancer in chronic illnesses and could thus reduce symptoms as pain and fatigue.

Studies with relatively low methodological quality, through cross-sectional design and the lack of follow-ups and comparison groups, also show similar relations between psychosocial factors and pain and fatigue in RA, even though these relations were less unambiguous than in higher qualitative studies. So, beyond inflammation markers (IL-6), social stress only had indirect effect on fatigue (Davis, 2008). Blood samples showed that social distress encouraged the production of IL-6 cells which further led to greater fatigue (β= .73). In addition, pain was related to fatigue in the way that pain made people concerned more susceptible for stress and thus perceived greater fatigue (R^2= .43). The cross-sectional study of Kojima (2009) has resulted in less social support (r= .59) being strongly related to pain and fatigue in RA as a lack of coping resources. However, the cross-sectional study of Riemsma (1998) found social support unrelated to fatigue but could nevertheless confirm a strong positive association to problematic social support (β= .13; R^2= .37). Similar results were emphasized by studies concerning the experience of pain. For instance, Minnock (2003), a research executively with women, found that satisfactory social support weakened pain perception in women with RA (r= .35). Moreover, a five-year longitudinal study of

people with early RA (Evers, 2003) suggested that a lack of social support intensely enhanced the experience of pain (r= -.28 at 5-year follow-up). Beside a long-ranging effect on pain as indicated by Evers (2003), several studies have also confirmed short-run effects of social support on the severity of RA symptoms. Thus, Holtzman (2004) detected that satisfaction with social support during the day could reduce the experience of pain significantly in the evening (r= .35). RA patients who reported to have much social stress during the week also reported more pain at weekends (Smith & Zautra, 2001). Later with a different sample, Zautra and Smith (2008) could reconfirm that social stress led to higher pain experience (B= 3.95, p< .001).

Several studies have examined the effect of self-efficacy on the experience of pain and fatigue in RA. Treharne (2008), for instance, has studied the Common-Sense-Model in people with RA. This model states that the way people make sense of the threats of an illness impacted their coping abilities and thus the disease outcomes, in this case fatigue (see figure 3). The results supported the model and showed that self-efficacy is strongly related to fatigue, currently as well as prospectively (r= .02 at baseline rising up to r= -.54 at 7-year follow-up). So, the lower someone's self-efficacy over consequences of RA, the more fatigue was experienced. Jump (2004) found the same direction for the relation of self-efficacy and fatigue (r= .49). Riemsma (1998) examined self-efficacy cross-sectional and also found a negative association between fatigue and self-efficacy (β=-.21; R^2= .33). The included article about pain in rheumatoid arthritis shows equivalent results concerning self-efficacy to the papers previously reviewed. In detail, Orengo (2001) has examined executively males cross-sectional and found that low self-efficacy resulted in greater pain-severity (β= -.26, R^2= .13).



Conclusion: In sum, the reviewed studies about psychosocial factors influencing pain and fatigue in RA found concordant results. Altogether, the outcomes suggested that pain and fatigue in RA do not occur entirely in an exclusive clinical setting which could only be treated medically, but that personal as well as social factors are of further importance. According to this, psychosocial resources as a high amount of satisfactory social support and an adequate to high self-efficacy serve as energy enhancer and can reduce the perception of

pain and fatigue. In contrast, psychosocial burdens which further stress people with RA, such as more dissatisfaction with social support, interpersonal stress and low self-efficacy can intensify the perception of pain and fatigue. Only one study could not confirm a direct effect of interpersonal stress to fatigue (Davis, 2008), but an indirect via inflammation (see table 4 for an overview of the results). Indeed it has to be mentioned that the included fourteen studies had very different methodological qualities (6= low; 3= medium; 5= high) but all of them detected outcomes with the same direction and similar strengths.

Table 4: Overview of relations between psychosocial resources/burdens and pain/fatigue

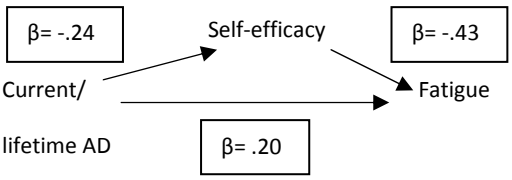
		Self-efficacy	Social Stress	Problematic social support	Amount of social support
Fatigue	Huyser, 1998	/	✓ (+)	/	✓ (-)
	Jump, 2004	✓ (-)	/	/	/
	Belza, 1989	/	/	/	✓ (-)
	Mancuso, 2008	/	✓ (+)	/	✓ (-)
	Treharne, 2008	✓ (-)	/	/	/
Pain & fatigue	Davis, 2008	/	✓ (+)	/	/
	Kojima, 2009	/	/	/	✓ (-)
	Riemsma, 1998	✓ (-)	/	✓ (+)	/
Pain	Minnock, 2003	/	/	✓ (+)	/
	Orengo, 2001	✓ (-)	/	/	/
	Evers, 2003	/	/	/	✓ (-)
	Holtzman, 2004	/	/	✓ (+)	/
	Smith & Zautra, 2001	/	✓ (+)	/	/
	Zautra & Smith, 2008	/	✓ (+)	/	/

✓ (-) = negative relation ✓ (+) = positive relation / = not studied

Are there psychosocial resources/burdens which mediate the relation between pain and fatigue in RA and problematic moods?

In this review, five papers were examined for their mediating relation of psychosocial resources and burdens on the association between fatigue and pain in RA and problematic moods.

Figure 4: Mediating effect of self-efficacy on depression/fatigue (Jump, 2004)



In studies about fatigue, Jump (2004) found that people with current/lifetime AD reported considerable more fatigue than the controls (Psy-) and determined that Psy+-subjects were definitely lower in self-efficacy, neuroticism and helplessness. Furthermore, the study identified that enhanced self-efficacy could weaken the relationship between fatigue and problematic moods (see figure 4). In a study about fatigue and pain, Riemsma (1998) detected similar results about the effect of self-efficacy on the relation between pain/fatigue and dysphoric moods. It was found that the degree of one's self-efficacy caused the ability to cope with chronic symptoms in RA and hence the experience of fatigue but not of pain. Thus, fatigue formed an interactive relation with depression and self-efficacy.

In studies about exclusive pain in RA, Zautra & Smith (2001) found that social distress weakened coping abilities and heightened people's attention on pain. This was, in addition, fostered by higher scores of depression ($\beta= 4.37$, $p< .001$). Some years later, Smith & Zautra (2008) determined an interacting effect of depression on subject's stress reactivity for social matters which further led to a higher pain perception ($\beta= 2.30$, $p= .018$). Similar findings were met with the study of Zautra & Parrish (2007). Here, an interacting effect of lifetime depression and rising social stress sensitivity also intensified pain experience in people with RA ($\beta= .07$, $p< .01$).

Conclusion: Of the five studies reviewed for this question, two were about self-efficacy and three about social stress. The papers about self-efficacy, which were simultaneously the two about fatigue, were of very different methodological quality (5 quality points; 2 quality points) but both examined very similar results. Self-efficacy related in the studies negatively to the association between fatigue and problematic moods. Thus, low self-efficacy was related to depression and anxiety and in turn, this relation increased

the perception of fatigue. A general statement about the effect of self-efficacy on pain could not be made because only one paper examined self-efficacy on pain but could not confirm a relation. The quality of the papers about social stress as mediator ranged within three and four quality points. Social stress was in the studies positively related with the relation of pain/fatigue and problematic mood. For instance, depression enhanced the sensitivity to social stress which further increased the experience of pain and fatigue. At this point it has to be explained, that the crucial factor in the included studies was not categorically the *quantity* of social stress people concerned perceive but rather an increased stress sensibility triggered off by the experienced severity of it which increased the pain experience. In a nutshell, the included studies could confirm, cross-sectional as well as longitudinally, a mediating effect of self-efficacy and social stress on the relation between pain/fatigue and depression and anxiety (for an overview of the results, see table 5).

Table 5: Overview of mediators on relation between pain/fatigue and problematic mood

	Author	Mood	Self-efficacy	Social Stress
Fatigue	Jump, 2004	MD/GAD	✓ (-)	/
Pain & Fatigue	Riemsma, 1998	D	✓ (-)	/
Pain	Zautra & Smith, 2001	D	/	✓ (+)
	Smith & Zautra, 2008	D	/	✓ (+)
	Zautra & Parrish, 2007	D	/	✓ (+)

MD/GAD = major depression/general anxiety disorder / = not studied ✓(+) = positive relation
✓(-) = negative relation D = subclinical depression

DISCUSSION

The aim of this review has been to critically summarize and evaluate studies about rheumatoid arthritis for checking four topics: 1) the progression of fatigue and pain over the course of RA, 2) pain and fatigue in relation to subclinical mood problems as depression and anxiety, 3) the effect of psychosocial resources/burdens on pain and fatigue and finally 4) the mediating effect of the psychosocial resources/burdens on the relation between pain/fatigue and mood problems.

First, it was examined, how pain and fatigue change over the course of RA. Fatigue seemed to be under-researched and results show that mean values were stable over trial duration but that individual subjects increased in fatigue proportionally to subjects which decreased (Treharne, 2008). Therewith, fatigue is very variable. Pain was examined with different results. Some good methodological studies found pain remaining stable over time. Some others found pain being highest in the beginning of the disease. This outcome was detected by studies with low and high quality. Thereof, several studies included subjects using anti-rheumatic drugs (DMARDs) which treat inflammations. Generally, medications should therefore indeed be noted as possible explanation for the reduction of pain perception over time. But in the current review they were nevertheless not a very strong one because of some studies examining a whole sample taking medications inclusive the controls and in some other studies only less than half of the samples were treated. Both variants came to the same results that medications have no effect on the course of pain in RA. The effect of pain reduction could possibly be explained by a coping effect. By paying attention and daily reporting the own pain intensity over a period of several weeks, people concerned could get a feeling of control over their complaints. This control perception could permit people to manage their disease-related problems (Aaron, 2005). A possible explanation for the stability of pain and fatigue, independently of disease and trial duration, could be the chronic manifestation of the constraints wherein nerve cells and the amounts of neurotransmitters (re-)act autonomously without sensory inputs (Zimmermann, 2004; Scholz & Woolf, 2007). Hence, the pain sensitivity raises and the pain threshold decreases Leffler, 2002; Baenkler, 2007). Beside the attempted explanations given, the findings of the studies must be interpreted with caution. Primarily since the exact disease duration was not known. The included studies defined disease duration counting from time of diagnosis.

Moreover, the results were based on self-reported data and were therefore susceptible for vague statements. But additionally, participations were voluntary and therewith giving *false* statements was at least unlikely. Another problem which emerged from the included studies about this topic as well as the following three one's, is that most of them utilized visual analog scales (VAS) for measuring pain and fatigue. Even though VASs are affirmed as a reliable method (Tamiya, 2002), they are nevertheless less precisely than arthritis-specific scales, i.e. Arthritis Impact Measurement Scale (AIMS) and Rheumatoid Arthritis Disease Activity Index (RADAI) and general fatigue/pain scales as the Brief Fatigue Inventory (BFI), the Fatigue Severity Scale (FSS) and the Present Pain Intensity Scale (PPI) for measuring pain and fatigue (Wolfe, 2004). Conclusively, the included studies did not present unitary results; the progress of fatigue and pain was very variable over the course of rheumatoid arthritis. Prospectively, this topic should be further researched.

Second, this review examined the relation between pain and fatigue and problematic moods, as anxiety and depression. The topics in demand were whether pain and fatigue in RA and mood problems could get associated with each other ones and if pain/fatigue predicts mood problems or if mood problems could explain pain and fatigue in RA. The results were very contradictory by partly confirming and partly conversing all of the three disposed hypotheses. Many papers could attest depression and anxiety as predictors of pain/fatigue, others confuted this and confirmed the reverse effect, pain/fatigue predicting mood. Again, other studies could not register any relation between the topics. Comparing the findings turned out to be very complicated because the included studies were very different from each other. For instance, a wide spectrum of measurement instruments was utilized whereof i.e. the HADS was already detected as a less feasible scale for measuring depressive symptoms. As mentioned in the method, this scale seemed to have a lower base rate for identification of depressed mood. Furthermore, various studies utilized mainly generic instead of the more suitable disease specific instruments for measuring depression and anxiety. With a generic instrument, which should estimate the prevalence and severity of depression, i.e. the CES-D, the rheumatic disease is rather reflected than the mental distress in demand (Smedstad, 1995). Statements as "I felt that everything I did was an effort", "I felt hopeful about the future", "My sleep was restless" and "I could not get going" may be influenced by physical aspects of the disease process

(inflammation, joint deviation, pain, fatigue) and, thus, are not necessarily indicative for a depression among persons with arthritis. Hence, depression could be mistakenly over-represented in RA (Blalock, 1989). Disease specific instruments as the AIMS2 aim for avoiding such a confounding. Questions for estimating the severity of depression are formulated even more clearly concerning the mood, as “How often have you enjoyed the things you do?”, “How often did you feel so down in the dumps that nothing would cheer you up?” and “How often have you been in low or very low spirits?”. Further questions of this scale regarding arthritis pain are also formulated more clearly on physical aspects: “How often did your pain make it difficult for you to sleep?” and “How often did you have severe pain from your arthritis?” (Meenan, 1992). Additionally to the instruments, the designs were also very variable through the studies. Many trials were of cross-sectional design which is not suitable for ascertaining a direction of the effects. Furthermore, several studies have utilized hierarchical regression analysis whereas some only accomplished correlation analyses which also give no indications for effect directions. Moreover, the investigated subjects of the studies differed highly in age, disease duration and medications. Some samples did not receive drugs, others did and those samples taking medications were treated very different through the studies. Besides, there was a distinction in the place of accomplishing the sample collection which ranged from general practitioners, over rheumatologists to patients of hospitals. Consequently, the samples of each included study distinguished in the severity of disease progression and led to different results. Finally, the studies varied in the amount of variables measured. Several researches controlled mood problems and RA symptoms for more variables than other studies (i.e. disability, sleep, education, gender, socio-economic status). Regarding all the differences through the studies, a conclusive picture over causality of the association between mood problems and pain and fatigue could not be drawn. However, a positive relation between them is mostly confirmed.

As third part of the paper, the direct effects of psychosocial resources/burdens on pain and fatigue in RA were investigated. Social support and self-efficacy were explored as resources and social distress, problematic social support and social isolation and loneliness were inquired as burdens. It was detected that psychosocial resources weakened and social burdens strengthened the perception of pain and fatigue in RA.

The fourth topic of this review researched the mediating effect of psychosocial resources/burdens on the relation between problematic moods (anxiety/depression) and pain and fatigue in RA. It was found that self-efficacy could dilute the relation between pain/fatigue in RA and problematic moods, whereas social stress could enforce it.

The complications of comparing the very different studies, as already mentioned at topic two also applies to the interpretation of the results of topic three and four. Nearly half of the studies used cross-sectional designs and were therefore not suitable for determining underlying processes and directions of effects and not all included studies reported multivariate comparisons but rather based on only bivariate correlates. Furthermore, these studies also utilized very different measurement instruments. Additionally, in most of the studies (about all four topics) mean values were the main indicator for drawing a conclusion about the constructs in demand. For instance, Treharne (2008) has detected that the mean values for fatigue at baseline and one-year follow-up were very similar to each other wherewith was concluded that fatigue remained stable. However, by unraveling the results it emerged that nearly all subjects changed in fatigue. This shows that means are not a very strong indicator for relations. All limitations together make the outcomes less reliable.

In addition to the variability in design, measurements and analyses of included studies, there were some further limitations denoted concerning the strategy of literature search. Thus, hardly no studies were included pertaining to other important factors. Personal characteristics as neuroticism, helplessness and extroversion which are confirmed from literature of great prominence (Morrison & Bennett, 2006) were only in the rarest cases kept in mind as influence factors on the sensibility for negative impacts as problematic moods or physical complaints. Also, the degree of perceived behavioral control (PBC) from the Theory of planned Behavior (TPB; Ajzen, 1985) which is determined multiply as important factor in the emersion of problematic moods and the effect of social influences is totally missing in the included studies. In this regard, there has been disagreement for a considerable time whether PBC forms a distinct construct to self-efficacy. According to Aijzen (2008) there is no difference between them. But in 1977 and 1991, Bandura already separated PBC in two distinct components. He argued that these would be the “self-efficacy belief” which is described as the extent to which performance of the behavior is easy or difficult for an individual and the “perceived control over one’s behavior” which reflects the

extent to which the individual perceives the performance of the behavior to be within one's control. In this connection, Tavousi (2009) implemented an exploratory factor analysis on self-efficacy and PBC. The author found two distinct constructs and defined self-efficacy as the confidence in one's ability to achieve the target grade and perceived behavioral control as the extent to which the behavioral outcome can be influenced by one's personal efforts. Therefore perceived behavioral control could provide an important contribution for the topics in demand of this review as it shed light on the locus of control of the people with RA and, thus, in a certain way on their ability to cope with the disease and the concomitant strains. However, the mentioned missing factors in the included studies are also a limitation regarding the literature search of this review. Keywords, searching for particular constructs as the above-mentioned PBC and hypotheses as the antecedent, consequence and scar hypothesis concerning the timing and relationship of mood problems to pain and fatigue are well-established for the questions in demand but were not applied in this review. Therewith, the field of research could possibly be not fully represented. In the antecedent hypothesis, depression precedes the development of pain, while in the consequential hypothesis the depression is a consequence and follows the development of pain. In the scar hypothesis, episodes of depression occurring before the onset of pain predispose to a depressive episode after pain onset. This implies that some people have a genetic predisposition to recurrent depression which can result in people becoming depressed when stressed by i.e. pain through physical illness (Fishbain, 1997).

Despite all the limitations, this systematic review has several implications for research, treatment and health care as well. First, as the course of pain and fatigue in RA is still unclear, this review indicates a need for further prospective research on these symptoms in people with RA, more controlling for the disease duration. Thus, treatment for reducing pain and fatigue could be better adapted on people's needs. Furthermore, the following studies about RA should consider more the ignored factors as personality traits mentioned above and should revert to more disease specific instruments for a comparative documentation of strengthens pain and fatigue and relations with moods and psychosocial variables. By replicating this review, the mentioned PBC and hypotheses should be accounted for keywords resulting in finding additive literature concerning the demanded topics. A literature search trial with the above-mentioned keywords offered good qualitative

studies which were previously not found (i.e. Fishbain, 1997; Wörz, 2004; Jordan, 1998; Smith, 1991). Moreover, prospective studies should cater to the ability of defining causal directions between moods and RA symptoms as this review could only detect a positive correlation between them. This could only be utilized by suggesting a shared treatment of people with chronic and incurable diseases such as RA, through medical professions and psychological support. The psychological support could be applied for preventing people from excessive demand by the disease and, thus, for an impairing combination with mood problems. The association between moods and pain and fatigue could be explained by a narrative destruction (Marks & Murray, 2006). In this connection, a disease as RA is seen as disrupting the narrative biography of people concerned. This means that the (planned) life story no longer fits in the everyday experiences which are affected by the physical constraints. Psychological support could help to reconstruct one's narrative biography that people learn to make sense of their illness and integrate it into their life (Bury, 2001). Thus, the coping abilities of the people concerned could increase regarding the disease-related symptoms and could minimize an emerging of psychological problems. Keeping the psychological aspect of treating RA, health care should offer standard psychological support for people with RA, especially at time of diagnosis as the results of the first topic indicated pain highest at the beginning of the disease. Additionally, tutorials for patients improving self-management and elucidating the importance of social support and its' quality for affiliated should be taken for granted as this review indicated direct upgrading effects of psychosocial resources on pain/fatigue as well as mediating effects on the relation of pain and fatigue with problematic moods. Finally, by involving prospective studies about the above-mentioned topics, over the years a biopsychosocial therapy model could be tailored on attending people with RA.

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Appendix A

Studies about fatigue in RA

Outcome measures	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
Depression/ Anxiety	Fifield, 2001	Fatigue results from the individual's history of affective disorder (altered biochemical processes following e.g. major depression (MD) explain sleep disturbance and fatigue/personality characteristics elevate symptom report in RA patients)	N= 415, Mean age= 58, 83% female	YES – people without AD history	10 years	Telephone interviews: DSM-IV psychiatric diagnoses of MD, generalized anxiety disorder (SSAGA), Depression/ distress (CES-D), Fatigue (VAS)	Fatigue initiated in middle range (β=49.68) 3% of between-subject variance in initial fatigue due to history of AD History of AD – higher levels of distress Higher levels of distress – higher initial fatigue in AD but less increase over time Levels of MD were similar Duration non-effective	Fatigue and distress related but not necessarily distress-contingent fatigue Fatigue is linked to history of AD (Fatigue 10% higher in subjects with AD, stable over 7 years)	Biochemical processes lack Only stable personality characteristics (no current states) Fatigue only via VAS (multidimensional measurement needed, e.g. Belsia's Multidimensional Assessment of Fatigue Scale)

Outcome measures	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
	Wolfe, 1996	Assuming, that fatigue is related to degree of inflammation. Therefore, non-inflammatory rheumatic disease should be associated with less fatigue. Reexamining fatigue and its correlates and the association with inflammatory markers	N= 1488 (RA= 628; OA= 535; FM= 325), Mean age= 60, Disease duration= 10 years, 81% female	NO – RA group partly compared to other rheumatic diseases (FM, OA)	Cross-sectional	Demographics, Fatigue (VAS), Disability (HAQ), Depression & Anxiety (AIMS), Pain (VAS), Sleep disturbance (VAS), Inflammation markers (ESR),	RA & OA reported 82% fatigue, FM only 22% Pain strongly associated (.568), sleep disturbance (.544), anxiety (.523), depression (.501), disability (.488), ESR not associated with fatigue 90% of variance explained by pain, depression, sleep	Demographics only weakly related to fatigue, Pain, anxiety, depression correlated over .50 All 3 groups similar R^2 and same predictors for fatigue (pain, sleep disturbance, depression) →Fatigue NOT related to inflammation	Only fatigue by VAS Global severity not measured
Social support	Belza/Tack (1989)	Absence/decrease of Fatigue = disease remission, Multidimensional nature of fatigue experience in RA, descriptors, aggravating/alleviating	N= 20, Mean age= 51, disease duration= 11.5 years, 85%	NO	Cross-sectional Interview lasted 30-45 minutes	Mood state (POMS), Fatigue (Fatigue Interview Schedule, VAS), Pain (VAS), Distress (VAS)	Fatigue most sig. problem (60%) Fatigue related to pain Frequency/duration of fatigue vary based on disease activity, emotional stress, work setting, treatment Social resources as energy		Small sample Long disease duration Qualitative data subjective interpreted by

Outcome measures	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		factors, management behaviors, cognitions, prodromal indicators	female				enhancers. Cognitive processes (distraction, comparison with others, energy audits (dealing with available energy), renormalizing (reducing activities) energy savers Fatigue leads to frustration (not completing a task), helplessness, strained relationships (misunderstanding overwhelming nature of fatigue), lack of control, less quality of life, increased pain		investigator Some interpretation controlled by external validators
Depression/ Anxiety/social support, social distress	Mancuso	Fatigue in RA similar to "normal" fatigue with predominantly psychosocial/lifestyle factors (anxiety, depression, stress…)	N= 122, Mean age= 49, 84% female	YES – Healthy subjects N= 122, Mean age= 49, 91% female	1 year Follow-up (FSS completed once more)	Fatigue (FSS), Anxiety (STAI), Depression (GDS), Social support/Stress (Duke scale), Activity/Exercise (PAEI), Sleep quality (PSQI), Disability (HAQ), Pain (VAS), Satisfaction with support at home, role satisfaction	Differences between groups in psychosocial and clinical factors associated with fatigue: More disability, anxiety, less social support independently associated with fatigue in RA In controls depressive symptoms	Social stress only independent variable in both groups Lack of relation between fatigue and depression in RA possible because of symptoms part of RA Psychosocial variables explain more	Sample represents not population (all employed) No biological markers of RA Control sample (urban dwellers) not good representation of healthy population (?) FSS a general instrument for overall fatigue (no recording of

Outcome measures	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
							independently sig. with fatigue Fatigue stable	variance in fatigue in RA	specific domains of RA)
	Huyser	General integrative model of Piper: subjective fatigue is determined by myriad biological (disease activity, accumulation of metabolites, activity/rest patterns, sleep/wake), psychosocial (support) and psychological (depression, anxiety, coping) parameters 57% of RA patients see fatigue as most problematic aspect	N= 73, Mean age= 59, 56% male, Mean disease duration= 12 years	NO	Cross-sectional	Fatigue (PFS), Self-efficacy (ASES), Health status (AIMS), Depression (CES-D, SCL-90), Anxiety (SCL-90, STAI), Pain (MPQ, VAS), Stress (DSI, HS), Coping (CSQ), Adequate social support (SRQ), Sleep duration, Disease activity (TCJ), Inflammation (ESR),	Women higher in fatigue than men Pain, depression, stress, anxiety, self-efficacy, functional disability and physical disability correlate with fatigue Regression: Depressive symptoms (11%), Pain (19%), Sex (being female; 6%) variables in model of best predicting components for fatigue Disease	Factors of statistic. Significance are of psychosocial and behavioral character Disease activity and biological indices (inflammation markers) are weak /not correlated with fatigue (low disease activity – high fatigue) Fatigue, Pain, Depression form an interrelated matrix in RA RA-related stress activity	Disease activity highly correlated with pain/depression/ functional losses (though no correlation) Cross-sectional design (no causal attributions) Small sample size for biological variables (for cortisol n=33) Sample disproportionally male (in contrast to normal sex distribution of RA) Personality not considered (neuroticism moderate factors as depression/pain)

Outcome measures	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
							duration and quality of social support further associated with the model (long duration more fatigue/low support more fatigue) Cortisol weak but sig. related to fatigue	may be associated with fatigue	
Depression, Anxiety, Sel-efficacy	Jump	Ineffective efforts to relieve from fatigue leads to helplessness which correlate with depression which further is associated with severe disease. Subjects with affective disorder history high in neuroticism and low in management. Self-efficacy (Bandura) important for management Trait marker hypothesis: personality are risk for affective disorder	N= 122, Mean age= 60, Disease duration= 21 years, 93% female (split into 2 groups: With ADH n= 48; without ADH n= 74)	YES – subjects without affective disorder history (n= 74)	Longitudinal (data compared with data of tel. interview in 1996	Current and lifetime diagnosis of Major depression (MD) and General Anxiety Disorder (GAD) (SSAGA by DSM-IV), Fatigue (MAF, qualitative aspects), Neuroticism (Neo-FFI) Self-efficacy (ASES) Joint stiffness	ADH subjects rate fatigue, stiffness and pain stronger. ADH subjects higher in neuroticism and lower in self-efficacy. Self-efficacy and neuroticism negatively associated (only SE directly linked to fatigue in ADH).	ADH subjects greater fatigue than controls. ADH subjects higher in neuroticism and lower in SE → increase of symptom awareness of fatigue etc. ADH likely influence fatigue through SE. Enhanced self-efficacy	Cross-sectional design (no possibility to distinguish trait marker hypothesis from scar hypothesis) Only subjects with long disease duration. Older subjects (special factors not attended) Sample included only 9 men

Outcome measures	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		OR Scar hypotheis: affective disorder change personality which impact management of chronic illnesses				and pain (VAS)	Self-efficacy partly mediated relation between fatigue and ADH	reduces depression and helplessness in RA	Pain and disability not measured Current depression not measured
Depression, Self-efficacy	Treharne	Common-Sense Model (CSM): how people make sense of threats to health and how these perceptions can drive attempts to cope with the health threat and how this may influence outcome. Potential predictors based on this model: demographics, disease impact factors, illness perception, efforts to cope.	N= 154, Mean age= 56, Disease duration= 1/3 under 6 months, 1/3 between 1-7, 1/3 over 7 years, 74% female, Follow-up n= 114	NO Sample divided by disease duration (early, intermediate, longstanding)	Longitudinal over 1 year	Fatigue (VAS), Inflammation (ESR), Pain (VAS), Frequency of sleep disruption (rating), Impact of disability (PI-HAQ), Depressed mood (HADS), Consequence perception (IPQ), Self-efficacy (ASES) → fatigue and mood,	Fatigue remains stable Baseline inflammation is positively related to pain, sleep disruption, and negatively related to fatigue (!!), Except depressed mood, all variables associated with fatigue Fatigue is mostly predicted by fatigue,	Perceptions of consequences of RA strongest impact on later fatigue, and accounted largely of relationship with baseline fatigue	Relatively small sample (?) Short follow-up Wide range of disease duration

Outcome measures	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
							inflammation, consequence perception and self.efficacy		

Studies about pain and fatigue in RA

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
Depression	Belza	Bio-psychosocial model for explaining arising from fatigue in RA	N= 133, Mean age= 67, Disease duration= 18 years, 75% female	NO	Longitudinal over 7 years	Depression, Functioning, Pain, Fatigue, Exercise, Sleep, Social support, Disability, Health care	Factors of fatigue: poor sleep (!), pain, being female, amount of functional limitations Fatigue leads to more health care visits		Pain/ Fatigue measured with single item Exercise scale exclude housekeeping tasks, Measures in one sequence
	Broderick	Attention worsens symptomatic with mood change	N= 105, Mean age= 56, 86% female	NO	Over 30 days with 6 measures per day	Pain, Fatigue, Depression, Mood protocol	Depression scores decreased from pre- (13.1) to post-protocol (11.4); scores of minimal depressed people in pre-protocol reduced the least at post-protocol	Paying more attention on negative symptoms of pain and fatigue has no increasing effect on depression Perhaps through recognizing the variability of symptom levels or expression of emotions through protocols	Depression not measured on momentary basis (increase in depression through protocol not detected)
	Covic 2006	Depression mostly independent from pain/fatigue and predicted by physical disability, coping (helplessness) and medication	N= 134, Mean age= 58, Disease duration= 13.2 years, 85% female	YES, the depression scale scores split into non-depressed and depressed	12 months	Pain/tension (AIMS2), Physical disability (MHAQ), Fatigue (VAS), Pain Beliefs (BPCQ), Self-	Predictors for depression: tension and self-esteem (strongest), pain, fatigue, coping, disability (modest, pain beliefs,	Depressed people more pain, fatigue, disability Depressed people found medication less effective and less important,	Results unstable No causality between factors Depression self-report scale is indicative

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
						esteem (RSE), Medication	medication (weak)	perceive more side-effects Depressed RA people more impact of disease	Self-report measurements are only subjective
	Fifield 1998	Major depression (MD) leaves a psychological "scar" which makes people concerned experiencing higher levels of pain, fatigue, disability when they are in dysphoric mood	N= 203, Mean age= 55, Disease duration= 17 years, 78% female	YES – subjects with RA but without MD history	6 years	Pain/Fatigue (VAS), Functional ability (HAQ), dysphoric mood (CES-D), Major depression (DIS-III-A, DSM-III-R), current arthritis medication →by telephone interview	No sig. differences between current depressive symptoms of people with or without MD history or a sub-threshold depression MD history with current dysphoric mood – highest levels of pain, fatigue, disability Without MD history but current dysphoric mood next highest Current disphoria irrespective of MD history more fatigue, disability than low disphoria	Experience of pain, fatigue, disability differs across categories of lifetime depression Evidence for a psychol. Scar in association between MD and current pain, but only under current-mood condition	Reports of major depression rely on subject's attribution of organic/nonorganic symptoms
	Pollard	Disease activity is one underlying factor in the	N= 512 (divided in 2 groups:	NO	Cross-sectional	Fatigue (VAS, SF-36), Treatment	80% clinical relevant fatigue, 50% high fatigue	Fatigue highly correlated with pain	Other fatigue measuring instruments

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		pathogenesis of fatigue in RA Inflammatory synovitis potententially important causal factor for fatigue in RA Little data on conventional disease-modifying antirheumatic drugs (DMARDs) Aim: define contribution of disease activity to fatigue in comparison with pain and depression in established RA	first (n= 238, Mean age= 60, Disease duration= 11 years, 80% female) fatigue measured via VAS, second (n= 274, Mean age= 64, Disease duration= 12years, 75% female) fatigue measured via VAS + SF-36)		Treatment responses followed for 3-6 months	(DMARDs, anti-TNF), Disease activity (swollen joints) patients global assessment (HAQ), Inflammation (ESR), Early morning stiffness	Fatigue sig. correlated with pain and disease activity (fall in fatigue correlate with pain improvement) Fatigue unrelated to treatment, age, disease duration, gender 53% of variance in fatigue explained (strongest through pain, then HAQ and depression) Anti-TFN higher in fatigue than DMARDs	Depression only comorbidity invariably associated with fatigue (depressed subjects more fatigue) Fall in fatigue accompanied decreases in disease activity BUT: Association with disease activity is secondary!	more valuable
	Belza, 1995	Compare self-report fatigue in adults with RA with age and sex matched controls without RA and determine relationships of fatigue to pain,	N= 97 (with RA n= 51, Mean age= 44, Disease duration= 10 years, 85%	Yes – healthy subjects (n= 46)	Questionnaires completed 3 times in 6-8 week-intervals	Inflammation marker (Blood sample for CRP & Hct), Fatigue (MAF with degree, severity, distress, impact on daily living	Women with RA not report more fatigue than men, but well women without RA Fatigue in RA subjects strongly affect exercise,	Fatigue in RAs more severe than in controls in all dimensions Controls are not fatigue-free! Fatigue is closely	Patients using methotrexate is overly represented Interpretation of fatigue scores difficult (MAF relatively new

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		sleep, functional status, depression and disease activitiy	female; without RA n= 46, Mean age= 42, 91% female)			activities, GFD, POMS fatigue subscale), Depression (POMS), Vitality (POMS), Sleep quality (SQI), Function (HAQ), Disability (HAQ), Pain (HAQ)	leisure, shopping Fatigue in controls affects exercise, leisure and sex. Activity but is mostly ascribed to occasion Fatigue stable over time in both groups Differences of Groups in pain, function, sleep No differences in depression Sig. association between high fatigue, high depression, pain, function, sleep, low Hct. Fatigue not related to CRP (except for blood sample all equal for controls)	interrelated (pain, sleep, depression, Hct, disability) Despite sig. differences in other variables, Depression NOT sig. different between the groups!! Fatigue remains stable over time → fatigue more characterized by trait than state ? Fatigue every day present in RA, In controls not every day	instrument) Relatively small sample Short follow-ups Blood sample not taken from controls
	Rupp	Fatigue is best distinguished consequence in RA and despite that is widely accepted little	N= 490, Mean age= 61, Disease duration= 11 years,	NO	Cross-sectional	Health-related quality of life (RAND-36), Fatigue (VAS, MFI-20), Depression	Mostly general/physical fatigue, moderate reduced activity and motivation and less mental	Physical aspects of Fatigue, pain and depression in RA interrelated but not as strong as assumed -->	Only correlations No controls Cross-sectional design

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		attention is paid to multidimensional nature effect of RA-fatigue on health-related QoL Study evaluate impact of fatigue on HRQOL with 2 other important factors: pain & depression	73% female			(CES-D), RA-related pain (VAS), Comorbidity (HIS),	fatigue General/physical fatigue strongly related with pain and depression Mental fatigue rather weak!! Physical/social functioning negatively influenced by physical fatigue, reduced activity, pain and depression	support for need of multidimensional treatment in RA Mental fatigue affect HRQOL but might be probably independent of RA Fatigue intervention strategies would gain extra improvement in HRQOL in RA subjects	Pain only via VAS
	Wolfe & Michaud	For identifying all of the factors that contribute to depressive illness and for quantifying the relative importance of these factors	N= 22.131, Split in depressed (n= 3.364, mean age= 57, Disease duration= 12 years, 84% female) and non-depressed Subjects (n=	YES – non-depressed people (n= 18.767)	Longitudinal (start 1999, end 2008) Measuring every year	Self-reported depression/mood (SF-36, MCS), Comorbidity (comorbidity score 0-9) RA severity (disability= HAQ, Pain VAS/RPS, Fatigue VAS, activity= PAS, SI (pain & fatigue)	Prevalence baseline= 15.4% Incidence depression at 9-years follow-up (in non-depressed people at baseline) 38.3% Depressed subjects sig. worse in all measured variables Variable	Cumulative risk of depression reaching 40% in 9 years follow-up Most important predictors for depression in RA are fatigue and pain	Prediction based on case identification, not causality Only subjects with long disease duration Self-reported depression, not clinical

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
			18.767, Mean age= 62, Disease duration= 13 years, 76% female				Importance: SI scores, comorbidity, RPS, PAS, Depression worsen in first 5 years		
Depression / Anxiety	Smedstad 1996	Anxiety and depression often mixed up (here called distress) Distress in RA higher? Can pain, fatigue and disability explain higher distress in RA?	N= 238, Mean age= 52, 73.5% female	YES, 116 healthy people, Mean age= 52, 69% female	Cross-sectional	General Health (VAS, HAQ), Depression, Anxiety, Social dysfunction, Somatization (GHQ), Disability, Pain, Fatigue (subscales of NHP), Pain (VAS), Depression (AIMS)	RA more symptoms of anxiety, depression, somatization, social dysfunction, 20% RA scored above limit to psychiatric caseness (controls 6%) Depression scores different between AIMS & GHQ Psyc. Distress not related to duration	RA has a high prevalence of psychiatric illness Disability, Pain, Fatigue act separately as intervening variables between inflammation and distress	Control group not ideal as reference sample AIMS depression scale is RA related and not distributed to control sample GHQ threshold score for psychiatric caseness raised for avoiding false positive cases (responses concerning somatic symptoms) Only self-report instruments Cross-sectional not grant causal

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
									relations
	Stone	Ecological momentary assessments (EMA) for better recalling of current states Topics: symptom variability, cyclicity of pain/fatigue, daily stressors, correlates of sleep	N= 35, Mean age= 52, 75% female	NO	7 days (EMA measures 7 times per day)	Neuroticism (NEO), Depression (BDI), Anxiety (STAI), →prior to EMA EMA: Mood (Mood adjective checklist), current pain (VAS), Disability (questions about activities, location, social settings, events since last beep) Stressfulness of events (VAS), Sleep (awakening time, duration, quality)	Pain and Fatigue moderate strength Pain variability associated with more fatigue/ pain, stiffness, poorer sleep quality (same for fatigue) Pain worse early in morning relative to later the day Fatigue different throughout the day Higher pain levels on stressful days, Sleep duration weakly related to pain/ not to fatigue, both strongly to sleep quality	Useful information about experience of RA and dosage of medication (related to biological cycles) Variability= marker for disease activity or for psyc. Reactivity to environmental stimuli Stress rapidly alter pain Pain/Fatigue influenced by sleep quality/duration and vice versa	Small sample (low statistical power) Length of study Results influenced by disease severity, activity and medication (90%), Causal relation between sleep and fatigue/pain impossible Personality, depression, anxiety not in results!!
Social stress	Davis	Pure physical relations: pain relates to degree of inflammation, Inflammation contributes to fatigue	N= 58, Mean age= 55, 60% female	NO	About 16 weeks	Fatigue/Pain (VAS), inflammation (IL-6 blood molecules), stressful, negative life events and sleep (daily	Interpersonal stress leads to more IL-6 production, If pain included in fatigue model no other variable correlate with fatigue (only pain),	Chronic stress impacts health of patients with RA (inflammation worsens → more effective variable than cortisol), IL-6 production	Sample took medication through measuring Mechanisms for stress effect not identified

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
						diaries), illness severity (MHI, SSS, NEO, SF-36, medication), BMI, alcohol use	IL-6 level predict fatigue and contributes it through pain	unrelated to pain, worsens relation of IL-6 and fatigue IL-6 circulation could be related to pain	Only IL-6 measured (only one-time!), pro-inflammatory cells would complete prediction Time between stress/inflammation measure varied enormously Relation only on correlation basis not causal
Depression, Anxiety, , Social support,	Kojima, 2009	Patients suffering from severe chronic disorders, accompanied by pain, disability and disfigurement are at greater risk to experience emotional disturbances How are psychosocial variables associated with clinical variables	N=120, Mean age= 58, 82% female, Disease duration= 11 years, 83% non-smokers	NO	Cross-sectional	Global assessment of disease severity (Swollen/tender joints, Steinbrocker's functional status), Inflammation marker (blood sample of CRP), Smoking habits (VAS), Pain (VAS), Fatigue (VAS), Depression (BDI-II), Social	Four factors measured: psychosocial items, disease activity, current symptoms, physical functional status Physical QoL highly sig. negatively correlated with all four factors (except satisfaction scale of SSQ), Mental QoL	Psychosocial factors strong influence on symptoms and patient outcomes but not on disease activity Depression influence patients' subjective symptoms (difficult to examine psychological status of patients based on routine	More than 50% did not undergo factor analysis (factor structure can be instable) Only people recruited who were able to complete a battery of questionnaires (healthier patients) Cross-sectional design

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		Assuming that QoL is the most important factor for people with RA				Support (SSQ), Generic perceived QoL (SF-36)	positively correlated with Social support and negatively correlated with the current symptoms (depression, anxiety, pain, fatigue, swollen joints) Disease activity not correlated with QoL	clinical examination) Despite poor physical status and pain, fatigue, distress, low social support, mental QoL can be high (matter of coping ability)	Study under assumption that QoL most important outcome → importance of each factor might vary according to outcome
Depression, Anxiety, Social Support, Self-efficacy	Riemsma	Fatigue related to anxiety and depression, also positive and problematic social aspects associated with depression and coping In studies of social support little attention paid to personal skills to mobilize support. Self-efficacy associated with coping with RA → less depression, stress and better sleep Chronic pain,	N= 229, Mean age= 63 years, Disease duration= 19 years, 61% female Blood sample only taken from 75 subjects	NO	Cross-sectional	Fatigue (VAS), Health status with depression/anxiety (physical functioning-, affect- & pain subscale of AIMS2), Social support (SSL-12-I), Problematic social support (Scale by Revenson), Self-efficacy with respect to coping with arthritis (Scale by Loring), Self-	Fatigue correlated with pain, physical function & affect (depression/anxiety) No association of fatigue with sex and age, ESR, Hb & RF (Hb would correlate sig. with fatigue if Blood sample taken from same amount of subjects as fatigue Fatigue not correlated with social support, but well strongly with	Relationship between psychosocial variables and fatigue are much stronger than "objective" measures as inflammation markers Self-efficacy toward coping most important factor in fatigue beside pain Problematic social support important in regression (not so	Fatigue only measured with VAS Cross-sectional design No controls Blood sample of only 75 subjects Mainly correlations

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		physical functioning and disease duration also of interest in this study				efficacy with respect to capabilities in obtaining help from social network (SMS), ESR, Hb, RF (blood sample)	problematic social support, disease duration and self-efficacy toward coping In regression, 37% variance in fatigue is explained by pain, self-efficacy toward coping with disability, depression and pain and problematic social support	positive support) Correlation between fatigue and affect and function not in regression Self-efficacy enhancement for treating fatigue in RA	

Studies about pain in RA

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
Depression	Brown 1989	Depression/Pain related to same Bio-psychosocial factors, thus occur simultaneously, active/passive coping strategies important determinant for handle a chronic disease	N= 287, Mean age= 50, Disease duration= 3 years, 75% female	YES, 75 excluded subjects	Over 6 months	Depression (CES-D), Pain coping strategies (PMI), Functional disability (AIMS),	Cross-sectional: functional disability/pain and pain coping strategies contributes for depression (passive strategies positive, active negative predictor) Longitudinal: passive coping and pain predict depression over time	Pain and depression not directly related, Passive coping strategies intensify relation depression and pain Active coping not buffer the negative effect of pain on depression	No conclusion concerning onset/recurrence of depression Variance in depression attributed to pain coping over time only modest
	Brown 1990	Pain through depression by lower pain tolerance thresholds Depression through pain by phys./soc. limitations Both simultaneously because related to similar factors	N= 234, Mean age= 53, Disease duration= 3 years, 75% female	YES, 126 excluded subjects	Over 3 years, questionnaire every 6 months (7 waves)	Pain (AIMS & VAS), Depression (CES-D)	CES-D scores higher in sample than population Pain-to-depression-model fit not worse than saturated model but better than null-model Depression-to-pain-model fit worse than saturated model and differs not from null model	RA patients more depressed than population Pain/Depression correlate positive Pain episodes result in increase in severity of depression (symptom duration moderates)	Direction of causality is interfered Depression onset/recurrence not addressed Causality limited by time series (in first 12 month not, but maybe in the first 6 month) Other etiological factors could be important (co existence of pain/depression)

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
	Chaney	Beck's cognitive model and learned helplessness conceptualizations of depression	N= 42, Mean age= 53, Disease duration= 9 years, 85% female	NO	Over 1 year, questionnaire 2 times	Depression (IDD), Functionality (ASQ), Pain/ disability (MHAQ)	Causal attributions for negative events predict later depressive symptoms beyond the influence of pain/disability Internal attributions (helplessness) leads to more depression		Psychiatric treatment history cannot be excluded (influence attribution-depression relation) Possible homogeneity in sample Quasi-experiment (causality on basis of statistical dominance)
	Covic 2003	Bio-psychosocial model with disability, helplessness and passive coping to predict depression and pain	N=157, Mean age= 58, 76% female	NO	12 months, measuring all 4 months	Pain (AIMS), Depression (CES-D), disability (MHAQ), Coping (CSQ),	Helplessness/coping mediators of relation between disability, future depression and pain Cross-sectional more effect than longitudinal	Disability, passive coping and helplessness impact level of pain and depression in RA	The hypothesized model only ONE causal possibility. Disability not the only indicator of clinical activity, 12 months short for RA disease
	Creed 1990	Previous personality, social stresses, current mental state related to depression			Systematic Review	Self-reliance, dependence on others, attitudes toward illness, stress response	Depression is in RA not more common than in other chronic disease (depression relates to somatic symptoms as	Psychiatric state has to be measured independently from somatic symptoms!	

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
						(MMPI, EPI) Anxiety, depression (HADS, BDI, PAS), social stress (SSS),	appetite, sleep, energy), Conflicting results concerning prevalence of depression in RA (some found no evidence for relation between severity, duration, pain, disabling with depression, others well → causality not defined), longitudinal: conflicting results (RA decrease/depression increase; increased depression not related to any RA symptomatic, more to demographics; social stress/lack of social support increase depression in RA)	Research interviews more reliable than questionnaires. Depression/Anxiety not directly related to disabling Depression/Anxiety directly related to pain, decreased grip strength Social support/social stress important aspect in rheumatology	
	Dickens	Psychosomatic relation between pain and depression moderated by demographics and illness related	Questions: relation and magnitude between RA and depression, Dependency of magnitude on definition and measurement of depression?		Systematic Review	Pain and depression, disability, disease activity, duration, coping, gender, social stress,	RA/Healthy (12): Subjects with RA more depressed than healthy subjects (and more pain/disability), RA/other painful	Excess of depression in subjects with RA depends on RA and not on demographics etc.	RA/Healthy: only 8 has matched subjects, 3 used HADS, only 4 included pain for both groups,

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		variables	Persist relation despite confounders? RA and depression related to pain?			social support,	condition (16): fibromyalgia subjects more depressed than RA, RA subjects more depressed than osteoarthritis subjects	HADS less suitable (questions get associated with physical illness, not psych. Symptoms) Depression increase in proportion to pain (relation) but direct attribution of depression to pain remains unclear	RA/other painful condition: not measured for disability, not homogenous → publication bias (9),
	Nicassio	About 2 thirds of RA patients report sleep problems A high incidence of disphoric mood and other symptoms of depression in RA Other psychosocial and cognitive variables (helplessness, catastrophizing,	N= 242, Mean age= 52 years, Disease duration= 3 years, 75% female	NO	Cross-sectional design and longitudinal with 2 measures in 24 months intervals	Pain (AIMS), Sleep problems (three items of different scales), Depression (CES-D), Functional disability (AIMS),	Cross-sectional: 57% reported sleep problems and attribute it to RA Greater pain – more sleep disturbance More sleep disturbance/ functional impairment – more depressive symptoms (pain not directly related to depression)	Significant autoregressive effects of prior pain and sleep problems found over time Prior pain exacerbate sleep over time (not reversed) People low in pain/high in sleep problems decline in depression over time	No causal interpretation possible (only correlations) Fatigue and depressive symptoms also found in healthy people with sleep disturbance Pain = a possible etiological factor in depression

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		passive pain coping, lower emotional support) influence relation of pain and depression Disturbed sleep interferes with effort to cope with disease					Longitudinal: severe pain independent predicts sleep problems Sleep problems no direct effect on depression, but in interaction with pain well sig.	People high in pain & sleep disturbance increase in depression over time (anergia, motivational deficits, high level of passive coping)	
Depression and Self-efficacy	Orengo	Depressive symptoms often coincide with greater pain and functional disability. But determination of which symptom predate the other is not possible yet.	N= 45, Mean age= 67 years, Disease duration= >5 years, 100% male	NO	Cross-sectional	Pain severity/functional disability (MPI), Depressive symptoms (CES-D), Self-efficacy (ASES),	Pain interference on daily life & pain severity negatively correlate with SE Pain interference positively correlated with depression/pain severity Depression correlate with SE Regression: Depression 10%, depression/pain severity 54%, depression/pain severity/ SE 67%	Psychosocial variables associated with disability/pain to same extent as disease itself Proper evaluation of depressive symptoms at clinical evaluation may improving RA patients' well-being	Small sample size And only elderly males → limited generalizability Cross-sectional design Directly disease related variables excluded Self-report questionnaires (patients unrealistic pessimistic; co-morbidity of symptoms of depression and RA)

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
Depression and anxiety	Eberhardt		N= 89, Mean age= 53, Disease duration= 11.5 month, 65% female	NO	2 years	Disease activity (HAQ, VAS for pain), Depression/anxiety (SCL-90 subscales)	Anxiety decreased over time, highest in beginning of RA, Depression fluctuated not significantly	Anxiety and depression related to RA but not to disease severity	Only self-rate questionnaire
	Kojima, 2009	RA patients are twice as likely to be depressed as general population Depression could promote inflammation by fostering poor health practices, hormonal dysregulation Alternatively, systemic inflammation might induce depressive symptoms by activating immune-brain pathways	N= 218, Mean age= 60, 82% female, Disease duration= 11 years	Subjects divided into two groups based on level of perceived pain (low= 146, high= 72)	Cross-sectional (all measures completed within a day)	Pain (VAS), Depression (BDI-II), Global assessment of disease severity (Number of swollen/tender joints, Steinbrocker functional status), Inflammation markers (Blood monsters of C-reactive Protein (CRP))	People with higher pain are older and less educated Positive, independent correlations between pain, BDI-II and CRP levels (high sig.), Functional disability moderate interrelated with all variables	Bidirectional association between depression and inflammation markers involving neuroendocrine and autonomic nervous system Each effect of depression and CRP on pain was more evident in the absence of the other Repetitive noxious stimulation leads to generating pain without input from spinal cord →depressed people with RA can report high pain without CRP	Cross-sectional design do not allow causality Sample might not reflect population (selected from people visiting rheumatologists with better prognoses) Mainly self-report measures (overestimating depressive symptoms/pain) Cognitive function not confirmed (frontal lobe dysfunction can cause depressive symptoms) Adiposity

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
								level elevation Chronic pain and depression share common mechanisms of peripheral and central nervous system (amygdale)	possible mediator between depression and inflammation Smoking associated with elevating CRP and bidirectional linked with depression (serotonin level decrease)
	Smedstad 1995	Increased prevalence of psychopathology in RA compared to general population overestimated because symptoms of RA mistakenly interpreted as symptoms of anxiety/depression Model A: inflammation-mental distress-pain Model B: Inflammation-	N= 238, Mean age= 52, 75% female, (Disease duration less than 48 months)	NO	Cross-sectional	Blood samples (ESR, CRP), Joint inflammation (Ritchie Index), Depression, Anxiety (AIMS), Pain (VAS), Quality of Life (NHP), Education (ISCE),	ESR/CRP, depression, anxiety, higher in women, Ritchie Index and ESR/CRP separately correlate with pain Sig. association between anxiety/depression and pain when controlling for inflammation Relation between inflammation and distress decrease when controlling for pain	Pain is an intermediate variable between inflammation and mental distress Mental distress mainly secondary to pain Model B: Inflammation-Pain-Mental distress (+ sample with all forms of disease activity + no bias from help seeking	AIMS gives no reliable evidence for prevalence of anxiety/depression (not validated for strict psychiatric case definition)

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		pain- mental distress					No association between socio-demographics and pain	behavior)	
	Sharpe	Rates of depression are at least as high for patients recently diagnosed with RA compared to those with chronic RA Depression is hypothesized to be associated with coping, beliefs about illness Depression is assumed to be stronger related to pain and disability than disease parameters	N= 53, Mean age= 55, Disease duration= 12 months, 70% female	NO	Cross-sectional (N= 53), longitudinal (n= 22) measurements at 3, 6, 9, 15 and 21 months	Anxiety and Depression (HADS), Clinical indices (RAI, ESR, CRP), Disability (HAQ), Pain (VAS 3 times per day), Coping (CSQ) Illness perception (IPQ)	Mood deteriorated over time and RAI improved Cross-sectional: ESR, CRP no relation with depression. Pain, disability & anxiety positive correlated. Anxiety explained 50% variance in depression, disability further 20% Prospective: Across all time periods, initial level of depression consistently predict between 37 & 58% Pain also contribute to variance at time 5 and 6	Depression increase over time and is not stable Only last assessment, depression scores are lower → peak reached? Clinical parameters dissociated with depression Disability and pain stable over time in relation to depression, coping is only early in disease important Depression is associated with RA, even early in illness	Small sample Pain only via VAS Mainly correlations Mood measured via HADS (over-represent prevalence)

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
								Initially depressed → more pain, disability and depression at time 5, 6.	
	Tamiya	Depression and anxiety measured by VAS may be useful in routine clinical settings and cause little burden in time or discomfort. People unfamiliar with psychological tests, especially the illiterate and members of cultures infrequently exposed to such scales may respond more easily to brief VAS.	N= 145, Mean age= 53, Disease duration= 11 years, 100% female	n= 47 marked pain 7 days after initial test	Cross-sectional design	Pain (VAS), Depression (VAS, SDS, DSSI/d), Anxiety (VAS, MAS, DSSI/a), Life satisfaction (VAS), Inflammation (CRP)	VAS depression/anxiety scores correlate with depression/anxiety scales VAS depression highly correlate with VAS anxiety Pain moderate positively correlated with Anxiety, depression and moderately correlated with life satisfaction Anxiety explains 30% in pain variance, depression 17% Pain after 7 days highly correlated with initial pain Higher CRP levels correlate with higher pain	VAS measures are reliable Anxiety and depression correlate more with each other than all anxiety scales → not separated? Pain relates to degree of inflammation VAS can be easily used as screening before deciding to administer longer tests	The different scales for depression etc. not filled in by all subjects Subjects all female Cross-sectional design

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
	Vaeroy	An episode of major depression, occurring prior to onset of RA leaves patients at risk for higher pain levels	N= 100, RA subjects= 32, Mean age= 43, Disease duration= ?, 78% female	NO	Cross-sectional	Depression, Anxiety (HADS), Pain (VAS), Functional disability (VAS),	24% indicating possible depression 32% indicating possible anxiety Anxiety (n=32) and depression (n= 24), both correlated with subjective functional disability and pain Anxiety and depression highly correlated	Anxiety and depression both correlate with pain	Only 32RA subjects No information about disease duration HADS has low specificity Cross-sectional design Only correlations
Social support	Evers	Fear avoidance and catastrophic pain cognition leads to enhanced physical impairment and pain in RA. Social networks, perceived support and pain coping resources inhibit activity avoidance and affect the course of functional disability and pain positively in people with RA. Combination of	N= 78, Mean age= 57, Disease duration= less than 1 year, 69% female, 23% used inflammatory drugs	NO	5 years (measuring at diagnose, after 3 and 5 years)	Disease activity (ESR), Functional disability (grip strength, mobility and self-care scales of IRGL), Pain (IRGL pain scale), Personality (EPQ), Pain coping (PCI), Social support (IRGL social functioning scales)	Passive pain coping related to increase in functional disability after three years Social support and social networks related to less increase in functional disability, Demographics, personality, disease activity, pain, active pain coping not related to functional disability at 3 and 5 year follow-up Passive pain coping is independent predictor for disability	Passive coping predict not long-term pain but future disability Self-reported physiological reactivity to pain more directly linked to pain than cognitive/behavioral pain coping Avoidance and support factors important in a very early stage of disease with lasting effects	Small sample Low statistical power Important cognitive mediators missed (pain fear, heightened attention on body with expectation of increased pain) Sample in early stage (medication effective)

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		cognitive-behavioral, social factors, personality and biomedical factors have long-term pain and modifying effects → Long-term-effects of pain coping and social support on disability and pain in beginning RA					Lower education and less social support related to higher pain at 5 year (other variables not related to pain) Medication (NSAID) decreased disability at 3 years but not at 5 years		Generalization on longstanding RA difficult No reciprocal effects known between the factors
	Holtzman	Satisfaction with social support betters pain intensity/severity (coping strategy); dissatisfaction worsens pain level and effectiveness of coping with pain; more time points for detecting relation between coping, pain and social support	N= 73, Mean age= 56, Disease duration= 11 years, 77% female	NO	1 week (2 time per day measured: at lunch and before bedtime)	Background: demographics, disability, Daily records: Satisfaction in social support (emotional, informational, instrumental), Dissatisfaction in social support (same as in satisfaction), Coping (WOC-R), Pain (VAS)	Coping strategies, satisfaction in support associated with more functional disability,	Support encourage use of specific coping strategies and impact the effectiveness with which these are employed →support as coping resource Satisfaction in support associated with more coping strategies and effective employing of them and less pain in evening,	Small sample Short study length Causality impossible
	Minnock	The individual's	N= 58 (+	YES –	Cross-	General QoL	Least satisfaction	Social support	Small sample

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		Health status may be determined more by their own actions than by health professionals and public policy QoL in RA is partly determined by the level of family support and its quality depends on caregivers' knowledge of disease and treatment	the same number of caregivers), Mean age= 50 years, Disease duration= 14 years, 100% female	caregivers knowledge also added	sectional, descriptive study	(AIMS2), Satisfaction with social support (SOS-A), Patients' knowledge of RA and its treatment (PKQ),	with pain, most satisfaction with social support (corresponding improvement is needed (support least, pain most) QoL relatively high in patients Patients have greater knowledge of disease than caregivers, Knowledge not associated with health status (QoL)	highly important for QoL of RA patients Knowledge effect on QoL could not be observed	Cross-sectional design Knowledge not especially trained before testing
Depression, Anxiety, Social support, Distress,	Odegard	People with RA rank pain as most important symptom to be improved Also other relevant outcomes should be addressed more extensively by researchers. Depression prevalence in RA up to 46% Depression and anxiety are	N= 149, Mean age= 50 years, Mean duration= 2 years, 76% female		Longitudinal, with 10 year-follow-ups (1-,2-,5-,10-years follow-up)	Pain (VAS), Functional disability, pain, social activity & psychological status (AIMS), Global psychological distress with depression, anxiety, social dysfunction (GHQ) Physical disability (HAQ), inflammation (ESR)	Subjects maintain health status according to pain. Depression improved over follow-ups (9.7 at baseline, 5.4 at 1-year follow-up, 12.6 at 10-years follow-up) Anxiety decreased slightly over time (30% increased scores at baseline, during follow-ups varied between 23-	During 10-years follow-up, about 1 third had clinical important pain Anxiety/depression longitudinally interrelated with little change from time to time Anxiety always higher than depression (explanatory factors: female,	Subjects received medications

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		mostly associated but are two separate mental dimensions with different treatments					25% Women higher depression and anxiety scores than men (at every follow-up	physical disability, disease activity) Anxiety more frequent problem in RA than depression	
Depression, Anxiety, Stress, affect	Smith & Zautra	Anxiety and depression are related to weekly elevations in pain and increase exposure and reactivity to interpersonal stress. Larger effects assumed for anxiety by negative affect and larger effects for depression through positive affect	N= 170 (RA= 82, OA= 88), Mean age= 64, Disease duration= ?, 100% female	NO	Cross-sectional and prospective over 12 weeks	Baseline: Anxiety/depression (MHI), Functional disability (HAQ), Prospective: Pain (VAS via phone), Interpersonal stress (ISLE), Positive/negative affect (PANAS)	RA more functional disability, less stress than OA Entered separately, both, anxiety and depression direct effect on pain next week and indirect effect through negative and positive affect Depression interact with stress predicting current pain When entered together, Anxiety only direct effect on pain and indirect effect through negative affect, depression only indirect effect on pain through positive affect	Anxiety stronger direct effect on pain, indirect effect through negative affect Depression has no direct effect, only indirect through lower positive affect. Further higher pain in stressful weeks Depression and anxiety has to be separated in treatment of RA	Sample only women Anxiety/depression only measured at baseline (possible fluctuation) Anxiety and depression not measured by DSM-IV criteria

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
Depression, Stress, Affect	Zautra, Parrish, 2007	History of major depression leads to less pain coping abilities, more negative mood and less positive mood Kindling hypotheses: episodes of depression increase likelihood of future episodes with greater stress sensitization Scar hypothesis: depressive episodes leaves lasting personality changes with higher vulnerability to affective disturbances	N= 138, Mean age= 55, Disease duration= 11.5 years, 70% female n= 74 used for laboratory stress inductions	NO Sample divided in 3 groups: no depression history (n=71), one episode of depression (n= 30), two or more episodes of depression (n= 37)	Cross-sectional	Depression history (Mood disorder modules by DSM IV), Current depression (HDI), Pain (SF-36, WOMAC, RADAR (arthritis joint pain)), Stress (VAS), Positive affect (PANAS),	Higher current depression more pain (not influences by positive affect or stress) One episode of depression, less pain than two or more episodes No difference between one and no episode Multiple episodes higher in stress Positive affect less in one/multiple episodes Multiple episodes, current depression, baseline stress have main effect on pain Rising stress interact with depression history for predicting pain. Positive affect at high stress reduce impact of relation between pain and multiple depression episodes	Scar-/ Kindling hypotheses confirmed (evidence of greater disturbance at baseline for recurrent depression/greater stress-reactivity) Multiple depression episodes related to more chronic pain, greater stress reduced by ability to sustain positive affect	Relatively small sample Causal relation between depression and pain cannot resolved Major Depression involves difficulties as sleep disturbance and anxiety →not measured, but could have impact on pain
Depression, Social stress	Zautra, Smith, 2001	A stress-diathesis model has proven to be a useful	N= 87, Mean age= 64, Disease	NO	Longitudinal over 12 weeks	Pain (VAS), Depressive symptoms	Depressive symptoms related to increased arthritis	In weeks of high stress subjects reported high	Small sample Only women

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		paradigm for understanding how stress and individual differences, as depression may play a major role in chronic pain. Relationship between stress response and pain predicted by psychosocial models of the role of stress in furthering attention to pain and reducing the capacity to cope successfully	duration= ?, 100% female			(MHI), Positive and negative affect (PANAS), Interpersonal events (ISLE), Interpersonal stress	pain, negative affect/events, perceived stress, and weekly decreases in positive affect. Perceived stress is related to increased pain (relation strengthens with depressive symptoms) Positive events predict less pain. Positive events buffer relation between perceived stress and pain	pain Depression as risk factor for stress reactivity and increased pain Positive events/affect decreased problems Biopsychosocial model fit	Only relatively old subjects No causality
	Frantom	Psychiatric history may complicate coping process of RA, alter neuro-hormonal pathways, impact immune functioning	N= 41, Mean age= 54, Disease duration= 12.3 years, 68% female, RA patients n= 21 (PSY+), antidepressant	YES – RA patients without psychiatric history (n= 20; PSY-) Antidepressant medication for 15	Follow-up at 3-, 6- and 15 months	Psychiatric history (5 questions), Depression (CES-D), Pain (PPI Subscale, AIMS-P, VAS), Coping (AHI, CA, PCRT, ASES), Stress (HS)	At baseline: no differences, except higher depression in PSY+! Depression decreased in both groups at 15 months follow-up! Higher pain in PSY+ at 6-,15-months follow-up (not at 3 months)	Stress PERCEPTION is associated with higher pain for RA PSY+ →no causal interpretation possible Psychiatric history doesn't alter effect of	Quasi-experimental design Only self-report information (pain, psychiatric history) Limited generalizability on RA patients

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
			medication for 15 months	months			Pain in PSY- decreased at 15 months, remained stable in PSY+! No differences in coping! Stress differs sig. at all follow-ups measures (higher in PSY+)	antidepressant medication in RA Antidepressive treatment positive effect on pain scores in PSY-, but not in PSY+	PSY-
Depression, social support	Riemsma, 2000	The more pain and functional limitations RA patients have, the more depressed they will be. This relation can be influenced by social support (positive and negative) →more positive support, less depression, more negative support →more depression RA patients with greater pain are more depressed when receiving less social support and more	N= 197, Mean age= 63, Disease duration= more than 5 years, 61% female	NO	Cross-sectional	Depression (AIMS-2), Functional limitations (AIMS-2), Pain (AIMS-2), Positive support (SSL-12-I), Problematic support (Scale of Revenson)	Mean depression scores = 3.15 (on a range from 1-10) The more pain patients have, the more depressed they are (r=.51) Social support and depression not sig. related Problematic social support direct effect on depression (r=.33) and pain (r=.19) <u>Hierarchical regression</u>: pain delivers 29% explaining value on depression	More pain leads to greater depression More positive support →less depression (when controlling for pain) More negative support →more depression Problematic support stronger related to depression and pain Positive and negative support independent	Sample relatively old Cross-sectional study (no causality) More depressed people report social support elder as probematic

Outcome measure	Author	Models/Theories	Sample	Control group	Length of study	Variables/ Measurements	Results	Conclusion	Limitations
		problematic social support People get less depressed when getting more social support (stress-buffering hypothesis). Stressors = pain and functional limitations					Social support and problematic social support deliver further 6% Support (either positive or negative) not mediating between depression and pain	variables Positive support has buffering effect on relation of negative support and depression	

Appendix B

Methodological quality of included studies

Fatigue	A	B	C	D	E	F	Quality score
Fifield (2001)	1	1	1	1	1	1	6 (high)
Wolfe (1996)	0	0	1	1	1	1	4 (high)
Belza/Tack (1989)	0	0	0	0	1	1	2 (low)
Mancuso (2006)	1	1	1	1	0	1	5 (high)
Huyser (1998)	0	0	0	1	1	1	3 (medium)
Jump (2004)	1	0	1	1	1	1	5 (high)
Treharne (2008)	1	1	1	1	1	1	6 (high)
Pain & Fatigue							
Belza (1993)	1	1	0	1	1	1	5 (high)
Broderick (2008)	1	0	0	1	1	1	4 (high)
Covic (2006)	1	0	1	1	1	1	5 (high)
Fifield (1998)	1	1	1	1	1	1	6 (high)
Pollard (2006)	0	0	0	1	1	1	3 (medium)
Belza (1995)	1	0	1	1	1	1	5 (high)
Rupp (2004)	0	0	0	1	1	1	3 (medium)
Wolfe & Michaud (2009)	1	1	1	1	1	0	5 (high)
Smedstad (1996)	0	0	1	1	0	1	3 (medium)
Stone (1997)	0	0	0	0	1	1	2 (low)
Davis (2008)	1	0	0	0	1	0	2 (low)
Kojima (2009)	0	0	0	1	1	1	3 (medium)
Riemsma (1998)	0	0	0	1	0	1	2 (low)

Pain	A	B	C	D	E	F	Quality score
Brown (1989)	1	0	1	1	1	0	4 (high)
Brown (1990)	0	1	1	1	1	1	5 (high)
Chaney (2004)	0	1	0	0	1	1	3 (medium)
Covic (2003)	1	0	0	1	1	1	4 (high)
Frantom (2006)	0	1	1	0	1	1	4 (high)
Nicassio (1992)	1	1	0	1	1	1	5 (high)
Orengo (2001)	0	0	0	0	1	1	2 (low)
Eberhardt (1993)	1	0	0	1	1	0	3 (medium)
Kojima (2009)	0	0	1	1	1	1	4 (high)
Smedstad (1995)	0	0	0	1	1	1	3 (medium)
Sharpe (2001)	1	1	0	0	1	1	4 (high)
Tamiya (2000)	0	0	1	1	0	1	3 (medium)
Vaeroy (2004)	0	0	0	0	1	1	2 (low)
Evers (2003)	1	1	0	0	1	1	4 (high)
Holtzman (2004)	0	0	0	0	1	1	2 (low)
Minnock (2003)	0	0	0	0	1	1	2 (low)
Odegard (2007)	1	1	0	1	1	1	5 (high)
Smith & Zautra (2008)	1	0	0	1	1	0	3 (medium)
Zautra & Parrish (2007)	0	0	0	1	1	1	3 (medium)
Zautra & Smith (2001)	1	1	0	0	1	1	4 (high)
Riemsma (2000)	0	0	0	1	1	1	3 (medium)