Patient reported outcomes in rheumatoid arthritis

Data from the Oslo Rheumatoid Arthritis Register

Thesis by
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5.1.1 Study design .................................................................................................................. 50
5.1.2 Representativity of study population ........................................................................... 51
5.1.3 RA patients and population included in papers I-IV .................................................... 53
5.1.4 Patient-reported outcome measures ............................................................................. 54
5.1.5 Changes in management of patients with rheumatoid arthritis ................................. 56
5.2. Discussion of main results .............................................................................................. 57
   5.2.1 Development in the Oslo RA population over 15 years ........................................... 57
   5.2.2 Sleep disturbance in rheumatoid arthritis ................................................................. 60
   5.2.3 Gastrointestinal discomfort, NSAIDs and self-reported disease activity ............... 65
   5.2.4 Health information important to patients: The RAID score .................................... 67
6. Conclusions ......................................................................................................................... 69
   6.1 Answers to research questions ....................................................................................... 69
   6.2 Clinical implications ..................................................................................................... 70
7. References ............................................................................................................................ 71
8. Papers I - IV ......................................................................................................................... 87
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Abbreviations

ACPA  Anti-citrullinated protein antibody
ACR  American College of Rheumatology
AIMS  Arthritis impact measurement scales (also AIMS 2)
Anti-CCP  Antibodies to cyclic citrullinated peptide
CDAI  Clinical disease activity index
CI  Confidence interval
COX  Isoenzyme cyclo-oxygenase, isoforms I and II (COX-I and COX-II)
Coxib  Cox-2 inhibitor
CRP  C-reactive protein
DAS  Disease activity score (also DAS-28, based on 28 joint counts)
DMARD  Disease modifying antirheumatic drug
bDMARD  Biologic DMARD, also biologic originator (boDMARD) and biosimilars (bsDMARD)
sDMARD  Synthetic DMARD, also conventional synthetic (csDMARD) and targeted synthetic (tsDMARD)
EULAR  European league against rheumatism
ESR  Erythrocyte sedimentation rate
GI  Gastrointestinal
HAQ  Health assessment questionnaire
HLA  Human leukocyte antigen
HRQoL  Health related quality of life
MCS  Mental component summary from SF-36
MCID  Minimal clinically important difference
MCII  Minimal clinically important improvement
MDHAQ  Multi dimensional health assessment questionnaire
MHAQ  Modified health assessment questionnaire
MOS SF-36  Medical outcomes study 36-item short form
MOS sleep  Medical outcomes study sleep questionnaire
MRI  Magnetic resonance imaging
NSAIDs  Non-steroidal anti-inflammatory drugs
NRS  Numeric rating scale
OMERACT  Outcome measures in rheumatology
OR  Odds ratio
ORAR  Oslo Rheumatoid Arthritis Register
PASS  Patient acceptable symptom state
PCS  Physical component summary from SF-36
PROM  Patient reported outcome measure
PtGA  Patient global assessment of disease
RA  Rheumatoid arthritis
RADAi  Rheumatoid arthritis disease activity index
RAI  Rheumatoid attitude index
RAID  Rheumatoid arthritis impact of disease
RF  Rheumatoid factor
SD  Sleep disturbance
SDAI  Simple disease activity index
SES  Self-efficacy scales
SF6D  Short form 6 Dimensions Disability Index (derived from SF-36)
SPSS  Statistical package for the social sciences
TNF  Tumor necrosis factor
VAS  Visual analogue scale
15D  15 Dimensional questionnaire
List of papers


II. Austad C, Kvien TK, Olsen IC, Uhlig T. Sleep disturbances in patients with rheumatoid arthritis are related to fatigue, disease activity and other patient reported outcomes. Scand J Rheumatol 2016; online first june 2016: 1-9


1. Background

1.1 Introduction to rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints characterised by synovial and systemic inflammation, and presence of autoantibodies. Joint inflammation causes joint pain and stiffness and leads to bone erosions and cartilage loss. Ultimately, irreversible joint destruction may occur causing disability, and extra-articular manifestations may be present (1). RA tends to symmetrically affect small joints of the hands and feet, although larger weight bearing joints may also be affected. The disease has a significant negative impact on the ability to perform daily activities, health-related quality of life and mortality (2, 3). The female: male ratio is approximately 3:1 in most studies (4). RA is heterogeneous and may be described as a syndrome with different causes and abnormalities that share clinical manifestations (5). It is a complex disease with multifactorial aetiology, i.e. both genes and environment play a part (6, 7). A major subset is anti-citrullinated protein antibody (ACPA)-positive patients, which represents the larger fraction of RA patients (5).

Having RA is associated with an increased risk of comorbidities and increased mortality (8-10). Other extra-articular manifestations include fatigue, myalgia, vasculitis, anaemia, neuropathy, ophthalmic involvement (e.g. keratoconjunctivitis sicca (secondary Sjögren syndrome), scleritis, episcleritis and ulcerative keratitis), neurological manifestations, rheumatoid lung disease, pleuritis, pericarditis and pericardial effusions, amyloidosis, glomerulonephritis, rheumatoid nodules and Felty’s syndrome (11-13). The treatment of RA has changed over the last decades with the main treatment at present being disease-modifying antirheumatic drugs (DMARDs) (14).

1.1.1 Classification criteria

Clinical presentation of RA may vary between patients due to the systemic nature of the disease. Classification criteria were developed to ensure that patient included in studies indeed had RA, and for more than 20 years the criteria developed by the American College of Rheumatology (ACR) in 1987 (then: American Rheumatism Association,
ARA) were the most commonly applied criteria (15). These criteria are outlined in table 1. Patients had to satisfy at least 4 of the 7 criteria.

Some features of the 1987-criteria are only seen in established / long-standing disease, e.g. rheumatoid nodules and bony erosions on x-rays. New classification criteria, with increased sensitivity in early stages of the disease, were published in 2010 as a result of the collaboration between the European League Against Rheumatism (EULAR) and the ACR (16, 17). The 2010 classification criteria, more applicable for identification of early RA, are outlined in table 2. These criteria are aimed at classification of newly presenting patients with RA before permanent joint damage occurs. Patients with synovitis not explained by another joint disease who do not have typical radiographic changes for RA are classified as RA/non-RA according to serology, joint involvement, acute-phase reactants and symptom duration (16). However, patients with a swollen joint and typical RA-erosive disease can also be classified as having RA. Erosive disease, for use with the 2010 classification criteria, has been defined as a cortical break (i.e. erosion) in at least three separate joints from a predefined list of joint sites in hands and feet assessed on bilateral radiographs of hands/feet (18).

**Table 1:** The 1987 ACR classification criteria for RA. The first four must have been present for at least six weeks (15)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Abbreviated definition</th>
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<tbody>
<tr>
<td>1. <strong>Morning stiffness</strong></td>
<td>In and around joints, lasting ≥ 1 hour before maximum improvement</td>
</tr>
<tr>
<td>2. <strong>Arthritis of three or more joint areas</strong></td>
<td>≥ 3 joint areas have simultaneously had soft tissue swelling or fluid (not bony overgrowth) observed by physician</td>
</tr>
<tr>
<td>3. <strong>Arthritis of hand joints</strong></td>
<td>At least one area swollen in a wrist, MCP or PIP joint</td>
</tr>
<tr>
<td>4. <strong>Symmetric arthritis</strong></td>
<td>Simultaneous involvement of the same joint areas on both sides of the body (bilateral involvement of PIPs, MCPs or MTPs is acceptable without absolute symmetry).</td>
</tr>
<tr>
<td>5. <strong>Rheumatoid nodules</strong></td>
<td>Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician</td>
</tr>
<tr>
<td>6. <strong>Serum RF</strong></td>
<td>Abnormal amounts of serum rheumatoid factor by any method</td>
</tr>
<tr>
<td>7. <strong>Radiographic changes</strong></td>
<td>Radiographic changes typical of RA on PA hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints</td>
</tr>
</tbody>
</table>

MCP: Metacarpal phalangeal. MTP: Metatarsal phalangeal. PIP: Proximal interphalangeal. RF: Rheumatoid factor.
Table 2. The 2010 American College of Rheumatology / European League Against Rheumatism classification criteria for RA

| Target population (Who should be tested?): Patients who  
1) Have at least 1 joint with definite clinical synovitis (swelling)  
2) With the synovitis not better explained by another disease | Points |
<table>
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<tr>
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<tbody>
<tr>
<td><strong>A. Joint involvement</strong></td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>B. Serology (at least 1 test result is needed for classification)</strong></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive ACPA</td>
<td>3</td>
</tr>
<tr>
<td><strong>C. Acute-phase reactants</strong></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>D. Duration of symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

Calculating the score: add score of categories A-D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA

ACPA: Anti-citrullinated protein antibody. CRP: C-reactive protein.  
ESR: Erythrocyte sedimentation rate. RF: Rheumatoid factor.

1.1.2 Epidemiology

The prevalence of RA in the adult population is generally estimated to be 0.5 - 1% (19, 20), with the prevalence for Norway (Oslo and Troms) in the low end of this range (21, 22). The incidence of RA in Oslo is 25–50/100 000 per year (23). The incidence increases with age up to the 7th decade when a plateau is reached (23-25). Some data suggest that the incidence of RA has been decreasing, while other data do not support a continued incidence rate reduction (23-26).

RA prevalence varies across different geographic locations and populations. The highest reported prevalence is in certain native American populations; the Australian Aboriginals seem to be more resistant to RA while the overall prevalence in Australia is high (7). A lower prevalence is reported in Western Europe, while the prevalence in Africa is very low (7, 27, 28). In general, the prevalence of RA is low in some regions of the developing
world. However, a rural-urban gradient has been described in several of these countries where the rural prevalence approaches that of developed countries with predominantly white populations (7). Autoimmunity is a complex process. In order understand the geo-epidemiology of RA, both genetic and environmental factors should be considered (7).

**Gender differences and hormonal influences**

Women with RA experience more difficulties conceiving, and pregnancy outcomes is less favourable than in the normal healthy population (29). Pregnancy-associated improvement and post-partum exacerbation of RA may be the result of multiple hormonal and immunological changes during pregnancy that gradually return to pre-pregnant states after delivery (30). Hormones have an important influence on RA, and the use of the oral contraceptive pill and pregnancy are both associated with a decreased risk, though the postpartum period has been highlighted as a risk period for the development of RA (14). A gonadotropin-releasing hormone antagonist was explored in RA-patients and found to produce rapid anti-inflammatory effect in patients with high levels of gonadotropins (31). RA is more common in women than in men with a ratio of approximately 3:1 in most studies (4). Female sex has been associated with worse patient reported outcome measures (PROMs) (32, 33), greater work disability (34) and a greater risk of requiring orthopaedic surgery (35).

**Comorbidity**

RA is associated with increased risk of a range of comorbidities leading to premature death in RA (9, 10), and this aspect of RA has received increased focus over the last years. Cardiovascular diseases (CVD) have a high prevalence in RA (36). This increased occurrence of CVD in RA-patients cannot fully be explained by increased prevalence of traditional cardiovascular risk factors, but seems to be associated with inflammatory activity and autoantibody positivity (10, 37, 38). During the last years there has also been an increased awareness on additional comorbidities in RA, e.g. the development of certain malignancies and increased incidence of infection. Comorbidities in RA patients seem to be important in the higher death rate observed on RA-patients (38). With respect to cancer, RA-patients are at an increased risk of lung cancer and lymphoma, but no increase in risk has been demonstrated for colorectal, breast, cervical and prostate cancer or melanoma (39).
The treatment of RA, e.g. glucocorticoids, and smoking influence the development of these comorbidities, and the presence of chronic inflammation further adds to this risk of developing these comorbidities. Comorbidities may have a negative impact on patients’ health by increasing functional impairment, reducing work productivity, decrease quality of life and shorten life-expectancy (38, 40). A higher degree of functional impairment is seen in patients with several and higher number of comorbidities, and osteoporotic fractures may influence the physical status in RA patients (38, 41). A comparison of malignancy-rates in RA patients from several registers across the world found age and sex to be the main determinants, while RA-characteristics were not strong determinants of cancer risk (42).

**Mortality**

Having RA is associated with increased mortality (9, 10, 43-45), and a widening mortality gap between the RA population and the general population has been described (44). On the other hand, a Canadian study found a decreased mortality rate in RA patients over time but an unchanged mortality gap compared with non-RA patients (46). Women with RA were found to have significantly increased mortality due to respiratory and CVD, although the increased risk of respiratory mortality was observed only in seropositive RA patients (47). A study of male veterans with RA demonstrated overall an increased mortality. However, use of methotrexate in this population was associated with a decreased mortality (48).

In a Swedish study, no increased mortality was seen for RA patients versus age- and sex-matched controls, and no RA disease-related factors predicted mortality (49). On the other hand, extra-articular RA was associated with increased mortality in the US (50). A meta-analyses of all-cause-mortality associated with exposure to Tumor necrosis alpha (TNFα) inhibitors in RA did not find an increased risk (51).

**1.1.3 Pathogenesis**

RA is a complex immune disease involving interplay between cellular and molecular pathways, genetic factors, environmental triggers and chance. These factors ultimately
lead to synovial joint inflammation and damage, although the exact mechanisms are not yet fully understood (6, 52, 53).

Normal synovium is thin, only a few cell-layers thick. Important cell-types found in inflammatory synovial tissue (synovitis) include T- and B-cells, macrophages, plasma cells, fibroblasts and natural killer (NK) cells. The immune activation in RA leads to inflammation that also includes blood vessel proliferation (hypervasculation) and increased tissue volume due to oedema. This process is partly determined by genetic predisposition and influenced by environmental factors. The inflamed synovium grows with villous like-projections on its surface making the tissue rough and uneven. This thickened tissue pannus) invades the small space between the joints’ bones and covers the surface of the bones and their articular cartilage. Pannus-development may cause joint damage in addition to inflammation, pain and swelling.

Both innate and adaptive immune systems are involved in RA pathogenesis. T-cells are triggered by dendritic cells through a two-signal activation. In the first antigen-specific signal, dendritic cells, major histocompatibility complex (MHC) class II molecules (e.g. HLA-DR) and interleukin (IL)-2 are involved. The second signal involves the co-stimulatory molecules CD80/86 on the antigen-presenting dendritic cell and CD28 on T-cells. Macrophages, mast cells, and natural killer cells contribute to production of cytokines such as TNFα and IL-6 (53, 54).

Synovial CD4 positive (CD4+) T-cells, also called helper cells, may be activated by T-cell receptor and co-stimulation pathways and by cytokine- or toll-like receptor driven stimuli. IL-12, IL-23, IL-6 and transforming growth factor are found in the inflamed synovial tissue. These factors promote the differentiation of T-helper-1 (TH1) and TH17 cells, which are characterized by IL-17 production. Activated T-cells promote activation of other cells, e.g. leukocytes, B-cells and cytotoxic activity of CD8+ effector T-cells. Other cells are activated through direct cell contact, e.g. macrophages, fibroblasts and endothelial cells (54). The inflamed synovium may cause degradation of bone and cartilage leading to joint destruction.

A key feature in the pathogenesis of RA is the activation of osteoclasts through the receptor activator of the nuclear factor κB ligand (RANKL)/osteoprotegerin (OPG)
pathway (55). RANKL is a member of the TNF superfamily whereas OPG belongs to the TNF receptor family. There is a complex system of bone remodelling that includes the sequential phases of activation, resorption, reversal, formation and termination. The coupling factor between bone resorption and formation is the RANKL/OPG pathway, and the balance between RANKL and OPG determines the degree of proliferation and activity of the osteoclasts (55).

1.1.4 Risk factors for disease development and progression

Genetics

RA tends to cluster in families, and results from twin studies indicate that approximately 50-60% of the risk of RA is attributable to genetic factors (6, 53, 56). First-degree relatives of a RA patient have about 1.5-fold increased risk of developing the disease (57). The heredity accounted for by the main genetic risk factor, the HLA-DRB1 alleles (also known as the shared epitope, SE), is around 30% and has consistently been demonstrated in many populations throughout the world. PTPN22 (protein tyrosine phosphatase non-receptor type 22) is another important genetic risk factor for developing RA (6, 58, 59). Having double copies of SE yields a higher risk than a single copy and the highest risk of developing RA is seen with double copy of SE in combination with PTPN22 in seropositive smokers (60, 61). Several susceptibility genes for RA have been identified. Genome-wide association studies (GWASs) for autoimmune diseases have identified different risk loci and provided insights into the aetiology of each disease. Many of these loci, such as PTPN22, STAT4 and IRF5, are not only found in RA but also shared among different autoimmune diseases (62, 63). The combination of risk loci may in part determine an individual’s susceptibility for the disease.

Genetic predisposition, caused by multiple genetic variants, is stable over time. On the other hand, epigenetic alterations are cell-type specific, can evolve over time and may have an effect on gene expression patterns, which ultimately determines cell function. Genetic influence on disease development may be by epigenetic changes, inherited through cell divisions, mutations or polymorphisms (64).
Biochemical and immunological markers

In RA, the most commonly used inflammatory biomarkers are the ESR and CRP. In patients with active disease these markers are usually, but not always, elevated. ESR and CRP decline with treatment, and can be used in the monitoring of disease activity (1). Elevated ESR and CRP at the onset of RA are predictive of a more aggressive disease and potentially worse prognosis (65, 66).

RA is commonly classified as seropositive or seronegative depending on whether or not ACPA and/or RF are present (6). ACPA is most commonly measured as anti-cyclic citrullinated protein (anti-CCP) antibodies. Anti-CCP antibodies are directed against the citrullinated residues of proteins. RF is an antibody directed against the Fc part of immunoglobulin G (IgG) although it can be of any immunoglobulin subclass (IgA, IgG, IgM). Approximately 60-80% of RA-patients will have RF detectable at some point during the disease, and RF is predictive of a more aggressive erosive disease with poorer long term function (67). Seropositive individuals have an increased risk of developing RA, and this risk increases with higher levels of RF and anti-CCP (6, 68-70). ACPA may be detected years before RA becomes a manifest disease (6). Sensitivity and specificity for RF and anti-CCP are high, with anti-CCP having a greater specificity and similar sensitivity as RF (70-72). Anti-CCP and RF are associated with erosive joint disease, functional disability and extra-articular disease (67, 73).

Smoking

Smoking is an important environmental risk factor (6, 74, 75). There is a substantial gene-environment interaction between HLA-DR shared epitope, PTPN22 risk allele and smoking leading to an increased risk of developing RA in anti-CCP positive male patients (6, 61, 76-78). Smoking is, among other mechanisms, thought to cause dysfunction of T-lymphocytes by modulating the immune system via reducing natural killer cells and depressing hormonal cells and cell-mediated immunity (74). Smokers are less likely to respond to methotrexate and TNF-inhibitors (79).

Microbiota

It has been hypothesised that exposure to infection may act as a trigger for RA, and a number of agents have been implicated e.g. Epstein-Barr virus, parvovirus, protest
mirabilis, mycoplasma, porforymonas gingivalis (p.gingivalis) and gut microbiota (80). A study by Block et al found that mice treated with antibiotics eliminating gut bacteria did not develop arthritis irrespective of whether or not they were IL-17 deficient (81), suggesting that gut microbiota regulates the differentiation of follicular T-helper cells that plays an important role in helping B-cell antibody response.

**Periodontitis**

Periodontitis has been linked to RA in epidemiological studies (82), in particular p.gingivalis. Periodontal infection with p.gingivalis may be involved in initiation and perpetuation of inflammation in RA as p. gingivalis can cause protein citrullination (82). A systematic review and meta-analysis suggest that non-surgical periodontal treatment of periodontitis could lead to improvement in markers of RA disease activity (83).

**Other risk factors**

Silica dust, mineral oils and other airway exposures have been associated with an increased risk of developing RA (84-88) Lower socio-economic status and low level of formal education are other factors associated with an increased risk of developing RA independent of smoking (89-91). These factors were more pronounced for RF positive patients and more in women than men (89). An inverse association with alcohol intake has been demonstrated (78, 90, 92), although others found no association (93). On-going work at the Karolinska Institute examines the effect of physical workload and cold environment on the risk of RA, based on the EIRA study.

**Associations and predictors of more severe RA**

Some factors may predict a more severe disease, e.g. the HLA-DRB1 locus that is associated with radiological severity, mortality and treatment response in RA-patients (94). The presence of ACPA is more strongly associated with the shared epitope than RF, and ACPA has been more directly implicated in the pathogenesis of RA. Anti-CCP antibodies and RF are associated with a more aggressive erosive joint disease with worse functional disability and extra-articular disease (65, 73, 95). Smokers are less likely to respond to methotrexate and TNF-inhibitors (79), hence may have higher risk of radiographic progression in early RA (96). Female sex has been associated with worse
PROMs (32, 33), greater work disability (34) and a greater risk of requiring orthopaedic surgery (35).

1.1.5 Pharmacological treatment

The emphasis in RA management today is on early diagnosis and intervention to prevent the development of joint damage and subsequent disability (97), and treatment usually includes both pharmacological and non-pharmacological interventions/treatments. In this thesis only pharmacological treatment is discussed, and due to the major changes that have occurred during the past decades, the different treatment options are presented chronologically.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) and thereby impairs the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes (98). The extent of enzyme inhibition varies among the different NSAIDs (99, 100). The two main COX-isoforms are COX-I and COX-II. COX-I is variably expressed in most tissues and may be described as a "housekeeping" enzyme that regulates normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function).

COX-II is usually undetectable in most tissues, but the expression is increased during states of inflammation. COX-II is constitutively expressed in the brain, in the kidney, in bone, probably in the female reproductive system (101). Most traditional NSAIDs inhibit both COX-I and COX-II. Selective Cox-II inhibition may produce less gastric toxicity, although there is a concern for delayed healing of gastric erosions/ulcers (102). According to half-lives, NSAIDs may be divided into "short-acting" (<6 hours) or "long-acting" (>6 hours).

Acute and chronic painful and inflammatory conditions may be treated with NSAIDs, and use of NSAIDs may reduce the need for stronger analgesics such as opioids. NSAIDs may worsen renal impairment, increase risk of gastropathy and cause GI-bleeding, reversibly inhibit platelet function, increase risk of CVD and worsen asthma.
NSAIDs may interact with a number of other medications, including glucocorticoids and methotrexate, that are commonly used in treating RA (103, 104). NSAIDs should be used with caution during pregnancy and avoided in the last trimester (105).

NSAIDs are effective in treating pain, however, NSAIDs do not halt radiographic progression in RA, and the importance for use has declined with the introduction of more efficient disease modifying treatments.

**Selective COX-II inhibitors (coxibs)**

Selective COX-II inhibitors (coxibs) inhibits COX-II 200- to 300-times more selectively than COX-I in therapeutic doses, and the analgesic effect is comparable to non-selective NSAIDs (106). Coxibs have reduced gastro-duodenal toxicity as COX-1 is involved in gastric cytoprotection, however, there is an increased risk of CVD. From the late 1990s onwards several coxibs were introduced. In 2004-2005 two coxibs were withdrawn from the market due to an increased risk of CVD. In the last few years, the knowledge of increased risk of CVD with both NSAIDs and coxibs has led to a more general warning limiting their use.

**Glucocorticoids**

Glucocorticoids have been used in RA-treatment since 1948 (107), and are still considered an important adjuvant to disease modifying antirheumatic drugs (DMARDs) (14, 108). Glucocorticoids are immunosuppressive and anti-inflammatory, and effectively suppress signs and symptoms of RA (108). Systemic glucocorticoids may reduce the rate of progression in the earlier phases of RA and may therefore be described as disease modifying (108-110). Glucocorticoids have a rapid onset of action and may be useful as bridging therapy while waiting for the full effect of DMARDs (108, 110). Due to dose-dependent adverse effects, such as bone loss/osteoporosis, peptic ulcers, infection and cardiovascular disease, the use of glucocorticoids has been limited. However, adverse effects can be reduced by using the lowest effective dose for as short a period as possible (108, 111, 112). Intraarticular glucocorticoids may be useful in localised treatment of arthritis without patients getting the systemic effects, and may be important in a tight control strategy (113).
Disease Modifying Antirheumatic Drugs

The main treatment of RA is disease modifying antirheumatic drugs (DMARDs), commonly described as either synthetic (sDMARDs) or biological (bDMARDs or biologics) (14, 114). These terms refer to the production of the drugs; biologics are created by biologic processes as opposed to sDMARDs that are produced by a chemical synthesis. An overview of synthetic and biological DMARDs is presented in table 3.

Synthetic Disease Modifying Antirheumatic Drugs

DMARDs have been available since gold was introduced in 1929 (115). Gold, applicated as injections or tablets was in regular use until the 1980s when use gradually declined due to the introduction of newer drugs with less side effects, better safety and efficacy and lower cost. The exact mechanism of action of gold in RA remains uncertain (116). A mechanism of action through MHC-II antigen class II antigen and human leukocyte antigen (HLA)-DRB1 or by blocking prostaglandin E2 production has been suggested (117-119).

Methotrexate (MTX) is an anti-metabolite that was developed as an anti-cancer drug in the 1940s. The first report of possible benefit in RA was published in 1951 with the first randomised controlled trial (RCT) published in 1985. This RCT demonstrated significant effect of MTX in RA (120). From this point onwards MTX has been part of the routine RA-treatment, and is generally recommended as the first DMARD in the majority of RA-patients by both EULAR and ACR (14, 114, 121, 122). In 2014, new nomenclature for DMARDs was introduced; sDMARDs were either classified as conventional synthetic (csDMARD), which included MTX, hydroxychloroquine (HCQ), leflunomide (LEF) and sulfasalazine (SSZ), or targeted (tsDMARD) that specifically targets janus kinases (JAKs). JAKs are so far not approved for use in Norway, hence not further described in this thesis. MTX, HCQ and SSZ may be used in combination as trippel-therapy.

MTX may be considered an “anchor-drug” to which other drugs can be added as combination therapy (14, 114). This combination of drugs may increase clinical and radiographic efficiency as well as reducing the production of anti-drug antibodies (ADAb) as opposed to bDMARD monotherapy.
**Biological Disease Modifying Antirheumatic Drugs**

From the late 1990s bDMARDs, which include a number of medications with different mechanisms of action, were included. On a group level, the bDMARDs were found to effectively reduce inflammation in RA and inhibit joint damage to a greater extent than what could be expected by non-biologic DMARDs (6, 123, 124). The effect of TNF inhibitors on mortality was evaluated in a meta-analysis based on 23 different studies with RA-patients. Use of TNFi in itself did not confer an increased mortality-rate (51).

**Table 3.** Disease modifying antirheumatic drugs for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synthetic DMARDs</strong></td>
<td>Methotrexate</td>
</tr>
<tr>
<td>(sDMARDs)</td>
<td>Sulphasalazine</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td></td>
<td>Leflunomide</td>
</tr>
<tr>
<td></td>
<td>Gold</td>
</tr>
<tr>
<td><strong>Biologic DMARDs</strong></td>
<td>Adalimumab (TNF inhibitor)</td>
</tr>
<tr>
<td>(bDMARDs)</td>
<td>Abatacept (selective T-cell co-stimulator blocker)</td>
</tr>
<tr>
<td></td>
<td>Anakinra (IL-1 inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Etanercept (TNF inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Infliximab (TNF inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Rituximab (Cell-depleting agent; monoclonal antibody, binding to CD20-antigen on B-lymphocytes)</td>
</tr>
<tr>
<td><strong>Available after the</strong></td>
<td><strong>Certolizumab pegol (TNF inhibitor)</strong></td>
</tr>
<tr>
<td>last data-collection</td>
<td><strong>Golimumab (TNF inhibitor)</strong></td>
</tr>
<tr>
<td>in ORAR 2009</td>
<td><strong>Tociluzimab (IL-6 inhibitor)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Etanercept biosimilar (SB4)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Infliximab biosimilar (CT-P13 and SB2)</strong></td>
</tr>
</tbody>
</table>

There are currently five different TNF-α inhibitors (TNFi): Infliximab (a chimeric human-murine monoclonal antibody), etanercept (a recombinant human TNF receptor), adalimumab (a human monoclonal antibody), certolizumab pegol (PEGylated anti-TNF) and golimumab (a human monoclonal antibody). During the last two years, biosimilar DMARDs (bsDMARDs) have also become available for infliximab (CT-P13 and SB2) and etanercept (SB4). All TNFi have been proved efficacious in patients with inadequate
response to MTX (97). Also, inhibition of bone erosions has been demonstrated in studies with TNFi (97).

bDMARDs with other mechanisms of actions have been introduced after the first TNFi: Rituximab is a chimeric anti-CD20 monoclonal antibody causing selective depletion of CD20+ B cells; abatacept is a selective T-cell co-stimulation modulator (CTLA4-Ig) and tocilizumab that is a humanised antihuman IL-6 receptor antibody (97). Anakinra is an IL-1 inhibitor that may be used in RA, with or without in combination with MTX. Rituximab is mainly used in seropositive RA-patients in combination with MTX (114), abatacept is also used in combination with MTX while tocilizumab may be used in monotherapy or in combination with MTX (97).

There is an increased risk of infection with the use of bDMARDs. It is especially important to monitor for infections at the beginning of treatment and in elderly patients (125).

1.1.6 Window of opportunity

The importance of early intervention in RA has been demonstrated in a number of studies. The concept of “window of opportunity” refers to an early phase of the disease where the disease process, at least partly, may be modifiable or reversible before joint damage occurs (126), and studies have demonstrated that all therapies work better in early disease than during established RA. This phase has been described as a “window of opportunity” for intervention (127, 128). Treatment is more likely to be successful in this period and the patients should ideally be referred to a rheumatologist at an early stage to establish a diagnosis and start treatment (14, 129). The concept of an early diagnosis was important when developing the new classification criteria for RA (16).

1.1.7 Treat to target

Several studies have shown that intensive patient management improves disease activity and halts radiographic progression better than routine patient management (130-132). This is achieved by combining different DMARDs and/or biologics, and is incorporated into the treatment recommendations for RA where the importance of starting treatment
early in the disease is emphasised (112, 114, 130). Early and more aggressive treatment for RA has been recognised as important to reduce long term joint damage and subsequent disability (129, 133), and the goal of treating to target is remission rather than merely improvement in signs and symptoms (134). The efficacy, toxicity, and cost of the available agents vary widely, and the course of RA and patients’ response to therapy is heterogeneous. Regular monitoring of disease activity and monitoring adverse events should guide decisions on choice and changes in treatment strategies (133, 134).

1.2 Patient reported outcomes and measures of health related quality of life

The patient perspective and patient reported outcomes have become increasingly recognised as important in rheumatic diseases over the last decades, and patient representatives participate in meetings such as the Outcome Measures in Rheumatology (OMERACT) (135).

Patients may suffer from functional disability and reduced Health Related Quality of Life (HRQoL), and PROMs are important in routine follow-up, in observational studies and clinical trials. PROM-questionnaires are easily administrated, feasible, can be answered in a short period of time, and may provide important information to the treating physician with respect to whether the patient perceives a change in disease activity that may warrant a change in medical treatment. Last, but not least, this information may also be time-saving for the physician (136).

The simplest forms of PROMs are single questions about e.g. pain, fatigue, morning stiffness (intensity or duration) and global disease activity scored on a Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) or Likert scale. These measures are widely applied in RA, either alone or as part of more extensive patient reported questionnaires.

1.2.1 Pain

Pain is common, perhaps the most prominent symptom in most patients with RA, and the symptom people with RA have prioritised highest for improvement (137, 138). Patient
reported pain can be measured by different questionnaires. The simplest pain question is a 0–100 VAS or a 0-10 numeric rating scale (NRS) where 0= no pain and 100 (for VAS) or 10 (for NRS) = worst possible pain. Pain is also measured as part of other questionnaires e.g. the Arthritis Impact Measurement Scale 2 (AIMS 2) pain scale (139), Rheumatoid Disease Activity Index (RADAI) (140), the Rheumatoid Arthritis Impact of Disease (RAID) (141) and the medical outcome study (MOS) Short-Form 36 questionnaire (SF-36) (142). For details on the individual questionnaires please refer to the respective sections below.

### 1.2.2 Patient reported health state

**Health Related Quality of Life**

Health related quality of life (HRQoL) is a multidimensional concept that incorporates physical, psychological and social aspects of life. HRQoL can be measured by different disease specific and generic questionnaires such as SF-36, SF-6D and EQ-5D.

**Medical Outcome Survey Short Form 36**

SF-36 is a generic measure used to assess HRQoL in patients capturing 8 health dimensions (physical and social functioning, role-physical, bodily pain, general health, vitality, role-emotional and mental health). Each of the eight scales are transformed into a 0–100 range (0= worst possible health state, 100=perfect health) (142). Mental (MCS) and Physical (PCS) Component Summary scores can be calculated from SF-36 (table 3 and figure 1).

**SF-36 Physical Component Summary**

The PCS captures the physical components of SF-36, i.e. physical function, role physical, bodily pain and general health. However, there is some overlap with the MCS as vitality and general health are included in both summary component and the PCS is not strictly measuring physical function. Please refer to table 4 and figure 1 for more details of SF-36 (142, 143).
### Table 4. The Short-Form 36 (SF-36) Measurement Model

<table>
<thead>
<tr>
<th>Item</th>
<th>Scale</th>
<th>Component score</th>
</tr>
</thead>
</table>
| Vigorous activities  
Moderate activities  
Lift/carry groceries  
Climb several flights  
Climb one flight  
Bend/kneel  
Walk mile  
Walk several blocks  
Walk one block  
Bathe, dress       | Physical function   | PCS             |
| Cut down time  
Accomplished less  
Limited in kind  
Had difficulty | Role physical       |                 |
| Pain magnitude  
Pain interfere | Bodily pain         |                 |
| EVGFP* rating  
Sick easier  
As healthy  
Health to get worse  
Health excellent | General health      | Both MCS and PCS|
| Pep / life  
Energy  
Worn out  
Tired | Vitality            |                 |
| Social extent  
Social time | Social function     |                 |
| Cut down time  
Accomplished less  
Not careful | Role emotional      | MCS             |
| Nervous  
Down in dumps  
Peaceful  
Blue/sad  
Happy | Mental health       |                 |

*EVGFP: Excellent, Very good, Good, Fair and Poor.

PCS/MCS: Physical / Mental Component Summary

In scoring the eight SF-36 scales, all but one of the 36 items (self-reported health transition) is used. Each item is used to score one scale only (142).
Figure 1. SF-36 Scales measure physical and mental components of health.

1.2.3 Patient Reported Disease Activity

Patient Global Disease Activity VAS

Patient reported global disease activity may be measured by a 0–100 VAS scale (0 = no problems and 100 = worst possible) or a numeric rating scale (NRS) 0-10 where 0= no and 10 = worst possible problems.

Rheumatoid Arthritis Disease Activity Index (RADA1)

The RA disease activity index (RADA1) is a five-item questionnaire reporting disease activity without the need for clinical examinations or blood tests (140, 144). The five questions are listed below:

(1) Global RA-disease activity (NRS, 0-10)
(2) Disease activity in terms of current swollen and tender joints (NRS, 0-10)
(3) Arthritis pain (NRS, 0-10)
(4) Duration of morning stiffness (Likert scale, 0-6)
(5) Self-assessment of joint tenderness on a mannequin or joint list (16 joint areas scored 0–3, a total score of 0-48 possible)
The joint list asks about pain in the left and right shoulders, elbows, wrists, fingers, hips, knees, ankles and toes. A higher score on the 0-10 NRS indicate more disease activity. The scores in 4 and 5 are transformed on the same scale as the first three questions, i.e. 0-10. If all items are answered, the scores are added and divided by the number of items to provide a single index of patient assessed disease activity (140).

1.2.4 Health utility

EuroQol 5-dimension

EuroQol 5-dimensions questionnaire (EQ-5D) is a standardised generic instrument for use as a measure of health outcome. The five dimensions are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels (EQ-5D-3L): no problems, some problems and extreme problems, i.e. a total of 243 health states can be defined. EQ-5D is applicable to a wide range of health conditions and treatments, and provides a simple descriptive profile and a single index value for health status range. The EQ-5D preference-based measure can be regarded as a continuous outcome scored on a -0.59 to 1.00 scale where 1.00 indicates full health, 0 indicates dead and the negative health states represent certain health states valued as worse than dead (145).

SF-6D

The generic measure SF-36 was not originally developed for use in health-economic evaluation (146). Utility measured by the short form 6 dimensions (SF-6D) was constructed by revising 11 items from the original SF-36 into a 6-dimensional health state classification (147), these six dimensions each have between two and six levels. The SF-6D provides a single index-measure of health (148), and defines 18,000 health states by selecting one level from each dimension (147). The range is 0–1. However, a living person will obtain a score of at least 0.29, and 1.00 denotes perfect health (149). All respondents to the 11 items (used in SF-6D) in the original SF-36 can be assigned a SF-6D score (149).

The 15 Dimensional questionnaire

The 15 dimensional questionnaire (15D) is a generic, self-administered instrument for measuring HRQoL across 15 dimensions. These 15 dimensions are mobility, vision,
hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Each dimension has five ordinal levels, range 1–5, where no symptoms/problems =1 and extreme problems/unable to do =5.

A single index, representing the overall HRQoL, is calculated by using a mathematical model considering the level of the answers and the weight of each dimension. On a 0–1 scale, 0=being dead, (0.0162 = being unconscious or comatosed) and 1=no problems in any dimension (150). 15D may also be used as a profile measure (150).

1.2.5 Physical function

The Stanford Health Assessment Questionnaire (HAQ) and its modifications

Measuring physical function in RA patients is important. A change in physical function may indicate a change in disease activity, e.g. poorer physical function with active disease causing pain and structural change. One of the most widely used questionnaires for RA is the Stanford Health Assessment Questionnaire (HAQ) (151). HAQ measures physical disability in RA (152), and contains 20 questions about performance of activities across 8 categories, each question scored 0: ”without any difficulty”, 1: ”with some difficulty”, 2: ”with much difficulty” or 3: ”unable to do”. The highest score for any of the questions in each category counts as the “category score”, and the use of aids or devices within a category automatically yields a score of 2 or more (“upgraded” HAQ). The total score may also be referred to as the HAQ disability index. HAQ is the overall score from the eight categories, with a range 0-3 where a higher score represents worse physical function.

Several modifications of HAQ have been published: The modified HAQ (MHAQ) is a simplified version with one question/item per ADL category (151). The scoring of MHAQ is the mean of the 8 items (dressing, arising, eating, walking, hygiene, reach, grip and outside activity). The MHAQ score originally had a range from 1 to 4 (corresponding to the old Steinbrocker classification of functional status), later it became more common to score MHAQ 0–3 as the original HAQ. Either way, a higher score represents worse physical function. There is a substantial “floor-effect” (i.e. a substantial number of
patients have normal scores) for both HAQ and MHAQ. This effect is more pronounced for MHAQ than for the original HAQ (153, 154).

Several other modifications of HAQ has been made: HAQ-II has 10 items and may be easier to administer and score than the original HAQ (155). MHAQ has 8 items and can easily be administrated in longitudinal studies as well as in clinical practice. Studies found HAQ and MHAQ to be strongly correlated and both are sensitive to change in clinical trials (153). The multi-dimensional HAQ (MDHAQ) questionnaire contains 10 ADL items, including “advanced” ADL items, in order to overcome the above-mentioned floor effect. 3 psychological items (sleep, anxiety and depression) are scored 0–3 as the original HAQ. In addition, MDHAQ includes 5 separate VAS for pain, global status, fatigue, morning stiffness duration and change in status (156). Upgrading of score is not allowed in shortened versions of HAQ such as the MHAQ (151) or the multi-dimensional HAQ (MDHAQ) (157). HAQ and MHAQ have been validated in Swedish, which is similar to Norwegian (158, 159).

The Patient-Reported Outcomes Measurement Information System (PROMIS) assesses physical function using the 20 items in the original HAQ, however an additional 5th response category (“with a little difficulty”) is added and there is a different scoring algorithm (160). This is a relatively new variation of HAQ, and has been used in the recently published ARCTIC study (134).

**Arthritis Impact Measurement Scale 2**

The Arthritis Impact Measurement Scales (AIMS), and its modification AIMS2, are multi-dimensional instruments assessing physical, emotional and social well-being in RA-patients (139). AIMS consists of nine subscales: mobility, physical activity, dexterity, household activities, activities of daily living (ADL), social activities, anxiety, depression and pain (139). AIMS2 contains 12 subscales that may be combined into a 5-component model reflecting the physical dimension, affect, social interaction, symptoms (pain) and role (work) (161). Each section is scored on a range 0-10, with a total health score of 0-60. AIMS was originally developed in 1980 as a multidimensional health status instrument specific for arthritis patients (139), and information on comorbidities in the
Oslo RA register (ORAR) was collected using the AIMS2 checklist of comorbidities (161).

1.2.6 Rheumatoid Arthritis Impact of Disease (RAID)

The RA Impact of Disease (RAID) score is a patient derived composite measure of the impact of RA. RAID consists of seven domains capturing pain, functional disability assessment, sleep, fatigue, physical and emotional well-being and coping (141). Each item is scored on a 0–10 NRS and weighted according to their importance for patients to produce a final RAID score (141, 162). The RAID score is computed using the standard weight of the domains: pain 0.21, functional disability 0.16, fatigue 0.15, sleep difficulties 0.12, emotional well-being 0.12, physical well-being 0.12 and coping 0.12 (162). Minimum Clinically Important Improvement (MCII) for RAID has been suggested, and a maximal value of 2 has been suggested as defining acceptable status (163).

1.2.7 Sleep disturbance

Sleep disturbance (SD) as a PROM in RA-patients has received less attention than many other PROMs. SD is a disruption or deviation from a normal sleep-pattern that may include difficulty falling asleep, poor quality of sleep, non-restorative sleep, numerous nightly awakenings, early morning awakening, excessive daytime sleepiness and fatigue (164). The quantity of sleep does not necessarily reflect the quality of sleep. Patients with RA may experience “non-restorative sleep” (165), and awake unrefreshed after what may appear to be uninterrupted sleep. To help distinguish secondary sleep disorders from non-restorative sleep, objective evidence may be obtained using an overnight sleep polysomnography (165). SD has been reported in a number of rheumatic diseases including RA (164), and the bidirectional relationship between SD and fatigue has been demonstrated (166). Sleep loss may worsen fatigue and pain in RA (167, 168), and pain may cause SD (166, 168-170). OMERACT has identified sleep as one of the key outcomes important to the patients (135, 171-173). Studies have demonstrated impaired sleep quality by pain, disease activity, fatigue, and depression (174, 175). Poor RA disease control has been associated with reduced sleep quality and daytime sleepiness.
(176), possibly because cytokines and immune functions have been found to have a direct effect on the central nervous system which again is linked to the sleep-awake regulation (165). These cytokines are known treatment targets in rheumatic diseases. Also, fatigue, pain and depression may be clinical manifestations of systemic proinflammatory cytokine activity (165).

Patients with various immune-mediated inflammatory diseases, including RA, have reported disturbed sleep and fatigue (167, 177). As a consequence of these factors, patients may enter into a vicious circle of pain, SD and fatigue with resultant reduced quality of life. Despite being important to these patients, and that questions regarding sleep and sleep-disturbance are included in some of the commonly used PROM-questionnaires, sleep has been infrequently reported in results from clinical trials in RA (178).

**RAID sleep**

The RAID questionnaire is described in more detail in section 1.2.6. This questionnaire has been validated for use in RA and includes one question on sleep, which is important to the patients (135, 162, 172). “Select the number that best describes the sleep difficulties (i.e., resting at night) you felt due to your rheumatoid arthritis during the last week (NRS 0–10; 0=no difficulty, 10=extreme difficulty).

**Medical Outcomes Study Sleep Scale and the Sleep Disturbance Scale**

The MOS sleep scale is a subscale of the MOS health status measure that consists of 12 items capturing 6 sleep dimensions during the “past 4 weeks” (179). It was found reliable and valid to assess aspects of sleep (180), and has been validated for use in RA (181). The 6 dimensions are: initiation (time to fall asleep), quantity (hours of sleep each night), maintenance, respiratory problems, perceived adequacy and somnolence. Question 1 is reported using a 5-item Likert-scale (0–15 min (1), 15–30 min (2), 30–45 min (3), 45–60 min (4) and >60 min (5); question 2 is reported in number of hours, and for question 3-12 a 6-item Likert scale ranging from “All of the time (1)” to “None of the time (6)” is used (179). The sleep disturbance scale is calculated as the mean from answers to question 1, 3, 7 and 8.
The MOS sleep questionnaire

1. How long did it usually take for you to fall asleep during the past 4 weeks?
2. On the average, how many hours did you sleep each night during the past 4 weeks?

How often during the past 4 weeks did you:
3. Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc.) while sleeping?
4. Get enough sleep to feel rested upon waking in the morning?
5. Awaken short of breath or with a headache?
6. Feel drowsy or sleepy during the day?
7. Have trouble falling asleep?
8. Awaken during your sleep time and have trouble falling asleep again?
9. Have trouble staying awaken during the day?
10. During your sleep?
11. Take naps (5 minutes or longer) during the day?
12. Get the amount of sleep you needed?

The MOS Sleep measure and scoring guide are available online:
http://www.rand.org/health/surveys/sleepscale/
http://www.gim.med.ucla.edu/FacultyPages/Hays/sleep.htm

MDHAQ sleep

MDHAQ is one of several questionnaires that was developed from the original HAQ (156). MDHAQ contains one question on sleep: “Within the last week, were you able to get a good night sleep?” (Circle one: 0, without problems; 1) with some problems; 2) with major problems; 3) unable to).

The 15 dimensional (15D) sleep

The 15D questionnaire was described in more detail in section 1.2.4. One of the 15 questions is on sleep with response categories: No, slight, moderate, great and severe problems with sleep. The scoring ranged from 1 (no problems) to 5 (severe problems)
15D sleep: “Which statement describes your current state best?”

1. I am able to sleep normally, i.e. I have no problems with sleeping.
2. I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking up at night.
3. I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4. I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5. I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

1.2.8 Fatigue

Fatigue has been described in rheumatic diseases such as RA for more than two decades (182), and has been increasingly recognised as an important symptom for patients with RA (183). Fatigue may be described as physical (physical exhaustion or reduced energy) or cognitive (problems with thinking, concentration or memory) (165), or as a constant exhaustion and lack of energy which is inadequately relieved by rest or sleep.

Fatigue has been included in recommendations on how disease activity should be reported in clinical trials (184). Sleep loss may exacerbate fatigue and pain in RA (167, 168). One study found fatigue to be common across rheumatic diseases (RA, osteoarthritis and fibromyalgia) (182), and about 40% of RA patients had clinically important fatigue (≥ 2/10 on VAS) (182). In multivariate analyses, the strongest associations to fatigue were seen for sleep disturbance, pain, depression, HAQ disability and tender point count. In the same study, a strong association was found between fatigue, work dysfunction and overall health status such as global severity VAS. Another study found depression and anxiety to be the strongest correlates with fatigue (p<0.001) with no significant associations with pain, disease activity score with 28 joint count (DAS-28, further described in section 1.3.2), HAQ or radiographic damage (185), while other studies found RA-patients to report disturbed sleep and fatigue adding further to disease burden (167, 177).
1.2.9 Gastrointestinal discomfort

Many RA patients report gastrointestinal (GI) discomfort, often related to use of NSAIDs, and GI-discomfort has been associated to exposure for all NSAIDs (186, 187). The best way of reporting GI discomfort has not been defined. No phrasing of the question has been identified as superior to another, and there are no defined cut-off levels for minimally clinically important GI-disturbance.

The COX-II inhibitors (coxibs) were developed as a less gastro-toxic alternative to traditional NSAIDs (188-190). However, many RA patients suffer from non-specific GI discomfort despite prophylactic use of gastroprotective medication or switching to coxibs (190, 191), raising the question whether other factors may contribute to perceived GI discomfort. Some evidence suggests that patients with RA may have a higher risk of GI side-effects from NSAIDs than the general population (192).

GI-discomfort can be measured by simply asking “do you currently / have you ever experienced GI-discomfort?” with possible options being "yes/no". GI discomfort may be further quantified on a 0-100 VAS-scale where 0=no GI-discomfort and 100= worst possible GI-discomfort. Specific questions on experienced GI-complications may include “Have you ever had gastroduodenal ulceration with or without complications (bleeding ulcer, perforated ulcer, non-bleeding and non-perforated ulcer)?” Asking about current and previous use of antacids using alphabetical checklists is an easy way of obtaining information about use of medications.

1.2.10 Coping and patient acceptable symptom state

Coping may be measured by a variety of instruments, including the short form Rheumatology Attitudes Index (RAI) and self-efficacy scales (SES) (193, 194). RAI is a short 5-item unifactorial questionnaire that can be used to construct a learned helplessness score. The overall score range is 5-25, where 5 represent the poorest score for learned helplessness (193). The items are the exact counterparts of the Arthritis Helplessness Index items that were identified as constituting a helplessness factor.
Self-efficacy may be defined as how the a person judge his/her capability of organising and executing tasks, i.e. what the person can do with the skill one has. In RA, an association between perceived self-efficacy and RA-related health status has been described (194). In ORAR we included questions on self-efficacy for function, pain and symptoms, and the patients were asked to circle a number on a scale from 10-100 representing how certain they were they could perform the different tasks: 10 (very uncertain), 50 (fairly uncertain) and 100 (very certain).

The patient acceptable symptomatic state (PASS) may be defined as “the highest level of symptoms beyond which the patients consider themselves well, i.e. an acceptable symptom state” (195). PASS was obtained in 2009 using two separate questions:

“Considering all the different ways your disease is affecting you. If you were to stay in this state for the next few months, would this be acceptable or unacceptable?”

Possible answers: Acceptable / Unacceptable

“Considering all the different ways your disease has affected you the last week, if you were to stay in this state for the next few months, how would you consider your health state?”

Possible answers: Very good / Good / Acceptable / Poor / Very poor

1.3 Measures of disease activity

1.3.1 Single measures

There are several measures available for assessing disease activity in RA such as the standard ACR core set which includes the following domains: tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function, and laboratory evaluation of acute-phase reactants (196). When evaluated together, these measures sample the broad range of improvement in RA (have content validity), and all are at least moderately sensitive to change (have discriminant validity). Many of them also predict important long-term outcomes in RA, such as physical disability, radiographic damage and mortality (51).
1.3.2 Composite measures

Evaluation of disease activity in RA is not easy, and no single marker can reflect all aspects of the disease. Disease activity instruments, in which single measures are pooled into a composite measure or index, have significantly improved the ability of the rheumatologist to evaluate the course of RA (197).

The RA Disease Activity Index (RADAI) is a self-reported questionnaire that includes questions on disease activity, joint tenderness, pain, morning stiffness and perceived joint pain in 16 joint areas. The scores from the five items are summarised into a disease activity index with a range from 0 to 10.

The most commonly used indices for disease activity in RA are the DAS-28, DAS and the simple and clinical disease activity index’ (SDAI and CDAI) (196). These indices are essentially based on the same single measures of disease activity in RA: tender and swollen joint counts (TJC/SJC), the patient's global evaluation of RA activity (PtGA), and acute-phase reactants (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)).

The range of DAS-28 is 0-10: Remission = DAS-28 < 2.6; low disease activity = DAS-28 ≥ 2.6 and 3.2; moderate disease activity = DAS-28 >3.2 and ≤5.1, and high disease activity = DAS-28 >5.1. DAS-28 is calculated using either of the following formulas:

\[
\text{DAS-28}(4) = 0.56*\sqrt{\text{TJC28}} + 0.28*\sqrt{\text{SJC28}} + 0.70*\ln(\text{ESR}) + 0.014*\text{PtGA}
\]
\[
\text{DAS-28-CRP}(4) = 0.56*\sqrt{\text{TJC28}} + 0.28*\sqrt{\text{SJC28}} + 0.36*\ln(\text{CRP}+1) + 0.014*\text{PtGA} + 0.96
\]

The SDAI and CDAI also include the physician's assessment of RA activity, while the CDAI is the only index that does not include a measure of an acute-phase reactant. These indices can be used to monitor disease activity, guide treatment decisions and as endpoints in clinical trials.

1.4 Imaging of joint damage

Joint damage includes erosions and joint space narrowing, and can be visualised by conventional radiography, magnetic resonance imaging (MRI) or ultrasonography (US). ACPA status, RF status, the number of swollen joints, and level of acute phase reactants are important predictive markers of joint damage in RA (95, 198). Radiographic damage
is a predictor of further radiographic progression, and findings on US and MRI also have predictive value for subsequent joint damage (198).

2. General aim and specific research questions

2.1 General aim

The general aim of this thesis was to explore the disease burden of RA, including changes over a 15-year period, in a cohort from a defined geographical area (City of Oslo) using a variety of patient reported outcome measures.

2.2 Specific research questions

- Was there a change in patient reported health status from 1994 to 2009 in the population included in ORAR? (Paper I)
- How did health status in the RA population develop in women versus men over 15 years? (Paper I)
- How were four different measures of sleep disturbance correlated in patients with RA, and which factors were associated with sleep disturbance in RA? Were the four different sleep measures consistently related to other measures of disease burden in RA? (Paper II)
- Was self-reported abdominal discomfort associated with other patient related factors, disease related measures and use of NSAIDs or coxibs in RA-patients? (Paper III)
- How does the patient reported impact of rheumatoid arthritis questionnaire (RAID) perform within a large population based cohort of patients with RA? (Paper IV)
- What was the distribution of the RAID score and how was it associated with other PROMs and demographic variables? (Paper IV)
3 Materials and methods

3.1 Study design

The Oslo RA Register (ORAR) was established during the years 1991-1994 (21, 23), with the first data-collection in 1994 (21). The aim was to include patients with RA aged 18 years or older from Oslo. Eligible patients for inclusion had to fulfil the 1987 ACR criteria for RA (15) and have a residential address within Oslo. Patients with juvenile arthritides were excluded. All data were collected from RA patients included in ORAR at five separate time-points in 1994, 1996, 2001, 2004 and 2009, and the questionnaires were sent to the patients’ residential addresses. There were no regular clinical study visits or laboratory monitoring. However, in conjunction with a study of osteoporosis in RA-patients, these patients were examined in 1994 and 1996 (199). Data has not been collected after the introduction of new classification criteria for RA in 2010 (16). The RF and anti-CCP status were manually extracted from patients’ files at inclusion in ORAR.

In 1994 ORAR was estimated to be 85% complete (21). ORAR was annually updated until 2009 with the inclusion of new cases and withdrawals due to death or moving out of Oslo. ORAR has been the basis for a number of studies on various epidemiologic aspects of RA with a strong focus on outcome research (200-205), genetic studies (206), and also demonstrating that RA-patients had milder disease in 2004 than 1994 (201).

The aim of ORAR was to establish a cohort of adult RA-patients representative for all stages and the broad spectrum of the disease, hence there were no exclusion criteria based on age (18 years or older), disease duration, disease activity or use of medication. The ORAR population represents the RA population seen in clinical practice in Oslo.

The initial search for eligible patients was performed by manually and/or electronically searching the hospital charts from the rheumatology departments in Oslo for the ICD-9 diagnosis 714.0 or 714.9, and by searching referrals to the multi-disciplinary teams (physiotherapists, occupational therapists and social workers). After permission from the Data Inspectorate, patients were included into the register database retrospectively. Disease onset was recorded as the date when at least 4 of the 7 RA-criteria (table 1) were fulfilled according to the review of the medical records (15). ORAR was estimated to be
85% complete for patients aged 20–79 years (21). Annual updates were performed by checking hospital records for new RA patients and for patients who moved out of the area or died.

### 3.2 Data collection

A selection of instruments was included in the compiled questionnaire-document sent to all patients in ORAR. These covered domains such as demographics and social aspects (education, work, marital and habitual status, body mass index (BMI)), health status (HAQ, MHAQ, AIMS2, VAS scales for pain, fatigue and global disease activity), comorbidity, disease impact and utility. AIMS2 was included in all but the 2009 data-collection, however the checklist of comorbidities from AIMS2 was included in 2009.

The data collection used in the four different papers is shown in table 5. Although the order of the questionnaires was not identical at all data-collections, all patients received identical sets of questionnaires at each separate data collections.

All questionnaires have been described earlier in this thesis, and the following questionnaires are available in validated translations in Norwegian (AIMS-2, EQ-5D, HAQ, RAID and SF-36) or Swedish that is very similar to Norwegian (MDHAQ and SES). Further details may be found at: [http://oml.eular.org/index.cfm](http://oml.eular.org/index.cfm).
Table 5 Measures included in paper I-IV.

<table>
<thead>
<tr>
<th>Demographics / covariates</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, gender, disease duration</td>
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<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Rheumatoid factor/anti-CCP</td>
<td>√</td>
<td>√</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Education, smoking</td>
<td>√</td>
<td>√</td>
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<td>-</td>
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<tr>
<td>BMI</td>
<td>√</td>
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<td>-</td>
<td>-</td>
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<td>Comorbidities (AIMS2 checklist)</td>
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<td>√</td>
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</table>

<table>
<thead>
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<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
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</thead>
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<td>√</td>
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<td>Fatigue†</td>
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<td>√</td>
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<td>-</td>
<td>-</td>
</tr>
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<td>SF-36 with MCS / PCS</td>
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<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>SF-6D</td>
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<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>EQ-5D</td>
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<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>15D</td>
<td>√</td>
<td>√</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SES (pain, function, symptoms)</td>
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<td>-</td>
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<td>√</td>
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<td>RAI-5</td>
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<td>-</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>MOS sleep disturbance scale</td>
<td>-</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>GI discomfort†</td>
<td>-</td>
<td>-</td>
<td>√</td>
<td>-</td>
</tr>
<tr>
<td>GI complications ‡</td>
<td>-</td>
<td>-</td>
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<table>
<thead>
<tr>
<th>Checklist of medication used past and present</th>
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<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
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<tr>
<td>Pain-relieving, NSAIDs, coxibs and antacids</td>
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<td>√</td>
<td>-</td>
</tr>
<tr>
<td>sDMARDs and bDMARDs</td>
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<td>-</td>
</tr>
<tr>
<td>Sleep-inducing / relaxing medication</td>
<td>-</td>
<td>√</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

† 0–100 mm VAS scale
‡ Complications: Ulcer, perforated or bleeding ulcer; if yes, was there a need for surgical intervention?
“Have you ever” and “are you currently”, suffering from GI pain or heartburn due to use of anti-inflammatory and pain-relieving anti-rheumatic medication?


3.2.1 Demographic and disease related variables

Table 6 gives an overview of the self-reported questionnaires that were mailed to the patients. The questionnaires obtained data on demographic and disease related variables, including sex, age, co-morbidity, current medication, smoking habits, education, civil status, height and weight.
### Table 6. Relevant questionnaires/data extracted from clinical files included in ORAR at the different time points

<table>
<thead>
<tr>
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<th></th>
<th></th>
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<td>Respondents aged 20-79 (all patients)</td>
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<td>1025</td>
<td>829</td>
<td>914</td>
<td>986</td>
</tr>
<tr>
<td>(1315)</td>
<td>(1375)</td>
<td>(1411)</td>
<td>(1454)</td>
<td>(1651)</td>
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<td>Self-reported height/weight</td>
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<tr>
<td>Smoking habits</td>
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<td>√</td>
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<td>RF/anti-CCP**</td>
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<td>√</td>
<td>√</td>
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<tr>
<td>Disease duration**</td>
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<td>√</td>
<td>√</td>
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</tr>
<tr>
<td>Use of DMARDs**</td>
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<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Use of corticosteroid***</td>
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</tr>
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<td>Use of NSAIDs***</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Use of coxibs***</td>
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<td>-</td>
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<td>Use of Z-hypnotics and benzodiazepines***</td>
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<td>15D Quality of life</td>
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<td>GI discomfort</td>
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<td>√</td>
</tr>
<tr>
<td>MDHAQ</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>MOS sleep disturbance scale</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>PASS‡</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
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<td>RADAI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>RAI-5</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>√</td>
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<tr>
<td>RAID</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>SES</td>
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<td>√</td>
<td>√</td>
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</tr>
<tr>
<td>SF-36 with MCS and PCS†</td>
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<td>√</td>
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<td>VAS scales</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- joint pain</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>- general pain</td>
<td>√</td>
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</tr>
<tr>
<td>- fatigue</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>- patient global assessment of disease</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

*Education, marital status, work status, pension support, **extracted from ORAR database. ***Alphabetical lists or generic- and trade names. †Joint pain, fatigue, global disease activity. ‡ Included 2- and 5-leveled PASS-questions

3.3 Data included in current thesis

All data included in current thesis are from ORAR. Patients aged 20–79 years at the time of data collection were included in the analyses for papers I, II and III (207-209), while paper IV used all respondents (aged 20–94) in 2009 (210). Papers II, III and IV used cross-sectional data from a single data-collection. In paper I, all patients in ORAR aged 20–79 years responding to the questionnaire survey at least once in 1994, 1996, 2001, 2004 or 2009, were included. This information is outlined in tables 6 and 7.

Table 7 Data used in paper I-IV

<table>
<thead>
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</tbody>
</table>

3.4 Statistics

All statistical analyses in this thesis were performed using the Statistical Package for the Social Sciences for Windows, versions 17-21 (SPSS, Chicago, Illinois, USA). As a conservative measure, non-overlapping 95% confidence intervals (CIs) and two-tailed p<0.05 were regarded as statistically significant.

3.4.1 Descriptive and explorative analyses

Continuous measures that were found to be close to normally distributed are presented as means with standard deviation (SD). Skewed measures are presented as medians with the 25th percentile – 75th percentile (also referred to as the interquartile range [IQR]). Categorical variables were presented as counts or proportions.
3.4.2 Univariate and bivariate analyses

To test for group differences, the 2-sample independent t-test for continuous variables that were close to normally distributed was used. The χ²-test was used for proportions or dichotomous measures. Pearson correlation coefficients were calculated within the 4 outcome variables measuring sleep as well as between sleep variables and the other PROMs. Bivariate associations between RAID score and other PROMs, age and disease duration are reported as Pearson correlation coefficients. In the same study, non-parametric correlation analyses were performed and results compared to the Pearson correlation coefficients. To display correlations between health status measures we also constructed matrix plots. Correlations between two variables below 0.40 were considered weak, between 0.40 and 0.70 moderate, and strong if above 0.70.

In paper IV all patients were included in the analyses looking at RAID, these patients were aged 18–94 years. In order to investigate whether this influenced our results, we did the same analyses including patients aged 20–79 years only.

3.4.3 Multivariate analyses

In paper I, longitudinal changes were examined using a mixed model approach with random intercept and Bonferroni correction to adjust for multiple testing. Using 1994 as reference year, we performed analyses for the patient population overall (adjusted for age, gender and disease duration) and by gender (adjusted for age and disease duration) to explore changes in PROMs over 15 years.

In paper II we used univariate linear regression analysis to identify variables associated with sleep disturbance (sleep disturbance scale, MDHAQ sleep, RAID sleep and 15D sleep). Candidate variables (p<0.20) were then entered into multivariate general linear models together with the pre-specified exogenous confounding factors age, gender and disease duration. Further selection of variables was performed using forward and backwards selection, with the robustness of the final models checked by re-introduction of excluded variables. The remaining covariates in the final model were tested for possible interactions. When more than one variable measuring the same domain was available, e.g. physical function with HAQ, MHAQ and PCS, we performed separate
analyses with each of the variables. The variable contributing the most to the final models was kept, e.g. MHAQ for physical function. We used adjusted $R^2$, the proportion of variance in the dependent variable explained by the final model, as measure of goodness-of-fit. The model assumptions were assessed using residual plots. The amount of missing data was low (less than 5%). Missing data were assessed as missing completely at random, and no further adjustments were made.

In paper III we used univariate logistical regression analysis to identify variables associated with GI discomfort. As for the linear regression analyses described above, we used a similar approach with a cut-off for candidate variables at $p<0.20$ before entering into the multivariate model. Further we used the same the pre-specified exogenous confounding factors as in the linear regression analyses, and if more than one variable measuring the same domain was available, we kept the variable contributing the most to the final model. Finally we applied the Hosmer and Lemeshow goodness-of-fit test to assess the overall model.

### 3.5 Legal and ethical aspects

ORAR has been evaluated and approved by the Regional Committee for Medical Research Ethics. The storage of data was licensed from the Norwegian Data Inspectorate, with the Norwegian Centre for Research Data (NSD) being the data protection official for our research. The NSD has been delegated the responsibility for the Personal Data Act and Health Register Act from the Data Inspectorate.
4. Summaries of results

4.1 Paper I

Health status has improved more in women than in men with rheumatoid arthritis from 1994 to 2009: results from the Oslo rheumatoid arthritis register.

Gender differences in PROMs have been reported for disease activity, functional capacity and treatment responses. During the past decades there has been a major shift in the care of patients with RA with the availability of new disease modifying drugs and treatment strategies. The objective of this paper was to examine whether there was a change in disease activity and PROMs over a 15-year period and in particular investigate whether there were any gender differences in these changes.

Data was collected by mailed questionnaires at five time points from 1994-2009 with a core set of measures included in all surveys; MHAQ, SF-36 and SF-6D, VAS for pain, fatigue and disease activity, use of medication, smoking and co-morbidities. Information on age, gender, disease duration and seropositivity was obtained from the database. The response rates varied from 59% to 75% with data available for 829-1025 RA patients at each time point.

The respondents had similar age, gender distribution and disease duration throughout the 15-year study period. Mixed model analyses were used to analyse longitudinal changes in PROMs from 1994 to all subsequent data-collections in 1996, 2001, 2004 and 2009. PROMs were statistically significantly improved from 1994 to 2009 (MHAQ, SF-36 physical component summary, utility, VAS pain, VAS fatigue and VAS disease activity; all p<0.001), and also with clinically important improvement. Men reported significantly better health status than women in 1994, but women improved significantly more than men over 15 years with a reduction of the gender gap in 2009. Antirheumatic medication was increasingly used over 15 years with no gender differences.

In conclusion, the RA patients reported statistically significantly improved health status for most PROMs from 1994 to 2009. Women improved most, and although they still reported higher disease impact than men, the gender differences were small at the final data collection.
4.2 Paper II

Sleep disturbance in patients with rheumatoid arthritis is related to fatigue, disease activity and other patient reported outcomes.

The objective of this study was to explore factors related to sleep disturbance in patients with RA and investigate whether these factors were similar across four different measures of sleep.

Cross-sectional data from 986 patients in the Oslo RA register collected in 2009 were included. Sleep problems were assessed by the MOS sleep disturbance scale and the sleep-components of RADAI, MDHAQ and 15D. Patient reported outcome measures were recorded using standard questionnaires for physical and mental function (HAQ, SF-36,), disease activity (RADAI), utility (SF-6D) and VAS for pain, fatigue and disease activity. Demographic variables including comorbidities were collected. Information about use of medication for RA and sleep disturbance was collected using alphabetical checklists. Multivariate analyses were used to identify factors independently associated with sleep problems by four different measures.

Mean (standard deviation (SD)) age was 59 (13) years, 77% were females, and mean (SD) disease duration was 14 (11) years. The correlation between various sleep measures was high. Sleep disturbance was moderately correlated to pain, fatigue, physical function, RADAI and utility. RAID sleep demonstrated the highest correlation with other PROMs. RADAI, fatigue, the mental component score of SF-36, physical function, body mass index and use of z-hypnotics/benzodiazepines were independently associated with two or more measures of sleep problems (all p<0.001).

In conclusion, sleep disturbance measured by four different measures were independently related to other patient reported outcome measures including fatigue, pain and disease activity in RA-patients.
4.3 Paper III

Abdominal discomfort in patients with rheumatoid arthritis is associated with physical and mental function, self-reported disease activity, and use of anti-inflammatory medication.

The objective of this study was to examine whether patient reported GI discomfort was associated with disease related measures, patient related factors and medication in a large group of patients with RA.

Cross-sectional data from 914 patients in the ORAR were included. Patient reported outcome measures were assessed by HAQ, SF-36, and VAS-scales for patient global assessment of disease activity, pain and fatigue. Use of medication was asked using alphabetical checklists of past and present use of NSAIDs, coxibs and DMARDs. Demographics including comorbidity were collected.

Multivariate analyses were used to identify factors independently associated with patient-reported GI-discomfort.

RA patients who self-reported current GI discomfort (n=193, 22 %) were older and had worse scores on almost all RA related health status measures than patients not reporting GI discomfort. In the adjusted multivariate analyses, patient global on a 100 mm scale (odds ratio (OR) 1.01, 95% confidence interval (CI) 1.00;1.02), poor physical function by HAQ (OR 1.62, 95% CI 1.15;2.28) and poor mental function measured by SF-36 MCS (OR 0.74, 95% CI 0.63;0.86) were independently associated with GI discomfort. In univariate analyses the use of NSAIDs and coxibs were associated with GI discomfort, but the multivariate results were statistically significant only for the use of NSAIDs (OR 1.99, 95% CI 1.30;3.05).

In conclusion, GI discomfort was common in this population of RA-patients and GI discomfort was associated with poorer scores on mental and physical functioning, higher self-reported disease activity in addition to use of anti-inflammatory medications.
4.4 Paper IV

Performance of the Rheumatoid Arthritis Impact of Disease (RAID) score in relation to other patient-reported outcomes in a register of patients with rheumatoid arthritis.

The objective of this cross-sectional study was to investigate how the seven-domain questionnaire in RA impact of disease (RAID) performed as a global measure. We wanted to investigate the score distributions and associations between the RAID score and patient reported outcomes (PROMs), and demographic variables in patients with RA included in ORAR.

The 1086 respondents to a postal survey in 2009 were included in the analyses. Mean age was 61.7 years, 77.1% were females and mean disease duration was 14.1 years. 56.6% were seropositive.

The mean (Standard deviation) RAID score was 3.37 (2.17). The distribution of the RAID score showed a slight floor effect: 17.5% had a score between 0 and 1, and 14.4% between 1 and 2, whereas only 1.0% and 0.3% had scores between 8 and 9, and 9 and 10, respectively. Correlations between the RAID score and the patient global assessment of disease activity, RADAI, SF-6D and EQ-5D were 0.82, 0.82, −0.77 and −0.73, respectively. Strong correlation was also seen between RAID score and pain VAS, the domain with highest weight in RAID, whereas correlations to measures of other RAID domains were moderate. The RAID score was higher in women than men (3.49 vs. 2.95, p=0.001).

In conclusion, the RAID score has a slight floor effect and correlated more strongly to global measures of health and pain than to other specific health dimensions.
5. General discussion

ORAR was designed to enable studying patient reported outcomes and burden of disease in a cohort representative of the RA-patient population within a defined geographical area. The main aim of the study was to examine the ORAR cohort using different PROMs assessed by mailed questionnaires. The PROMs chosen covered central aspects of epidemiological research considered important by patients and physicians. All papers in the current thesis are based on data from ORAR, and the findings from this research are important to rheumatologists in clinical practice. Whereas the first three papers focus on burden of disease measured by PROMs, the fourth paper investigated the rather newly developed RAID measure and its performance against other PROMs. Overall, the aim of the studies were to increase knowledge on patient reported disease consequences and burden of disease in RA, and the time-period for data collection provided an opportunity to study changes in health status during a period with major improvement in treatment strategies and access to new therapies.

In RA patients, persistent inflammatory disease activity in joints ultimately results in irreversible joint damage with persistent functional loss as a consequence. Assessment of disease activity is important to evaluate the course of the disease or to judge the efficacy of a treatment. In this study only patient reported outcomes are available as all data were patient-reported through mailed questionnaires, thus we do not have any clinical data available, i.e. no clinical examination, no laboratory results and no imaging. This means that composite measures commonly used in RA such as DAS, DAS-28, CDAI and SDAI are not available. However, disease activity reported by RADAI was available, as this composite measure does not require clinical examination or blood tests.

The first part of the general discussion covers methodological aspects of the studies presented in this thesis. In the second part, main results with clinical implications are discussed.
5.1 Methodological aspects

Methodological strengths and limitations are discussed in this section.

5.1.1 Study design

The current work is based on data from a repeated cross-sectional study. Patient-reported data on various outcome measures were collected at five separate time points from 1994 to 2009. The last data-collection in ORAR was in 2009, prior to the publication of new classification criteria (16). Patient-records have not been manually examined to see whether the patients fulfilling the 1987 criteria also fulfilled these new criteria.

A core set of PROMs was included at all data collections, while some other PROMs were included only once or twice. There was no pre-defined interval to which the data-collections would take place. The sets of questionnaires were mailed to all patients included in ORAR at the respective time-points; although the questionnaires differed slightly between the data-collections, all patients received identical sets of questionnaires at any given data-collection. After the introduction of new RA classification criteria in 2010 it was decided not to include new patients in the ORAR, and after 2009 no further data has been collected. There is a concern that patients included in one dataset using different classification criteria will introduce bias in the analyses. There is, however, ongoing work looking at mortality in the ORAR population, and we are awaiting the first results in the near future.

Strengths of the study design include the large number of RA-patients reflecting the range of disease activity and disease consequences seen in clinical practice. Data was collected over a 15-year period in which there were major advances in available treatments and improved treatment strategies. As our patient population was not subject to stringent exclusion criteria our findings are assumed to be representative for the RA-population in Oslo.

Known weaknesses include the self-reporting of data, which may introduce reporting bias. Clinical examinations at all time points would also have allowed for a better assessment of disease activity and other objective outcomes. Further, it is difficult to
account for all possible confounders in cross-sectional studies. Another weakness is the lack of data for the non-respondents or those who declined to participate.

5.1.2 Representativity of study population

A potential challenge in all observational studies is the selection of subjects. If the sample is not representative of the population, the results will be unreliable and of dubious value. This problem is usually referred to as selection bias, which includes non-random sample, omission of hard to trace patients, number of non-participants, number of dropouts and number of non-respondents. In ORAR, where all data was collected by mailed surveys, the most important selection biases are patients declining participation and non-respondents. In Norway every person has a personal ID number and through a national population register the living address was obtained. Thus we were able to send the surveys to the correct patient addresses. The patient population included patients with an RA diagnosis living in Oslo (15). At the time the register was started there were two separate hospitals treating RA-patients in Oslo. Only patients treated at one of the hospitals, Diakonhjemmet Hospital (DH), were included at the start. From 2004, DH treated all patients with inflammatory rheumatic diseases, including RA, while the remaining systemic rheumatic diseases were followed by the National hospital (Rikshospitalet). Patients treated by private rheumatologists were generally not identified and included in ORAR. However, if these patients were referred to Diakonhjemmet Hospital for other reasons, e.g. rheumatic orthopaedic surgery, then they would be included. A study to investigate the representability of the register was performed; this is described in more detail below. Patients not responding were sent one reminder, and no other actions to increase the response rate were taken.

During the inclusion period from 1991 to 2009 the database was updated yearly by manually going through patient records to include new patients and remove those who had died or moved out of Oslo (21). During the 15 years, approximately 3500 unique patients were included in ORAR.

Over the last decades response rates in observational studies have decreased (211). A high non-response rate means a reduced sample size, which affects survey estimates precision. Also, non-response may lead to bias if there are systematic differences between
respondents and non-respondents (212). In ORAR we observed a reduced response rate from 1996 to 2001. As an incentive to reply in 2004, all ORAR respondents were included in a lottery with the price of a travel-value cheque. We observed a slightly increased response rate in 2004 compared to 2001, but in 2009 it decreased to approximately the same level as in 2001. Overall, the reduction in response rate was from 70.4% in 1994 to 59.7% in 2009, which is similar to what has been seen in other observational studies (211).

There have been studies describing differences between respondents and non-respondents. In some studies non-respondents were more likely to have worse health-status, lower health care utilization, higher age, lower education and more often being unmarried (212-214). On the other hand, other studies did not find any systematic differences between respondents and non-respondents, and one study on RA patients report higher pain in responders than non-responders (212). Respondents and non-respondents in ORAR from 1994 to 2004 were compared in a previous study with respect to age, gender distribution and disease duration (201). In 1994 there were small differences in age and disease duration, just reaching clinical significance, and in 2001 there was a significant age difference. Other variables were similar in respondents and non-respondents. This is an important issue in epidemiological research. While it does not appear to be any systematic differences between respondents and non-respondents in ORAR, we have no information on e.g. disease activity in the non-respondents and cannot exclude this as a possible bias. Overall, we do believe the respondents are representative of the ORAR patient population.

ORAR was validated at the beginning in 1994 and found to include 85% of known RA patients in Oslo. This validation was performed by inviting 10 000 inhabitants in Oslo to respond to a questionnaire focusing on self-reported musculoskeletal symptoms and diagnoses. Patients self-reporting RA were checked against ORAR (n=158). Of the 158 patients 30 were already included in ORAR. The remaining 128 were invited to attend a clinical examination by a rheumatologist at Diakonhjemmet Hospital, with blood tests and X-rays as necessary. Of the 128 patients, five were diagnosed with RA. Thus, the completeness of the register was assumed to be 30/35 or 85.7 % (21). The register was thus assumed representative for the entire RA-population from 1994 onwards.
In ORAR, the female to male predominance was approximately 3:1 at all time points, the mean disease duration increased from 12.6 years in 1994 to 13.8 years in 1996 and was from then onwards unchanged (13.9 years in 2001, 13.6 years in 2004 and 13.9 years in 2009). These demographic findings are important as they indicate that our study population did not change much over time as well as being comparable to other observational studies. From the observed reduction in mean age and slight increase in disease duration, one may hypothesize this being due to the fact that patients are referred to rheumatologists at an earlier stage of the disuse. This is, however, impossible to verify with the study design in ORAR. Females had longer mean disease duration than males at all data collections although the gap decreased over time. The number of seropositive patients was unchanged until 2001 with an increase from 2004 onwards, this may be due to the introduction of anti-CCP in addition to RF.

In the time period spanning from 1994 to 2009 there was an increasing awareness of the importance of early diagnosis, starting treatment early, tight control, aiming for remission, and early RA-clinics were established. Overall, and as a result of these above-mentioned factors, the disease duration at the time of being diagnosed RA may have been shorter in the more recent data collections than in the earlier years. This, however, was not reflected in the overall mean disease duration, which increased from 12.6 years in 1996 to 13.7 years in 2009.

5.1.3 RA patients and population included in papers I-IV

In paper I we used data from all data-collections from 1994-2009 (table 7) For papers II and IV we used data from 2009 while data from 2004 was used in paper III.

Papers I-III included patients aged 20–79 years, while paper IV included data from all respondents aged 20-94 years. This choice was made, as the aim of the study was to investigate how RAID performed as a global measure and to investigate the score distributions and associations between the RAID score and other PROMs. These elderly RA-patients, i.e. ≥ 80 years, are a relevant part of the RA-population to include in the validation of a new instrument as patients with RA on average are getting older and they are commonly encountered in daily clinical practice. A potential drawback of this approach is the lack of validation of ORAR for patients older than 79 years. To
investigate whether this had influenced our results, the same analyses were performed with an age-limit of 20-79 years. We found only slight numerical differences and there was no change in significant variables, probably because the number of patients aged ≥80 years or older was low (table 8).

**Table 8:** RAID values in ORAR patients aged 18-94 years and 20-79 years (Paper IV)

<table>
<thead>
<tr>
<th></th>
<th>Patients aged 20-94 years (N=1086)</th>
<th>Patients aged 20-79 years (N=914)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Overall (1.0)</td>
<td>3.37</td>
<td>2.17</td>
</tr>
<tr>
<td>Pain (0.21)</td>
<td>3.88</td>
<td>2.45</td>
</tr>
<tr>
<td>Functional disability assessment (0.16)</td>
<td>3.59</td>
<td>2.65</td>
</tr>
<tr>
<td>Fatigue (0.15)</td>
<td>3.59</td>
<td>2.68</td>
</tr>
<tr>
<td>Physical well-being (0.12)</td>
<td>3.43</td>
<td>2.40</td>
</tr>
<tr>
<td>Emotional well-being (0.12)</td>
<td>3.02</td>
<td>2.41</td>
</tr>
<tr>
<td>Coping (0.12)</td>
<td>2.72</td>
<td>2.31</td>
</tr>
<tr>
<td>Sleep (0.12)</td>
<td>2.99</td>
<td>2.45</td>
</tr>
</tbody>
</table>

SD = Standard deviation

### 5.1.4 Patient-reported outcome measures

Patient-reported measures of health status are important to patients and have become widely used in rheumatology research and clinical practice, and they form part of the core set of measures to assess disease activity, severity, and response to treatment in randomised controlled trials (RCTs) and clinical practice (122, 184, 215, 216). PROMs may not always correlate with more objective measures of disease activity, and may be influenced by other factors than the disease itself, such as mood, motivation and current condition. Ideally, patient questionnaires for standard clinical care should be pragmatic, not take too long for patients to complete, and be rapidly reviewed and easily scored by the clinicians. Instruments like the HAQ, AIMS and SF-36 are quite elaborate, and shorter alternatives exist. A simple questionnaire like the 8-item MHAQ provides similar information to the more widely used and more comprehensive HAQ, even if the instruments differ with regard to score distribution, i.e. floor effects (74). Self reported VAS-scales of pain, fatigue and global disease activity provide important information,
although it is known that these measures may show considerable variation over time (183). The minimal clinically important difference (MCID) of several PROMs, e.g. SF-36 MCS and PCS, RAID and HAQ, have been used to define the clinical improvement threshold level for use in clinical trials (163, 216, 217). In paper I we investigated trends in PROMs over time, and as examples found PCS to be improved above the MCID level for both genders while women reported important and clinically relevant improvement in MHAQ of -0.29 over the 15 years. A change in HAQ or MHAQ between 0.22 and 0.25 is suggested MCID for these variables (217).

In observational studies, the patients are often exposed to a number of questionnaires to ensure that important aspects of the disease are covered. The total burden of questions to the patients must be balanced against the researchers “quest” for information. If a new questionnaire is to be included, one must consider removing another while trying to avoid the risk of loosing valuable information. There is a risk of lower response-rate if the total number of questions becomes too extensive. In ORAR, all questionnaires were carefully considered according to these premises before each mailed survey.

In ORAR, a number of PROMs measuring different aspects of RA were included, some at all data collections (to investigate trends over time), while other were included once or twice. As a consequence of sleep being highlighted as important to the patients at OMERACT (172), the sleep disturbance scale of MOS was included in the 2009 data-collection. To balance the total number of questions, other questions deemed less essential at the time of data-collection were removed, e.g. questions related to GI discomfort and use of gastroprotective medication.

Valuable information on aspects of RA important to the patients has been gained from ORAR. Although some of these are "common complaints" encountered in daily clinical practice, there are a limited number of studies from registers with as large RA-patient populations as ORAR looking at PROMs. From our results we have been able to identity factors associated with better and worse PROMs, which is important to both patients and physicians. There may, however, be discrepancies between patients’ and physicians’ evaluations with respect to the most important aspects of the disease and the burden they represent to the individuals, e.g. fatigue, sleep and wellbeing (141, 218, 219).
Quality of life, captured by several of the PROMs, is, above all, a subjective measure where the personal evaluation of function in relation to individual and/or cultural standards, values, expectations and goals are important (220). This is different from health status, which merely assess physical, mental and social functioning.

5.1.5 Changes in management of patients with rheumatoid arthritis

Over the last decades the field of rheumatology has gone through major changes. Some of these important aspects are "treat to target", "aiming for remission" and "tight control", as well as the availability of an increasing number of DMARDs with different modes of action (111). At the start of ORAR there were no bDMARDs available. In the time-period from 1994 to 2009 the recommendations with respect to referring and treating RA-patients changed with increasing focus on earlier referral to rheumatologists, tighter control and a closer follow-up, as well as improved DMARD treatment regimens (129).

It would have been valuable to have information on the time of first RA related symptoms and on the time point when treatment was initiated. Due to the design of the ORAR database such information was not available. We did, however, observe a somewhat lower mean age and longer disease duration in the ORAR-population over the 15-year period, suggesting that the ORAR patients had been referred to rheumatologists earlier. The increased use of sDMARDs and bDMARDs over the study period may also reflect a more aggressive treatment approach.

RA-patients living in Norway have equal rights in getting treatment for their disease, with similar access to care for all patients. If there is inadequate response to one treatment (e.g. sDMARD) and indication to try another (e.g. bDMARD), the patients will be offered this treatment. In ORAR, we observed an increasing number of patients using sDMARDs and/or bDMARDs and there was no gender difference (Paper I). MTX was the main sDMARD used by the patients at all data-collections, with an increase in use from 36.4 % in 1994 to 59.5% in 2009. The use of glucocorticoids was largely unchanged until 2004 with an observed reduction from approximately 40% to 34.5% in 2009. The use of bDMARDs increased to approximately 20% in 2009. Information about use of NSAIDs was not available in 2009.
5.2. Discussion of main results

In this section main results from the four papers included in the thesis will be discussed.

5.2.1 Development in the Oslo RA population over 15 years

Disease burden can be measured by applying a number of PROMs that capture different aspects of the disease. In the ORAR-cohort, this was done measuring important aspects of RA over five waves of data collection over 15 years. This allowed us to investigate whether there were any secular trends for changes in the PROMs in the Oslo RA population. This core set of outcomes included SF-36, MHAQ, VAS-scales (for pain, global disease activity and fatigue), utility (SF-6D) and use of medication (glucocorticoids, sDMARDs and bDMARDs).

In the longitudinal study over 15 years (paper I) we were able to demonstrate an improvement in PROs, in particular in females, and the gender gap observed in the 1990s was considerably diminished in 2009. These improvements may be due to a number of reasons. Due to the multiple cross-sectional study design it is, however, not possible to determine causality. Increased awareness among the primary care physicians of the importance of early diagnosis may have lead to earlier referrals to rheumatologists.

We observed improvement in PROMs in a period where the paradigms in RA treatment changed to treat patients more aggressively. The ORAR population gradually used both more sDMARDs and bDMARDs, with similar findings for both genders. This observation is also consistent with data from the multicentre Norwegian-Disease-Modifying Antirheumatic Drug (NOR-DMARD) study. Aga et al have shown that RA patients in NOR-DMARD gradually started both sDMARDs and TNF-inhibitors earlier during the period from 2000 to 2010 and that the remission rates also increased during this time period (221). Also, the size of remission rates and low disease activity depend on how remission is defined (222).

The incidence of RA increases with age reaching a peak in the seventies (23-25, 223). The female: male ratio is generally reported to be 3:1, which as mentioned is also seen in ORAR with approximately 75% females. We observed slightly longer disease duration in women than men in all data-collections with no difference in mean age. In other words,
the women in ORAR received their RA-diagnosis at a younger age than men, suggesting that RA may present at a younger age in females than males (Paper I). As a result of longer disease duration, one would expect a higher accrued disease impact in women than men, which indeed was seen in this study as women reported worse PROMs than men at all time-points.

The increasing level of education observed in the ORAR population coincides with the general increase in level of education in Norway during these years (224). RA is uncommon in the younger age groups, and thus less likely to have had an impact on ability to complete education. Also, patients with juvenile inflammatory arthritis (defined as disease onset before age 16 years) were not included in ORAR.

Overall, RA patients reported less burden of disease measured by a number of PROMs. The trends over time were seen for physical function (MHAQ and PCS), pain, fatigue, patient global disease activity and fatigue. These findings extend findings from the 2004 data from ORAR (201), as well as support findings in other studies (225-228). Some of these other studies also demonstrated less painful and swollen joints with reduced sick leave in RA-patients after improved RA treatment, lower disability after the introduction of sDMARDs and further improvement after bDMARDs introduction. However, we did not analyse patient groups separately based on disease duration (229-231) A Finnish study observed similar increase in HAQ for the general population and in RA patients with increasing age from 2000–2005 (229). We are not aware of similar studies from Norway.

In addition to improved health status and reduced sick-leave it has also been shown that RA patients undergo less surgical procedures than before (232). These research findings support the impression from experienced clinicians – RA patients have less physical disability and require less surgery than before.

We were intrigued to find the apparent discrepancy in improvement in the male and female populations. The gender-gaps observed in 1994 were considerably diminished in 2009 as the health of the women had improved more than men. These gender differences in improvement could not be explained by difference in use of medication between genders. As mentioned previously, the data were collected in a period with increasing
awareness of the "window of opportunity" for use of DMARDs (233). These factors, combined with the increased use of sDMARDs (mainly MTX) and marked increase in use of bDMARDs, may reflect the increased availability of medication and adherence to new treatment recommendations (121).

Our observation of women reporting more somatic symptoms than men in 1994 is consistent with results from other studies (33, 226, 234). However, comparing these populations directly may not be correct due to varying inclusion and exclusion criteria, follow-up schedules, sample sizes and measured PROMs. Previously there have been concerns with respect to whether observed gender differences in RA may originate from the disease activity measures rather than actual gender differences in disease activity (33). This does not appear to be a problem in the ORAR population as a core set of disease measures were used throughout the 15 years, and the women reported significantly more improvement than men (234). Our results suggest that the observed closing of gender gap is real, and not related to methods inherent to assessment of health status.

The improved physical function is important, clinically relevant and may have a large impact for the RA patients in aspects such as daily functioning, quality of life, and ability to work. The entire ORAR population, and especially women, reported improvement in physical function which exceeded the suggested range for MCID over the 15-year study period (217). MCID is discussed in more detail in section 5.1.4. This important message may be considered a reward for a health care system that consistently has improved with the provision of better access to early diagnosis and treatment. The improvements in health care may also have contributed to better disease knowledge and awareness among the patients. This may be reflected in improved treatment adherence and behaviour, which subsequently may lead to better health.

Pain and fatigue are two important aspects from the patient’s point of view (137, 181, 200, 216). In the ORAR-population, we observed improvement over time at a clinically important level. These improvements were also seen for men and women separately, and although no longer statistically significant in 2009, the women reported higher levels of pain and fatigue than men at all time points.
Reduction in global disease activity (PtGA) and disease burden (utility, SF-6D) reflects the global improvement in the ORAR cohort. These are important aspects of RA, yet it has been difficult to define cut-off values for MCID applicable across populations as a number of factors (e.g. ethnicity, education, initial disease activity) could influence the above mentioned outcome measures. Our results indicate a gain of 5.6 quality adjusted life years (QALYs) per 100 RA patients (4.1 for men and 6.2 for women). These findings are significant on a group level, important to the individual patients and may be relevant for payers and decision makers who make priorities about costs across different disease areas.

Since the final data collection in 2009 further development have occurred in the management of RA. EULAR has published recommendations for drug management and “treat to target” for patients with RA (14, 112). It may be expected that the Treat-to-Target approach may lead to further improvement in the health of RA patients, and in the recently completed ARCTIC study, ACR-EULAR Boolean remission was achieved in about 50% of the patients after 2 years (134).

5.2.2 Sleep disturbance in rheumatoid arthritis

Sleep disturbance in RA has been highlighted as an important issue by patients, yet it has not been addressed in many clinical studies. The increased focus on patient participation and patient perspective in OMERACT led to the inclusion of sleep as one of the core outcome measures to be studied in RA (135, 171, 172), and the bidirectionality between disturbed sleep and other PROMs has been described (166).

The sleep disturbance scale from MOS has been validated in RA (235). Sleep is also included in some questionnaires already used in rheumatological research (RAID, MDHAQ and 15D). Our study was not designed to validate the sleep questions from RAID, MDHAQ and 15D against the MOS sleep disturbance scale. Nevertheless our results are interesting, because if they are confirmed in future studies, sleep disturbance in RA could be studied using the sleep components of PROMs already in use without increasing the amount of questions posed to the patients.
In our study we found sleep disturbance, measured by the sleep disturbance scale from MOS (235) and the sleep-components of RAID, MDHAQ and 15D, to be common and consistently associated with other PROMs (i.e. fatigue, SF-36 MCS and RADAI), as well as use of z-drugs and/or benzodiazepines. These associations were all significant in multivariate analyses adjusted for age, gender and disease duration. Of the four sleep measures, RAID sleep demonstrated the highest correlation to these other PROMs, with increased sleep disturbance being associated with worse PROMs. This finding supports previous studies that reported poor RA-disease control, pain, disease activity, fatigue and depression associated with reduced sleep quality (174-176).

RA patients with established disease may have extra-articular manifestations of disease as well as comorbidities. Sleep disturbance is a common complaint (if queried) in RA. Patients with a number of immune mediated inflammatory diseases, including RA, reported disturbed sleep and fatigue further adding to disease burden (165, 167, 177, 185, 236, 237). In our study we found fatigue significantly associated to all measures of sleep in multivariate models supporting these previous studies.

Threshold values for the MOS-sleep disturbance scale and the sleep questions from RAID, MDHAQ and 15D have not been set, thus it is difficult to determine the exact level of sleep disturbance our patients experienced. The overall RAID-value of maximum 2 has been proposed as the optimal threshold (163). The ORAR patients reported mean overall RAID and mean RAID sleep around 3, suggesting that they, in addition to experiencing a high impact of disease, also experienced a high level of sleep disturbance.

The association between pain and sleep disturbance has been documented (238), and our results support these findings as pain is an important component of RADAI, which was significantly associated with all four sleep measures. For RAID sleep, we found pain measured by VAS independently associated in addition to RADAI. A further exploration of the individual components of RADAI against sleep disturbance was not performed. The association between depression and sleep disturbance has been documented previously (238) and we carefully considered including a depression-questionnaire when planning the 2009 data collection. However, after evaluating the total number of questions included in the questionnaire this was not included.
Our findings indicate that RAID may have a slight advantage above MDHAQ and 15D with regard to assessment of sleep. Another important factor is that after RAID was validated for use in RA it has become increasingly used as a feasible, easily administrated and scored questionnaire.

Use of Z-hypnotics are considered safer with less side effects and risk of abuse than benzodiazepines for use in insomnia (239). Use of z-hypnotics/benzodiazepines was reported by 18.7/8.5 % of the ORAR patients (data not included in Paper II). The high number of RA patients reporting any use of sleep-inducing medication indicates that sleep disturbance was present in our patient population and medical attention was given to the problem.

During our analyses we compared these rates to the prescription rates for the entire population of Oslo (available from the Norwegian prescription database, [www.norpd.no](http://www.norpd.no)). The ORAR patients are included in the Oslo-population. However, the 986 patients constitutes approximately 0.2% of the 431 000 inhabitants of Oslo aged 20-79 years, and as such will not convey any large influence on the overall Oslo numbers. Sleep disturbance is more common in the elderly (240), and the increased use with age is expected. The use of z-hypnotics per 1000 patients was approximately doubled in the ORAR-population compared to the overall Oslo population, whereas these differences were less striking for benzodiazepines (figure 2).

Breaking these figures into 5-year age groups, we found an almost linear increase in use with age for z-hypnotics and benzodiazepine for the Oslo population, whereas the use in the ORAR-population was higher also at a younger age (illustrated in figure 3). This may further support that RA-patients experience significant sleep disturbance. The total number of ORAR patients using benzodiazepines was small, and caution must be taken when interpreting the results.
Figure 2. Use of Z-hypnotics and benzodiazepines per 1000 in people aged 20-79 years in 2009. Results presented for males, females and overall for people included in ORAR and the population of Oslo.
**Figure 3.** Use of z-hypnotics and benzodiazepines in the ORAR-population and Oslo inhabitants per 1000 in 5-year age-groups from 20-79 years presented for females, males and overall.
5.2.3 Gastrointestinal discomfort, NSAIDs and self-reported disease activity

NSAIDs are commonly used to reduce pain and stiffness and improve function. GI side effects from use of NSAIDs are common and are associated to exposure for all NSAIDs (186, 187). Selective iso-enzyme COX-II inhibitors (coxibs) were developed as a less gastrotoxic alternative (188-190). Some evidence suggests that patients with RA may have a higher risk of GI side effects from NSAIDs than the general population (192).

ORAR was established before the coxibs were introduced (in 1998-1999), and in the first years after introduction coxibs were more commonly used than today. The expectations to the new coxibs were high, and indeed the patients reported less GI side effects in a number of clinical trials, with a reduced rate of endoscopic ulcers and GI ulcer complications (188, 241). However, due to concerns regarding increased risk of CVD, rofecoxib and valdecoxib were withdrawn from the marked in 2004-2005. At the time of our data-collection in 2004, both were still in use and the data are included in the analyses.

In our study we found evidence suggesting that worse physical function (HAQ), higher disease activity (PtGA VAS) and poorer mental functioning (SF-36 MCS) were independently associated with current self reported GI-discomfort. These associations were highly statistically significant with narrow 95% CIs. As an example, we found a 62% increased risk of NSAIDs related GI-discomfort with every unit increase in HAQ, and a two-fold increased risk with current exposure to NSAIDs. Improved self reported global disease activity score and better mental functioning (SF-36 MCS) were associated with a small reduction in reporting GI-discomfort. Multivariate analyses, adjusted for age, gender, and disease duration, showed that poorer physical function (HAQ), current use of NSAIDs, self-reported disease activity (patient global), and worse mental function (SF-36 MCS) were most strongly associated to abdominal discomfort (Figure 1 in Paper III).

A review of comorbidities in RA found a decrease in physical function, measured by HAQ, with increasing number of comorbidities (40), one of the important comorbidities being GI-disease. An American study found more GI symptoms in RA patients compared
to controls. Disability, as indicated by HAQ score of at least 1, was associated with some GI syndromes in RA (242).

Our findings further support the hypothesis that RA related factors, in addition to traditional risk factors, may influence self-reported GI discomfort in patients with RA and thus pose a challenge to the treating physicians. Our results confirm that coxibs seem to increase GI discomfort less than NSAIDs, although no statistically significant conclusion can be drawn for the direct comparison of these two anti-inflammatory agents in this study.

It is important to bear in mind that this study was performed in 2004 when coxibs were still widely prescribed to RA patients. Use of coxibs was indicated in patients not tolerating traditional NSAIDs, thus a proportion of the patient group taking coxibs had already experienced GI side effects from medication. This previous experience may have influenced their tendency to report side effects from use of coxibs. After our data collection the prescription pattern of coxibs has changed due to documented increased risk of cardiovascular disease. Importantly, also non-selective NSAIDs use may confer an increased risk of cardiovascular disease (243-245), and caution in prescription is generally advised.

Limitations of our study included the cross-sectional design of the analyses limiting the opportunity to assess causality, the lack of clinical examination and blood test results in addition to possible reporting bias. Some concerns with respect to potential confounding by indication needs to be addressed. The high number of patients using coxibs reflects a possible channelling of patients with high risk of GI side-effects (246). As our data were collected prior to the withdrawal of rofecoxib and valdecoxib, this situation is expectedly different today. Anti-inflammatory medication was at the time of data collection an important constituent of symptomatic RA treatment. GI discomfort may not only be a consequence of anti-inflammatory medication in RA, but also of active disease in itself, of disability or of mental distress experienced by the RA patient. As a consequence for clinical practice, rheumatologists should be aware that patients might report GI discomfort that may be related to RA or related to a personal trait of complaining about many different types of symptoms.
Previous research has focused more on endoscopic ulcers or clinically significant ulcer complications, and less on self-reported intensity of GI discomfort and contributing factors (247). Many RA patients suffer from non-specific GI discomfort despite prophylactic use of gastroprotective medication, even after switching to coxibs (190, 191), suggesting that also other factors may contribute to experienced GI discomfort. There have been numerous studies documenting the increased risk of gastrointestinal ulcers with subsequent bleeding related to use of NSAIDs, and many of these patients experienced GI-discomfort in advance.

5.2.4 Health information important to patients: The RAID score

The RAID instrument was developed to better identify and capture the patients’ perspectives of the impact of having RA, and the RAID score includes seven domains of major importance to people with RA. Each domain has a weight that reflects the importance to patients. The main purpose of RAID is to provide a single score that can be used in clinical research and daily practice.

In this study of RAID we found that the distribution differed between the scales with lowest floor effect for the pain scale. This is consistent with the perceived importance of pain to patients with RA. The overall RAID-score demonstrated a weak floor-effect, and the distribution differed between the scales. Floor effect is a general limitation of most health status measures, and indeed, in our study we demonstrated floor effects also for patient global VAS, RADAI and HAQ. For the utility instruments SF-6D and EQ-5D we found different distributions, similar to previous data published from ORAR (248).

An unweighted RAID score, calculated as the mean of the seven NRS, was considered. This may be more feasible than a weighted score, but will have less face validity, as the influence from the patients’ perception of impact of the domains would not be incorporated. We examined the performance of an unweighted RAID score in exploratory analyses and found that the weighted versus unweighted version had slightly higher correlations to global measures and less floor effect. It is a possible concern that the RAID score was significantly higher in women than men. This difference was more strongly statistically significant for the RAID score than for other PROMs with the exception of HAQ (1.01 vs. 0.67, p<0.001). The ten patients who identified the initial
major dimensions in the first elaboration step were all women. Both genders were represented in the following data-driven steps in the elaboration of the RAID score, but as many as 82.5% were women in the weighting procedure (141). Whether or not the RAID score has a bias towards selection of health problems of special importance to women has to our knowledge not been explored in other studies as far as we have found.

Our results support the concept of RAID being a global measure as RAID correlated strongly to other global measures of health (patient global VAS, RADAI, EQ-5D and SF-6D). We found the correlation coefficients of associations between RAID score and other PROMs, age and disease duration, being of the same magnitude with Pearson and non-parametric correlation analyses. Disability measured by HAQ correlated moderately to RAID. The HAQ score was more associated to age and disease duration than RAID, which is consistent with lower responsiveness of HAQ in established versus recent onset RA (249). HAQ measures physical functioning, which only constitutes one of the seven domains in the RAID score.

The representativeness of ORAR discussed previously indicates that our results are complementary to the more stringent validation of the RAID score (162). A strength in our study was that we found similar results using different instruments capturing similar domains, e.g. for sleep and physical function. RADAI was the only measure for disease activity in our study. The RAID score captures health domains important to patients with RA, and the domains have different weight according to this, e.g. pain 0.21, fatigue 0.15 and sleep difficulties 0.12 (162). RAID has been developed and translated across several countries and languages; it is free of charge and short, which makes it feasible and widely applicable. Our results support that RAID may be an attractive PROM when studying the patient perspective on disease.
6. Conclusions

6.1 Answers to research questions

We were able to provide the following answers to the specific research questions posed in section 2.2:

- Improvement of self-reported health status was seen in patient reported disability, physical function, pain, global disease activity and fatigue from 1994 to subsequent time points. (Paper I)

- Health status improved more in women than men with RA over the 15-year period. The gender gap observed in 1994 was considerably diminished in 2009, although there was still a trend towards worse patient reported health status in women. (Paper I)

- The four different measures of sleep were highly correlated. Sleep disturbance in RA was independently associated to fatigue, disease activity, RADAI, mental health and use of sleep medication, and these findings were consistent across all four sleep measures. (Paper II)

- Abdominal discomfort was common in RA-patients and independently associated with impaired physical and mental function, self-reported disease activity (VAS), and use of NSAIDs. (Paper III)

- RAID performed well in capturing and combining information about health domains that are important to RA-patients. This makes RAID an attractive global composite PROM when taking the patients' perspective into account. (Paper IV)

- The overall RAID-score demonstrated a weak floor-effect. RAID correlated strongly to other global measures of health status. (Paper IV)
6.2 Clinical implications

The findings in this thesis highlight the importance of measuring disease burden by PROMs in the follow-up of RA-patients. The focus of patients and physicians may differ, and the perspective of the patient is important to help identify disease aspects where there is a discrepancy. As doctors we should aim to be as considerate to the patients’ needs as possible, but also maintaining the clinical and medical perspective, as well as provide the best medical treatment for the individual patient.

The focus on early diagnosis, tight control, treat to target and access to bDMARDs has led to improved care of patients with RA during the last 15 years. Our findings demonstrate that patients report considerably less burden of disease. We would encourage the use of PROMs in the routine follow-up of patients as this may benefit the individual patients in achieving the best possible quality of life. From a society perspective, investment in improved patient health may enable RA-patients staying in work for a longer period of time, remain more self-sufficient and become less dependent of help. To further improve the effect of using PROMs in patient follow-up, the use of composite measures that include objective measures of disease activity should also be used, e.g. SDAI, CDAI and DAS-28.

SD and fatigue were highlighted as important PROMs by patients at OMERACT. As a result of this, PROMs measuring sleep have received more focus from the physicians. Our study demonstrates the high correlation between RAID sleep and other sleep measures, the highest correlation of the four sleep measures to other PROMs and an independent association with disease activity (RADAI). We had already demonstrated a high correlation between RADAI and the overall RAID-score in an earlier study. These findings suggest that patients reporting sleep disturbance also may have active rheumatic disease, and health personnel should be encouraged to have an increased awareness of this aspect. If our findings are repeated in future studies, the sleep component of RAID may indeed be used to measure SD in RA. This would be valuable in future studies as RAID is feasible, widely applicable and often included in studies of patients with RA.
References


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8. Papers I - IV