# The efficacy of rehabilitation in warm and cold climates for patients with rheumatic and neurological diseases

## Three randomised controlled studies

Doctoral Thesis by

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2010



*Series of dissertations submitted to the*
*Faculty of Medicine, University of Oslo*
*No. 1127*

ISBN 978-82-8264-166-1



Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

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***To Sunniva Annette (10) and Sigrid Louise (3)***
***waiting all their lives for "mum to finish her article soon"***

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# PREFACE

## ACKNOWLEDGEMENTS

First of all, I want to express my gratitude to the study participants who generously gave their time and effort to take part in one of the three studies included in this thesis.

The research was carried out at the Section for Climate Therapy, Department of Rheumatology at Oslo University Hospital Rikshospitalet. I am grateful to Åse Lindrupsen, the Head of the Section for Climate Therapy, and Jan Tore Gran, previous head of the Department of Rheumatology. The main funding of my research was provided from the Norwegian Foundation for Health and Rehabilitation (EXTRA), through the Norwegian Rheumatism Association, thank you. And I am obliged to the Sunnaas Rehabilitation Hospital and the University of Oslo for hiring me in an university position for a specially important period of time.

My deepest gratitude goes to my main supervisor Berit Flatø, who initiated the study concerning the rheumatic patients and trusted me to conduct it. I admire her high standards both in medical research and clinical rheumatology. Her supervision has been especially important for the recognition of this study. I am very grateful for her quick responses to my requests for help in spite of a constantly high working pressure.

I am especially grateful to my co-supervisor Johan K. Stanghelle for being the one to introduce me for research in rehabilitation medicine. I want to thank him

for his never ending encouragement, which has supported my confidence in my own ability and giving me strength to complete this work.

I would like to give some special thanks to my colleagues at the Department of Research at Sunnaas Rehabilitation Hospital. Petra Ahlvin Nordby for being an inspiring person and including me in the manuscript preparation concerning the patients with neuromuscular diseases. Liv Utne for her help with the english translation of the postpolio article. Ellen Kathrine Svendsby and Johan K Stanghelle as important members of the "Dream team" conducting the postpolio study, and giving me a taste for more research in rehabilitation medicine.

BROR (BehandlingsReise og Opptrening ved Revmatiske sykdommer), the acronym of the main study of this thesis, could never have been conducted without my very important fellow workers. I want to thank Bjørn-Yngvar Nordvåg for taking part in all aspects of the conduction of this study, especially for the 234 medical examinations of the participants in the Norwegian arm. Pär-Arne Pajunen for being my very best, flexible and trustable project nurse, an inspiring support and a good friend through a busy time with collection of thousands of data from Turkey to Lillehammer. Anne Winther for taking care of all logistical and cooperational challenges between the North Norway Rehabilitation Centre, the University Hospital of North Norway and Rikshospitalet, in addition to the collection of data in the participants being treated in the North of Norway. Mona Røisland for her professional evaluation of the physiotherapy interventions and physical tests of some of the participants in Igalo and at Skogli rehabilitation centre. Torhild Garen for the preparation and scanning of an enourmous number of questionnaires. Her practical help and moral inspiration kept me survive trough an intensive phase of this study.

In addition, I want to thank Karin Øien Forseth, Gunnstein Bakland and Allan Didriksen for their help with some of the patient examinations, Marianne Strand Svendsen for coordinating the participants of the BROR study, consultant Johan Kofstad at the Department of Medical Biochemistry for help with the blood tests analysis, and the staticians Geir Aamodt, Kathrine Frey-Frøslie, Marte Olstad and Are Hugo Pripp at the Biostatistic unit at Oslo University Hospital Rikshospitalet for help with the statistics. I greatly value the help I received from all of you!

A special thank you goes to Karin Øien Forseth, not only for the 132 medical examinations of a group of study-participants treated in Turkey. But also for being a perfect colleague, which I appreciate much in my current position as a Medical Advisor at the Section for Climate Therapy. I am grateful to Tori Smedal and Anne-Cathrine Clarke-Jenssen for interesting discussions concerning the conduction of comparable studies at our section, and for inspiring meetings with my reseach fellows at the Department of Rheumatology, especially Anne-Kristine Nitter and Helga Sanner.

My research fellows Ingeborg Beate Lidal, Vegard Strøm and Iren Lindbak Matthews have had a special position for me. The combination of your specialized knowledge and quality of a friend, have made our statistics study group to a highlight. Thank you for giving me the opportunity to follow you through your excellent defence for the doctoral degree, this has inspired me to complete my own.

Finally, I want to express my deepest gratitude to my caring parents, Arna Oddveig and Yngvar Staalesen, who always have given their children the highest priority. Thank you for your sympathy and encouragement, and for being the very best babysitters. To my brother, my two sisters, and all, my good friends waiting for

me to have leisure time again, thank you for your understanding and valuable friendship.

Most of all, thank you to my loving husband, Håkon, for his never ending support, and my two girls Sunniva Annette (10) and Sigrid Louise (3), who have been waiting all their lives for “mum to finish her article soon……”.

# PUBLICATIONS INCLUDED

(1) Staalesen Strumse, Y.A.; Nordvåg, B.Y.; Stanghelle, J.K.; Røisland, M.; Winther, A.; Pajunen, P.A.; Garen, T. and Flatø, B. The efficacy of rehabilitation for patients with rheumatoid arthritis: comparison between a 4-week rehabilitation programme in a warm and a cold climate. Scand J Rheumatol 2009;38(1):28-37.

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# ABBREVIATIONS

| | |
|---|---|
| 6MWT | 6 Minute Walking Test |
| ACR | American College of Rheumatology |
| AS | Ankylosing Spondylitis |
| ASAS-IC | The ASsessments in Ankylosing Spondylitis working group's Improvement Criteria |
| BASDAI | Ankylosing Spondylitis Disease Activity Index |
| BASFI | Bath Ankylosing Spondylitis Functional Index |
| BDI | Beck's Depression Inventory |
| BMD | Bone Mineral Density |
| CLA | Cutaneous Lymphocyte Antigen |
| CSF | Cerebrospinal Fluid |
| DAS28 | 28-Joint Disease Activity Score |
| DMARD | Disease Modifying Anti-rheumatic Drugs |
| EFNS | European Federation of Neurological Societies |
| EMG | Electromyography |
| ES | Effect Size |
| ESR | Erythrocyte Sedimentation Rate |
| EULAR | European League against Rheumatism |
| FSS | Fatigue Severity Scale |
| HMSN | Hereditary Motor and Sensory Neuropathy |
| ICD-10 | The International Statistical Classification of Diseases and Related Health Problems |

| | |
|---|---|
| ICF | International Classification of Functioning, Disability and Health |
| IFN-γ | Interferon Gamma |
| IL | Interleukin |
| LSS | Life Satisfaction Scale |
| MCSD | Minimum Clinically Significant Difference |
| MHAQ | Modified Health Assessment Questionnaire |
| NMD | Neuromuscular disease |
| OA | Osteoarthritis |
| P-ADL | Primary Activities of Daily Living |
| PBMC | Peripheral Blood Mononuclear Cells |
| PHA | Phytohaemagglutinin |
| POMS | Profile of Mood States |
| PPS | Postpolio Syndrome |
| PT | Physiotherapy |
| RA | Rheumatoid Arthritis |
| RCT | Randomised Controlled Trial |
| RNNK | North Norway Rehabilitation Centre |
| ROM | Range of Motion |
| SD | Standard Deviation |
| SHC | Subjective Health Complaints (=Ursin Holger Inventorium) |
| SJC | Swollen Joint Counts |
| SunRH | Sunnaas Rehabilitation Hospital |
| TNF α | Tumour Necrosis Factor Alpha |
| TJC | Tender Joint Counts |
| TUG | Timed Up and Go |

VAS Visual Analogue Scale

# BACKGROUND FOR THE STUDIES

## THE DIAGNOSES INCLUDED

### RHEUMATOID ARTHRITIS

Rheumatoid arthritis has an annual incidence of approximately 0.2 per 1000 in males and 0.4 per 1000 in females. A prevalence of 0.5–1% is reported in diverse populations worldwide, although a greater prevalence has been reported in certain Native Americans and the disease is reported to be absent in parts of rural Africa (1). The currently accepted classification scheme for rheumatoid arthritis (RA) is the 1987 American Rheumatism Association (ARA) criteria as presented in Table 1 (2).

| | Table 1. The 1987 American Rheumatism Association (ARA) criteria for rheumatoid arthritis (RA) | |
|---|---|---|
| 1 | Morning stiffness | Morning stiffness in and around the joints, lasting at least one hour before maximal improvement |
| 2 | Arthritis in three or more joint areas* | Soft tissue swelling or fluid (not bony overgrowth) observed by a physician, present simultaneously for at least six weeks |
| 3 | Arthritis of hand joints | Swelling of wrist, MCP or PIP joints for at least six weeks |
| 4 | Symmetric arthritis | Simultaneous involvement of the same joint areas (defined in two) on both sides of the body (bilateral involvement of PIP, MCP or MTP joints is acceptable without absolute symmetry) for at least six weeks |
| 5 | Rheumatoid nodules | Subcutaneous nodules over bony prominences, extensor surfaces or in juxta-articular regions, observed by a physician |
| 6 | Rheumatoid factor | Detected by a method positive in fewer than 5% of normal controls |
| 7 | Radiographic changes | Typical of RA on posteroanterior hand and wrist radiographs; it must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (OA changes alone do not qualify) |
| At least four criteria must be fulfilled for classification of RA; patients with two clinical diagnoses are not excluded. *Possible areas: right or left PIP, MCP, wrist, elbow, knee, ankle, MTP | | |

In the past decade, treatment strategies for patients with rheumatoid arthritis (RA) have changed dramatically. Patients are being treated earlier and more aggressively than in the past and a much greater number of therapeutic options are available, which has increased the complexity of the management of patients with rheumatoid arthritis (3).

# ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease that affects the axial skeleton, causing characteristic inflammatory back pain, stiffness, and often peripheral arthritis. Prevalence figures for ankylosing spondylitis that can be extrapolated from population studies and HLA-B27 frequency yield figures ranging from 0.1% in the Netherlands to 1.1-1.4% in North Norway. Clinical features, age at onset, survival time and incidence have remained stable over time (4-7). Most, but not all, studies have reported a male/female predominance, with ratios in the order of 2-3:1. (6;8)

Different criteria sets for AS have developed over time. The New York classification criteria, modified in 1984, are widely accepted, Table 2 (9).

**Table 2. The 1984 Modified New York Criteria**

| | |
|---|---|
| 1 | Low back pain for at least three months' duration improved by exercise and not relieved by rest |
| 2 | Limitation of lumbar spine motion in sagittal and frontal planes |
| 3 | Chest expansion decreased relative to normal values for age and sex |
| 4a | Unilateral sacroiliitis grade 3-4 |
| 4b | Bilateral sacroiliitis grade 2-4 |
| Definite ankylosing spondylitis if: (4a OR 4b) AND any clinical criterion (1-3) | |

Actually, the modified New York criteria are classification criteria with typically high specificity (98%). The sensitivity (83%) is acceptable, and the modified criteria are proposed to serve as diagnostic criteria as well. However, these criteria are not

appropriate for an *early* diagnosis since 'limitation of the lumbar spine' and 'limitation of chest expansion' reflect disease duration, and these features are usually not present in early disease (10).

## POSTPOLIO SYNDROME

Approximately 10 000 persons with sequelae after acute poliomyelitis are currently living in Norway. The majority of these persons are probably suffering from the "second polio illness," i.e. postpolio syndrome (PPS) (11). This condition afflicts persons with polio sequelae 20 - 40 years after the acute stage of the disease (12). The term post-polio syndrome was introduced by Halstead in 1985 to cover medical, orthopaedic and psychological problems possibly or indirectly related to the long-term disability occurring many years after the acute viral polio infection. Halstead's criteria for PPS were as follows:

1. Confirmed history of polio.
2. Partial or fairly complete neurological and functional recovery after the acute episode.
3. Period of at least 15 years with neurological and functional stability.
4. Two or more of the following health problems occurring after the stable period: extensive fatigue, muscle and/or joint pain, new weakness in muscles previously affected or unaffected, new muscle atrophy, functional loss, cold intolerance.
5. No other medical explanation found (13).

Halstead revised these criteria in 1991 and added -gradual or abrupt onset of new neurogenic weakness- as a necessary criterion for PPS, with or without other co-

existing symptoms (14). An electromyography (EMG) may be used to verify the sequelas after a polio infection with typical lower motor neuron involvement: neurogenic EMG findings, normal sensory findings and normal motor findings except for parametres reflecting muscle atrophy (15).

## HEREDITARY, CONGENITAL NEUROMUSCULAR DISEASES

The umbrella term 'neuromuscular diseases' incorporates a range of conditions that vary appreciably depending on the site and progression of the disease (16). The number of persons suffering from a neuromuscular disease in Norway is approximately 5000 (17-22). The heterogeneous group of neuromuscular diagnoses can be divided into three main groups: myopathies where the disease is located in the muscle fibre or its energy metabolism, disease in the peripheral nerves (neuropathies) and neuromyopathies where both the muscle fibers and the nerves are affected (17-22). The patients included in our study suffered from hereditary, congenital neuromuscular diseases of all of these three main groups, the most frequent diagnoses included are presented in Table 3. These diseases were considered relatively slowly progressive (18;19;22).

| **Table 3 Diagnoses of the Hereditary, Congenital Neuromuscular Diseases included in the study** | |
|---|---|
| Hereditary motor and sensory neuropathy, HMSN (n) | 23 |
| Limb-girdle muscular dystrophy (n) | 10 |
| Myotonic dystrophy (n) | 11 |
| Spinal muscular atrophy (n) | 3 |
| Others (n) | 13 |

Charcot-Marie-Tooth disease (CMT) is the most frequent form of the Hereditary Motor and Sensory Neuropathies (HMSN). Distal palsy, atrophy and loss of sensibility are clinical signs characterising these patients, the underextremities are typically affected first (20;21). The hereditary myopathies typically affect proximal, axial and sometimes facial musculature, and the affection is often symmetrical. Muscular fatigue and reduced tolerance for physical activity are typical signs of a myopathy (23). Dystrophia Myotonica (DM) is the most frequent diagnosis among the hereditary myopathies, characterised clinically by a combination of muscular weakness caused by the dystrophia, and myotonia as a consequence of changed stability over the muscular cell membrane (17).

Even though neuromuscular disorders are a heterogenic group both in terms of pathophysiology and clinical manifestations, it is still possible to identify common impairments that influence quality of life and the ability to cope with everyday living. Some of the common problems and complaints are muscle weakness of various severity, exercise intolerance, reduced endurance, fatigue, pain and problems with ambulation (17;24;25).

# EFFICACY OF PHYSICAL ACTIVITY, EXERCISE AND AN IN-PATIENT REHABILITATION PROGRAMME

Physical activity is “any bodily movement produced by contraction of skeletal muscle that results in increased energy expenditure.” Physical activities, which include sports and recreational activities, occupational activities, and daily-living activities, are important for maintaining general health and for modifying the risk of chronic diseases. Exercise, a sub-set of physical activity, is specially designed to maintain or improve physical fitness. It consists of planned, structured and repetitive movement of parts of or the whole body (26).

Comprehensive rehabilitation may be defined as systematic multidisciplinary treatment given by physicians and health professionals. The rehabilitation programmes should include physical therapy with exercise aiming at improved aerobic fitness, muscle strength, mobility and balance, occupational therapy, and self-management programmes. A rehabilitation programme must include individual assessments and treatment plans targeting defined treatment goals.

## RHEUMATOID ARTHRITIS

People of all ages with RA tend to exhibit cardiovascular deconditioning, muscle weakness, stiffness, poor endurance and decreased lean body mass (27). Rest

therapy, the antithesis of exercise, was earlier prescribed because of the fear that vigorous motion of arthritic joints could damage delicate periarticular tissues. Rest or immobilization was thought to have a specific salutary effect on inflamed joints. Ytterberg et al. reviewed the data available concerning exercise for arthritis in 1994, and concluded that range of motion (ROM), strengthening and aerobic conditioning exercises were safe for patients with osteoarthritis (OA), RA or AS (28).

The objectives of exercise therapy in patients with RA are restoration, preservation or increase of joint range of motion, muscle strength or cardiovascular condition (28). Several studies have demonstrated that different exercise interventions are profitable for RA patients (27;29;30).

Whether the effects of physical training persist in a long-term perspective was studied by Hansen et al. in 1993. The participants of his study followed different exercise programmes over the course of two years and were evaluated by objective parametres like ESR, SJC and X-ray, concluding that although most patients appreciated training, the present study could not support that training lessons affect the disease activity or the progression of the disease (31). Stenström et al. ascertained the effects of once-weekly, intensive dynamic training in water of patients with RA after a four-year training period, demonstrating significantly better grip strength and higher activity level in the intervention group compared to a control group, and significantly more admittances for acute hospital care in the latter. The conclusion supports Hansen et al. that dynamic training does not seem, even from a long perspective, to lead to any undesirable consequences (32).

In 1998, van den Ende et al. reviewed the available studies on dynamic exercise therapy of durations of eight weeks to two years in rheumatoid arthritis (33). On the basis of the six included studies, they concluded that dynamic exercise

therapy is effective in increasing aerobic capacity and muscle strength, and that no detrimental effects on disease activity and pain were observed (31;34;35). Still, further research on the long-term effect of dynamic exercise therapy on radiological progression and functional ability is needed.

In 1994, Stenström found no correlation between radiologically observed progression of joint destruction and self-selected exercise frequency in patients with rheumatoid arthritis during a four year study period (36). A two year high-intensity exercise programme showed to be more effective than usual care in improving the functional ability of RA patients in the randomized, controlled, multicentre trial of de Jong et al. in 2003. The intensive exercise did not increase the radiographic damage of the large joints, except possibly in patients with considerable baseline damage of the large joints (37).

In 2003, Stenström and Minor reviewed the evidence for the benefit of aerobic and strengthening exercise in RA, supporting van den Endes' conclusion about efficacy and lack of detrimental effects, now including "no radiological joint damage" as well (38). As early as 1981, Nordemar et al. had presented a follow-up study of physical training in RA patients for a four to eight year period, revealing a significantly less pronounced progress of X-ray changes in the joints of the active patients compared with comparable control patients (39).

Regular dynamic strength training combined with endurance-type physical activities improves muscle strength and physical function, but not Bone Mineral Density (BMD), in patients with early RA, without detrimental effects on disease activity. This was the conclusion of the randomized two-year study of the effects of dynamic strength training of Häkkinen et al. in 2001 (40). In a follow-up study, they demonstrated that the muscle strength gains were maintained throughout a

subsequent self-monitored training period of three years. Despite substantial training effects in muscle strength, BMD values remained relatively constant. Radiographic damage remained low even at five years (41). On the other hand, a long-term high-intensity weight-bearing exercise program for RA patients has been shown to be effective in slowing down the loss of BMD at the hip (42).

In conclusion, there is high evidence for the immediate efficacy of different exercise modalities in RA patients, as well as the lack of detrimental effects on disease activity, radiologic progression and BMD values even in the long-term aspect. Some studies have even suggested exercise therapy to be effective in slowing down the progress of X-ray changes in the joints and the loss of BMD in the hip (39;42). The results of some long-term studies of the benefits of aerobic and strengthening exercises are more conflicting. This might be explained by the differences in the outcome measures chosen. It seems to be harder to demonstrate improvements in disease activity measures than in measures of aerobic capacity, muscle strength, physical function and symptoms.

Little is known about the optimal model(s) for providing rehabilitative care for patients with RA and AS. Rehabilitative care may be provided by single health professionals or by a multidisciplinary team coordinating their activities. There is some evidence that a comprehensive package of care, delivered in the community and addressing patient specific needs through education, exercise and pain relief modalities has long-term benefits for self-efficacy, disease management knowledge and some measures of disease activity and function (43;44).

Studies of intensive in-patient multidisciplinary treatment of arthritis patients have shown to be more effective than regular physical exercise and physiotherapy alone (Table 4) (45-48). In spite of this, reviews in this field are cautious in their

conclusions. Vliet Vlieland concluded in her review from 1997 that favorable effects on disease activity were seen in most trials comparing short inpatient team care with regular outpatient care. However, proof of efficacy of prolonged outpatient team care is scanty and results of trials comparing inpatient with outpatient team care remain inconclusive (49). Rehabilitation of people with rheumatoid arthritis was the subject of a Best Practice and research publication of the same author in 2003 (50), concluding that despite widespread positive clinical experience with rehabilitative interventions, the scientific evidence of their effectiveness is, in general, scanty, owing to a lack of studies with sufficient methodological quality.

In Hammond's critical review of rehabilitation in rheumatoid arthritis from 2004 (51), the author concludes thoughts on evidence to date in this way. Over at least a one-year period, the following are effective in reducing pain and maintaining function: patient education and joint protection training using behavioural approaches; dynamic exercise therapy, hand exercises and hydrotherapy; and cognitive-behavioural therapy. Symptomatic relief results from thermotherapy, laser therapy, acupuncture and assistive devices. In the short-term, comprehensive occupational therapy, orthoses, and mind-body approaches can help maintain function. Many trials have recruited people with moderate to severe, established RA and relatively little is known about the long-term effectiveness of early rehabilitation, although this is becoming much more common in practice. Despite the increased availability of guidelines and systematic reviews, most conclude there is insufficient evidence for many areas of rheumatology rehabilitation. Further well-designed clinical trials recruiting people with early disease using patient-centred outcomes are needed.

Uhlig et al. have reviewed the effectiveness of comprehensive rehabilitation programmes, concluding that when effects on the various outcome measures are demonstrated, improvements can only with difficulty be attributed to a specific component of a comprehensive program (52). Economic analyses for the effectiveness of comprehensive programs are scarce, but are needed by policy makers to allow the optimal allocation of resources. Preferably the overall performance of comprehensive rehabilitation programs, not the individual components, should be evaluated (52).

**Table 4. Studies of comprehensive in-patient multidisciplinary treatment of Rheumatoid Arthritis patients**

| First author, year of publication | Number of patients (n), design, | Results |
|---|---|---|
| Vliet Vlieland 1996 (46) | N=80,<br>RCT of 11 days in-patient multidisciplinary treatment versus routine out-patient care | Improvements in favour of the in-patient group:<br>• Disease activity<br>• % with an ACR response<br>• Emotional status<br>The improvement in laboratory and functional measures did not differ between the groups |
| Vliet Vlieland 1997 (47) | N=80,<br>A two-year follow-up of the RCT of Vliet Vlieland in 1996 (46) | • Improvements in favour of the in-patient group in all endpoint measures, except for the ESR and HAQ score<br>• The beneficial effect on disease activity persisted over a period of one year |
| van den Ende 2000 (45) | N= 64,<br>RCT of an intensive versus a conservative exercise programme during an in-patient hospital stay with a mean length of 30 days | • The mean improvement in DAS was −1.4 (1.5) and −0.7 (1.4) in the intensive and conservative exercise group, respectively (week 24)<br>• Physical functioning improved for patients in the intensive exercise group<br>• Muscle strength differed between the groups |
| Y. Bulthuis 2007 (48) "The DAPPER study" | N=98,<br>RCT of an intensive in-patient exercise training (IET) for three weeks immediately after discharge from hospital compared to usual care (UC) | The IET showed a better and faster improvement than UC on all outcome measures for:<br>• Range of motion<br>• Disability<br>but not for the HRQoL measures. The DAPPER programme results in regaining of function which lasts up to 52 weeks |

RCT; randomised, clinical trial, ACR; American College of Rheumatology, ESR; erythrocyte sedimentation rate, HAQ; health assessment questionnaire, DAS; Disease Activity Score, HRQoL; health-related quality of life

# ANKYLOSING SPONDYLITIS

Physiotherapy and supervised exercises are widely accepted as part of the non-pharmacologic treatment of patients with AS (53). The physiotherapy intervention aims to prevent and/or retard restriction of spinal mobility and the development of disability but also to improve the symptoms of pain and stiffness (54). In order to reach this goal, patients are encouraged to perform daily exercises at home and weekly group physical therapy, as well as to participate in moderate sport activities such as swimming and cycling. These exercises should be continued regularly lifelong, and the patient's own efforts are the key to future success (54).

Kraag et al. included 53 AS patients in a RCT comparing a home physiotherapy programme combined with patient education versus no intervention at all. They demonstrated significantly improved fingertip-to-floor distance and function after four months compared to the control group, and concluded that physiotherapy with disease education is effective in the treatment of patients with AS (55). Between four and eight months, fingertip-to-floor distance did not change in experimental patients; however, initial improvement achieved was maintained (56). Thus, an individual home-based or supervised exercise program has shown to be better than no intervention.

Hidding et al. (57) and Analay et al. (58) have compared home exercises to supervised group exercises. They found that group exercises were superior in improving movement in the spine and overall well-being, but did not improve self-reported physical function more than home exercises. Exercises were done for six weeks (58) to nine months (57), and included strengthening, aerobic exercises, hydrotherapy, sports activities and stretching.

According to the Best Practice evidence evaluation, there is poor-quality evidence for long-term effects on improved mobility following an inpatient physiotherapy programme for AS patients. This evaluation is based on the retrospective study of Viitanen et al. in 1992 and their 15 months' follow-up study in 1995. The efficacy of a three or four-week intensive inpatient physiotherapy programme was retrospectively analysed in 505 adult patients with ankylosing spondylitis (AS) admitted to a rehabilitation hospital in Finland during a two year period (59). Eight different measures of thoracic and spinal mobility were collected from the patients' medical records. They demonstrated a 7-37% improvement immediately after the rehabilitation period in all mobility measures. Long-term effects were studied in 141 of these patients 15 months after the in-patient rehabilitation. Only chest expansion CE) and vital capacity (VC) had significantly deteriorated from the baseline, while cervical rotation (CR), finger-to-floor distance (FFD) and fitness index were still significantly better. Disease duration did not influence treatment results. The authors conclude that it is possible by means of intensive rehabilitation courses to prevent for more than one year the deterioration of spinal function and fitness in AS patients irrespective of disease duration (60).

In 2001, van Tubergen et al. demonstrated that spa-exercise therapy improved pain and overall well-being more than weekly group exercises alone (61), and that the beneficial effects may last for at least 40 weeks. The standardized spa exercise therapy of three weeks' duration consisted of group physical therapy, walking, correction therapy (lying supine on a bed), hydrotherapy, sports and visits to either the Gasteiner Heilstollen in Austria or to the sauna in The Netherlands. After spa-exercise therapy, all patients followed weekly group physical therapy for another 37 weeks. The Best Practice evidence evaluation reports medium-quality evidence that

spa therapy provides additional effects over self-exercising and group exercising alone, based on a review of van Tubergen and Hidding in 2002 (62).

A questionnaire among international ASAS members reveals that the awareness of published evidence on physiotherapy in AS are unsatisfactory among experts in the field (63). However, according to the Best Practice evidence centre, there is good-quality evidence that exercise therapy improves mobility in AS patients. This conclusion is based upon the Cochrane review of Dagfinrud et al. (64). No harm to the patients was reported in any of the studies included in this systematic review. And "silver" level evidence (www.cochranemsk.org) was found that supported the idea that exercise programs, home-based or supervised, are better than no exercise and that they improve movement and physical function. Group exercises are better than home exercises; they improve movement and overall well-being. Adding a few weeks of exercising at a spa resort to weekly group exercises is better than just weekly group exercises. We still need more information about the different types of physiotherapy and exercise, and how long, how intensive and how often physiotherapy should be done for the most improvement.

## POSTPOLIO SYNDROME

Traditionally, energy conservation strategies such as the reduction of activity level and increased use of orthopaedic devices and technical aids have been the main goal in the rehabilitation of PPS patients (65). Because the initial theories concerning new weaknesses focused on a dysfunctional or deteriorating motoneuron that was already overextended, the preliminary belief among most clinicians was that appropriate management of these overused motor units was to minimize further overwork. This meant either no exercise or, at the most, very limited exercise. It is now clear that

new muscle weakness in many persons may have a reversible or "treatable" component that responds well to certain types of exercises. However, it is also clear that the same exercise programme cannot be prescribed to every individual, as the extent of involvement, and possibly the cause of new weakness, may vary from individual to individual as well as from limb to limb within the same person (66).

Studies of muscle morphology and oxidative capacity in the tibialis anterior muscle indicate a high muscular activity because of gait and weight bearing. Reduced capillary supply in the remaining, hypertrophied muscle fibres and a shortage of substrate during muscle work might be of importance in the muscle fatigue, myalgia and transient decrease in strength which are commonly occurring symptoms in PPS patients (67). However, there are no prospective studies which show that increased muscle activity or training lead to loss of muscular strength compared with the absence of training or less muscular activity. On the contrary, patients who reported regular physical activity had fewer symptoms and a higher functional level than physically inactive patients (68).

One randomized controlled trial reports significant improvement in muscular strength after a 12 week training programme with isometric contraction of hand muscles (69). Nonrandomized trials with training programmes lasting from six weeks to seven months involving both isokinetic, isometric and endurance muscular training show a significant increase in both isokinetic and isometric muscle strength (70-72). No complications or side effects are reported. Hence, there is evidence at class II and III (lower class, better evidence) that supervised training programmes increase muscle strength in patients with PPS (73).

Ernstoff et al. report an increase in work performance by a reduction of heart rate during exercises; hence, endurance training seems to improve cardiovascular

conditioning (Class IV) (72). It should be added that the long-term effects (years) of training are not documented and deserve prospective studies.

Even though the efficacy of physiotherapy and regular, physical exercise in PPS patients has become more clear, a study of different treatment aspects in combination during an intensive, in-patient rehabilitation programme has not yet been reported in scientific literature.

## NEUROMUSCULAR DISEASES

Muscle weakness and reduced muscular endurance are prominent symptoms in patients having neuromuscular diseases (17;24;25). The role of strengthening exercise to potentially improve weakness and the functional abilities of persons with neuromuscular diseases is controversial. David D. Kilmer has reviewed the response to resistive strengthening exercise training in humans with neuromuscular disease (74). The studies reviewed were mainly home exercise programmes of durations lasting between nine weeks and one year. He was not able to make any conclusions about the response in rapidly progressive NMDs, and the response in slowly progressive NMDs span from lack of deterioration only to moderate increase (10-80%) in muscle strength after systematic muscle training. The largest improvements were found in the patients with highest functional level at baseline (74-76). In the study of Aitkens et al., a 12-week moderate resistance exercise program was performed by 27 patients with slowly progressive neuromuscular diseases (NMD) and 14 control subjects. They found this intervention to be practical and safe in slowly progressive NMD and also that it provided moderate improvement in measured strength (75). Modest increases in strength in knee extensors, but a slight decrease in elbow flexor strength was observed with a maximal resistance exercise

protocol in the study of Kilmer et al. Thus, a high resistance training programme may cause some deleterious effects to diseased skeletal muscle, and only moderate resistance training programmes are recommendable in this population (76).

Kilmer concludes his review that resistance exercise may be beneficial if the degree of weakness is not severe, and the rate of disease progression is relatively slow. However, the studies available have some methodological limitations, such as an inadequate number of subjects or a mixed group with different NMDs, ignoring the natural history of each disease; therefore future studies are recommended (74).

Individuals with NMD generally represent a very sedentary and deconditioned population. Their responses to exercise testing are similar to deconditioned able-bodied subjects: lower VO2, minute ventilation, stroke volume, cardiac output, work capacity, peripheral blood flow, and strength (77). One of the primary questions for researchers and clinicians is whether reduced exercise performance is directly due to the muscle or nerve disease through loss of muscle tissue or to the effects of physical deconditioning. If it is primarily the latter, endurance exercise training may be helpful to reverse untoward effects of the deconditioned state.(78)

There are no studies examining aerobic exercise training in the more rapidly progressive NMDs of amyotrophic lateral sclerosis and Duchenne muscular dystrophy (78). In slowly progressive hereditary NMDs, three studies exist that combine multiple types of NMD into a group. In Florence and Hagberg, 12 subjects performed 12 weeks of cycle ergometry training for 30 minutes, three times per week, for 12 wk, at 70% VO2max. This resulted in a 25% increase in maximal oxygen uptake, which was similar to control subjects. However, there was significant variability between individual subjects (79). Conversely, Wright et al. used a 12

week home walking programme, 3–4 times a week for 12 weeks at 50–60% heart rate reserve and found no change in peak VO2, but a reduced heart rate at the same submaximal workload supported a training response (80). In an eight week study of treadmill exercise in subjects with various dystrophies at 70–85% estimated maximal heart rate reserve, Taivassalo et al. demonstrated similar improvements in estimated aerobic capacity in both myopathic (15.7%) and control (10.1%) groups. Heart rate was significantly reduced at a comparable submaximal workload in the myopathic group (81).

In summary, this small number of NMD investigations support these conclusions: (1) Most studies demonstrate positive response to aerobic exercise training, although VO2max may not be affected; (2) cardiorespiratory adaptations to submaximal aerobic exercise training are qualitatively similar to adaptations in able-bodied persons; (3) although short-term adaptations may be demonstrated, the effect of long-term aerobic training is unclear and may ultimately be limited by the loss of muscle mass; and (4) individuals have a variable response to aerobic training, probably due to effects of the individual disease and level of conditioning at the time the study began (78).

Actually, both strengthening exercises and aerobic exercise training are supposed to improve health in NMD patients when given individually and with moderate intensity, as with the patients having postpolio syndrome. A study of different treatment aspects in combination during an intensive, in-patient rehabilitation programme for NMD patients has not yet been reported in scientific literature. Furthermore, there is a need for randomised controlled trials with a long-term follow-up.

# CLIMATE THERAPY DEFINITIONS

## HYDROTHERAPY

The Encarta encyclopedia defines hydrotherapy as the treatment of diseases by the external use of water, for example, by exercising weakened limbs in a pool. Hydrotherapy uses the physical qualities of water like buoyancy and resistance; the temperature may be either cold or warm (82).

## THALASSOTHERAPY

The Encarta encyclopedia defines thalassotherapy as sea-water therapy, a therapeutic treatment that involves bathing in sea water.

## BALNEOTHERAPY

Balneotherapy is the medical practice of treatment by immersion in baths, especially those in spas containing water with a high mineral content according to the Encarta encyclopedia's definition. Verhagen et al. defines balneotherapy in their review as an ancient and popular therapy which involves spending time in an indoor pool filled with mineral water at a temperature of between 31 to 36 degrees Celsius (88 to 97 degrees Farenheit). Different types of mineral water may be used in this therapy, for example, Dead Sea salt or mineral baths, sulphur baths, and radon-carbon dioxide baths (83). Furthermore, Bender et al. define balneotherapy to be the use of thermal waters, not only naturally warm (>20°C) but with a significant mineral content. In Hungary, a recognised mineral water should have minerals of one g/l or more, but no nitrites, nitrates, or bacterial growth (82).

One of the aims of balneotherapy is to soothe pain and improve joint motion and, consequently, to relieve people' suffering and make them feel well (83). Balneotherapy is either provided as the solitary component of the therapeutic approach or in the context of spa therapy (84).

## SPA THERAPY

Spa therapy, in addition to balneotherapy, employs various modalities such as physiotherapy, and even the change in environment and lifestyle (84). Thus, while some researchers have regarded balneotherapy and spas as more or less interchangeable terms (85), others disagree (82). Van Tubergen and Hidding define SPA therapy to be a composition of  a wide range of strategies, including balneotherapy, hydrotherapy, massages, physical exercises, mud applications and relaxation (62).

## CLIMATE THERAPY

Climatotherapy is the use of climatic factors for therapy according to Gutenbrunner et al. (86). Climatotherapy includes the planned medical application of climatic factors that are effective for the prevention or treatment of diseases and the improvement of functioning (rehabilitation). Climatotherapy is performed in specific climates, e.g. high altitude climates, sea coastal climates, and includes changes of climatic environment. Climatic factors with relevance for therapy are radiation (ultraviolet, light, infrared), thermal stimuli (temperature,
wind, humidity, etc.) and air composition (pO2, therapeutic aerosols, absence of pollution and allergens, etc.). Psychological reactions from the experience of landscapes may be a factor as well (86).

When a comprehensive rehabilitation programme is offered in a stable, warm, sunny and dry climate, climatotherapy is supposed to be part of the intervention. However, the main interventions offered through the Section of Climate Therapy are intensive physiotherapy, spa therapy and ”self management” group therapy (87).

# CLIMATE MIGHT INFLUENCE PREVALENCES AND SYMPTOMS

## CLINICAL, RADIOLOGIC, AND SEROLOGIC EXPRESSION OF RA

Drosos et al. compared the clinical, radiologic, and serologic expression of rheumatoid arthritis (RA) in 108 Greek and 107 British patients with RA (88). They demonstrated that the British patients had more severe articular involvement than did Greeks, as judged by the duration of morning stiffness, grip strength, and the numbers of swollen and tender joints. The British RA patients also had more severe joint damage on radiologic examination, and more extraarticular manifestations, including rheumatoid nodules and Raynaud's phenomenon. Greek RA patients, however, more frequently presented with sicca manifestations and serum antibodies to Ro/SS-A. Furthermore, Ro/SS-A antibodies were associated with a high incidence of side effects to D-penicillamine only in the Greeks. They concluded that both genetic and environmental factors may be responsible for these striking differences in disease expression between these two European populations with RA.

## PREVALENCES OF RA

Epidemiological studies show different geographic distributions of a variation of diseases. Hameed et al. (89) studied the prevalence of RA amongst Pakistanis living in England and in Pakistan, in order to ascertain the impact of environmental factors on the causation of rheumatoid arthritis (RA). They calculated that a standardized morbidity ratio (SMR) of RA in England was to be 2.1 compared with Pakistan, a difference that was entirely attributable to females. The SMR for women was 3.0 and for men 0.86. Furthermore, the colder climate was frequently invoked as a cause of more symptoms in England. Thus, several factors may have influenced the observation that RA is more common amongst Pakistanis in England compared with Pakistanis in Pakistan. An environmental factor cannot be excluded.

## PAIN AND RIGIDITY VARY ACCORDING TO SEASON AND WEATHER CONDITIONS

Despite the pervasiveness of the idea that arthritis is influenced by the weather, scientific evidence on the matter is sparse and non-conclusive. However, many patients seem to be convinced of this influence. In Aikman's study of 25 patients with RA and/ or osteoarthritis (OA), 92% of participants perceived their symptoms to be influenced by the weather, while 48% claimed to be able to predict the weather according to their symptoms (90).

AS patients report variation in health status according to season and weather conditions. According to the self-administered questionnaire, the AS-AIMS2 validated for AS, a higher lumbar spine flexibility (Schober index) was associated with a higher climatic temperature and lower wind speed. Physical QOL improved in the summer, as did Social Interaction in the summer and fall, while Role QOL

decreased in the winter (91). Ikuni et al. found definite seasonal differences in RA patients, both subjectively and objectively. RA disease activity was higher in spring and lower during fall (92).

Smedslund et al. aimed to explore how reported joint pain in patients with rheumatoid arthritis (RA) relates to weather and solar variables. The patients differed in the variables they responded to and in which direction, except for consistent negative associations between pain and ultraviolet light dose, and between pain and solar radio flux/sunspot count. The associations were mostly with same-day weather, but also lagged up to three days. Thus, they were not able to fit a statistically significant model at the group level. The conclusion that weather sensitivity seems to be a continuum and a highly individual phenomenon in patients with RA may explain the wide gap between the patients' conviction and the scientists' difficulty in finding evidence of the climatic influence on arthritic symptoms (93).

While the majority of RA patients report that their pain is influenced by the weather, studies examining the impact of weather on RA pain have yielded equivocal results. It is not clear from the existing studies if the mixed results are due to limited statistical power (e.g. small sample sizes and restricted variability in weather indices) or the failure to consider individual differences.

## THE INFLUENCE OF TEMPERATURE, ATMOSPHERIC PRESSURE AND HUMIDITY ON PAIN AND RIGIDITY

*PAIN*

Low temperature and low atmospheric pressure increase the risk of joint pain in rheumatic patients (94) and intensify pain in arthritic rats (95). Sato et al. examined the effects of change in meteorological parametres on pain-related behaviors in a

simulated arthritic condition exposed to low barometric pressure (20 mmHg below the natural atmospheric pressure) and low ambient temperature (7 degrees C lower than 22 degrees C) in a climate-controlled room. When the arthritic rats were exposed to these environments, the already-increased number of hindpaw withdrawals in response to noxious mechanical stimulation (hyperalgesia) was further increased and a hindpaw withdrawal response to innocuous mechanical stimulation (allodynia) began to occur. Such exposures did not influence any of the pain-related behaviors of the control rats. These results show that lowering barometric pressure and ambient temperature within the range of natural environmental fluctuation can intensify pain in arthritic rats (95).

The correlation between low temperature and low atmospheric pressure and increased joint pain are demonstrated in different rheumatic patient groups. Guedj and Weinberger found that pain was positively affected by barometric pressure and temperature in RA, by temperature, rain, and barometric pressure in osteoarthritis (OA), and by barometric pressure in fibromyalgia. Women were more sensitive to weather than men (62% v 37%) (96).

Gorin et al. studied 75 RA patients recording their daily pain severity for 75 consecutive days (97). They demonstrated highest pain levels on cold, overcast days and following days with high barometric pressure. Pain levels also increased as a function of change in relative humidity from one day to the next. Individual difference analyses revealed significant variability between patients in their weather sensitivity patterns. In general, patients with higher levels of self-reported pain demonstrated more weather sensitivity. When considering the magnitude of these effects, however, weather variables accounted for only a small amount of change in pain scores. This pattern was true even for patients with the most pronounced pain-

weather relationships. Therefore, although weather sensitivity was found, the effect sizes were not clinically meaningful (97).

*PAIN AND RIGIDITY*

Aikman sought to establish a possible relationship between the pain and rigidity of arthritis and the weather variables of temperature, relative humidity, barometric pressure, wind speed and precipitation. Mean pain and rigidity scores for each time of each day were found to be correlated with the meteorological data. Correlations between mean symptoms and temperature and relative humidity were significant. Stepwise multiple regression analysis indicated that meteorological variables and time of day accounted for 38% of the variance in mean pain and 20% of the variance in mean rigidity when data of all months were considered. Hence, the results suggest (1) decreased temperature is associated with both increased pain and increased rigidity and (2) increased relative humidity is associated with increased pain and rigidity in arthritis sufferers (90).

According to Patberg and Rasker's review, RA variables are positively correlated with the humidity of the microclimate at the patient's skin, and the classic opinion, "Cold and wet is bad, warm and dry is good for RA patients," seems to be true only as far as humidity is concerned (98).

# SECTION FOR CLIMATE THERAPY, HISTORY AND PRESENT PRACTICE

In Norway, it has been a tradition to admit patients with rheumatic diseases to comprehensive rehabilitation in a warm climate (87). The very first patients were

sent in 1976 because of low treatment capacity for rheumatoid patients in Norway. This tradition was continued for three to five years at a time until 1984, when it was defined as a separate item on the national budget. Initially, the arrangement was considered as an alternative to existing hospital treatment for patients with rheumatic diseases. Gradually, as departments of rheumatology became more numerous in Norway, warm-climate rehabilitation increasingly became a supplementary regimen. In 1997, the Norwegian Parliament decided to make this arrangement a permanent therapeutic option (99). This decision was based on documented efficacy of physiotherapy in warm climate and a relatively low cost. In 2000, an official Norwegian Report called "Treatment Abroad:  a Public Responsibility?" was published (99). This report examined the concept, the rationale for and existing evidence of additional efficacy of physiotherapy in warm climates, and generated some guidelines for future practice. From 2001 to date, this therapeutic option has been administered by the Section for Climate Therapy at the Department of Rheumatology at Oslo University Hospital, Rikshospitalet.

The rehabilitation programme is generally provided at selected institutions in the Mediterranean area with warm and stable climatic conditions, by multidisciplinary rheumatology teams for periods of four weeks. The therapy consists of intensive physiotherapy, spa therapy and "self management" group therapy. When a comprehensive rehabilitation programme is offered in a stable, warm, sunny and dry climate, climatotherapy is supposed to be part of the intervention (86).

# REHABILITATION IN WARM CLIMATE; WHAT IS THE EVIDENCE?

Studies evaluating the efficacy of inpatient rehabilitation in a warm climate for patients with rheumatic diseases are presented in Table 5. The intervention given in these studies meets the definition of comprehensive rehabilitation given in the second subheading of this chapter.

**Table 5. Studies of 3-6 weeks inpatient rehabilitation in a warm climate. *In the RCTs, only the outcome measures with significant difference between warm and cold climate are given.**

| Authors, year of publication | Diagnosis, number of patients (n) | Design, location | Outcome measures with immediate significant improvements* | Follow-up (post discharge) |
|---|---|---|---|---|
| Johansson and Sullivan (100) 1975 | RA (females), n=79 | **RCT**, crossover, Spain vs. Sweden (outpatient) | **Disease activity** (Lansbury, s Rheumatoid Activity Index and Salicylate need) **Physical function** (ROM and grip strength) **Patient's assessments** | four months: Uncertain efficacy |
| Kapstad and Noreik (101) 1994 | RA and AS, n=130 | Uncontrolled, prospective, Turkey | **Patient's assessments** | three months: sustained efficacy among the most affected patients at baseline |
| Hafström (102) 1997 | RA and SpA n=149 | Uncontrolled, prospective, Montenegro, Spain and Canarias | **Patient's assessments:** Physical function (HAQ) and VAS global | three and six months: sustained, but reduced efficacy |
| Cronstedt and Stenström (103) 2002 | SpA, n=48 | Uncontrolled, prospective, Canarias | Mobility (BASMI) **Patient's assessments:** Disease activity (BASDAI), Physical function (BASFI) and VAS global (BASG-1) | three weeks (without BASMI): sustained efficacy in all outcome measures, three months: sustained improvement in BASDAI og BASG-1 only |
| Hashkes (104) 2002 | RA, AS and PsA (RA or AS like), n=136 | Uncontrolled, prospective, Israel | Mobility (Schober's test, OWD and FFD) **Improvement criteria:** 57% ACR20 responders 60% ASAS20 responders | None |

| | | | | |
|---|---|---|---|---|
| Hafström and Hallengren (105) 2003 | RA/JRA and SpA, n=93 | Uncontrolled, prospective, Israel and Canarias | **Patient's assessments**: Physical function (HAQ) Symptoms (VAS pain and VAS global) Health-related quality of life (NHP) | three and six months: sustained efficacy in all outcome measures |

RA; rheumatoid arthritis, RCT; randomised controlled trial, ROM; range of motion, AS; ankylosing spondylitis, SpA; spondylarthropathy, HAQ; Stanford Health Assessment Questionnaire, VAS;visual analogue scale, BASMI; Bath Ankylosing Spondylitis Metrology Index, BASDAI; Bath Ankylosing Spondylitis Disease Activity Index, BASFI; Bath Ankylosing Spondylitis Functional Index, BAS-G; Bath Ankylosing Spondylitis Patient Global Score, PsA; psoriasisarthritis, ACR; American College of Rheumatology, ASAS; The ASsessments in Ankylosing Spondylitis working group, OWD; Occiput-Wall Distance, FFD; Finger-Floor Distance, JRA; juvenile rheumatoid arthritis, NHP;Nottingham Health Profile

## RHEUMATOID ARTHRITIS

The only reported controlled study of the outcome of a rehabilitation programme in a warm climate for RA patients showed that physiotherapy in warm climate was superior to outpatient treatment in Sweden immediately after the treatment period, whereas the long-term effect was uncertain (100). Some uncontrolled studies of physiotherapy in a warm climate of three to six weeks' duration have reported sustained improvements in patients' self-reports after three to six months (101;102;105). Hashkes achieved 57% ACR20 responders according to the American College of Rheumatology (ACR) response definition (106), but his uncontrolled study did not include any long-term follow-up (104).

## ANKYLOSING SPONDYLITIS

Some uncontrolled studies of physiotherapy of three to six weeks duration in a warm climate have reported sustained improvements in self-reported health status after

three to six months (101-103;105). Hashkes found 60% responders to climatic therapy using the ASAS criteria for improvement (IC) (107), but this study was uncontrolled and did not include any follow-up (104).

## POSTPOLIO SYNDROME

Norwegians with PPS have subjectively reported that staying in countries with warmer climates for a period of time has shown positive effects on their health problems (108). However, there has been a lack of scientific publications on treatment of PPS patients in warmer climates.

## NEUROMUSCULAR DISEASES

Individuals with NMDs also report subjectively positive effects of physiotherapy in a warm climate setting. One randomised, controlled trial of a four-week rehabilitation programme for patients with neuromuscular diseases in warm contra cold climate has been accomplished. This study demonstrated immediate effects in patient's assessments after physiotherapy in warm climate only, but sustained improvements in physical tests three months after intervention in both climate groups. No significant difference was found between the improvements in warm and cold climates, but the improvements in warm climates tended to sustain longer, even six months after the rehabilitation period (109;110).

# AIMS OF THE STUDIES

The overall aim of our studies was to investigate the influence of a four week intensive rehabilitation programme on the health status of patients having chronic rheumatic or neurological diseases, and to ascertain whether the efficacy of this intervention varies according to warm and cold climate settings.

Study 1 (Papers 1 and 2):

We wanted to investigate if a four week rehabilitation programme influences health status for patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), and to compare the eventual effect of this intervention given in a Mediterranean or a Norwegian climate. We intended to focus on:

- internationally accepted core sets and improvement criteria and objective tests of physical capacity.
- a 3(-6) months follow-up aspect.

Study 2 and 3 (Papers 3 and 4):

We wanted to investigate if a four week rehabilitation programme in a cold climate (Norway) influences health status for patients with postpolio syndrome (Paper 3), and if a four week rehabilitation programme in a warm climate influences health status for patients with postpolio syndrome (Paper 3) and neuromuscular diseases (Paper 4). We intended to focus on:

- the physical, psychological and social dimensions of health according to WHO's International Classification of Functioning, Disability and Health.

- a follow-up after 6 months for the PPS and after 3 months for the NM study.

# METHODS

## DESIGN OF THE STUDIES

The three studies of this thesis are designed as randomised controlled trials (RCTs). Long-term effect was defined as a sustained effect in at least three months after the four week rehabilitation programme. Design, number of participants (n), and the centres attended in the different studies are presented in Table 6.

**Table 6. Design, number of participants (n), and the centres attended in the different studies**

| Diagnosis | Design | Follow-up | n | Centres attended |
|---|---|---|---|---|
| RA and AS | RCT, 2 groups: warm versus cold climate | three and six months | 124(RA) / 107(AS) | **Warm climate:** Institute Igalo in Montenegro, or Balcova Thermal Therapy Centre, Izmir, Turkey **Norway:** North Norway Rehabilitation Centre (RNNK), Tromsø, or Skogli Rehabilitation Centre AS, Lillehammer |
| PPS | RCT, 3 groups: warm versus cold climate versus control | three and six months | 88 | **Warm climate:** Clinica Vintersol, Tenerife **Norway:** Hokksund Kurbad, Hokksund or Vikersund Kurbad, Vikersund |
| NM | RCT, crossover, 2 groups: warm climate versus control | three months* | 60 | **Warm climate:** Reuma-Sol Centre, Costa Blanca, Spain |

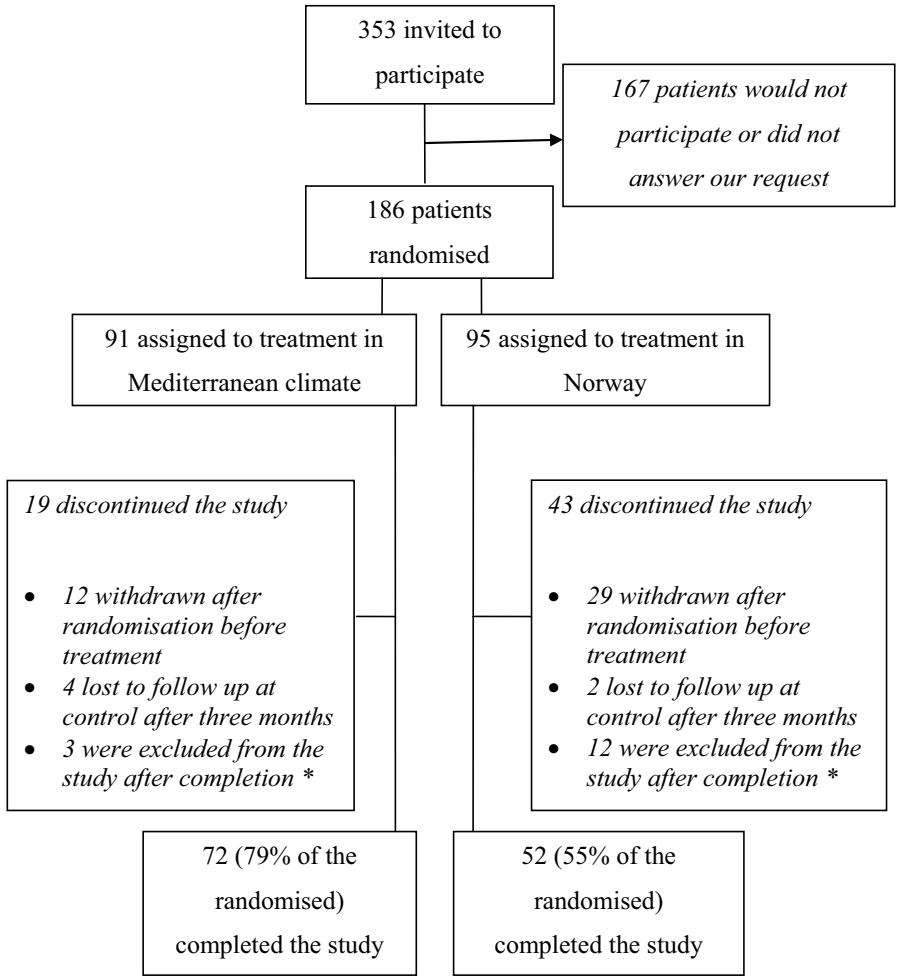
RA, rheumatoid arthritis; AS, ankylosing spondylitis; PPS, postpolio syndrome; NM, neuromuscular diseases; RCT, randomised, controlled trial; n, number of participants. * a second baseline at 11 months after the first intervention

# PATIENT FLOW

## FLOW OF THE PARTICIPANTS IN THE RA STUDY

The 124 participants of this study were recruited from the population of adult patients with rheumatic diseases who applied for a four week rehabilitation programme either in a Mediterranean country through the Section for Climate Therapy at Rikshospitalet in Oslo or at the North Norway Rehabilitation Centre (RNNK) in Tromsø.

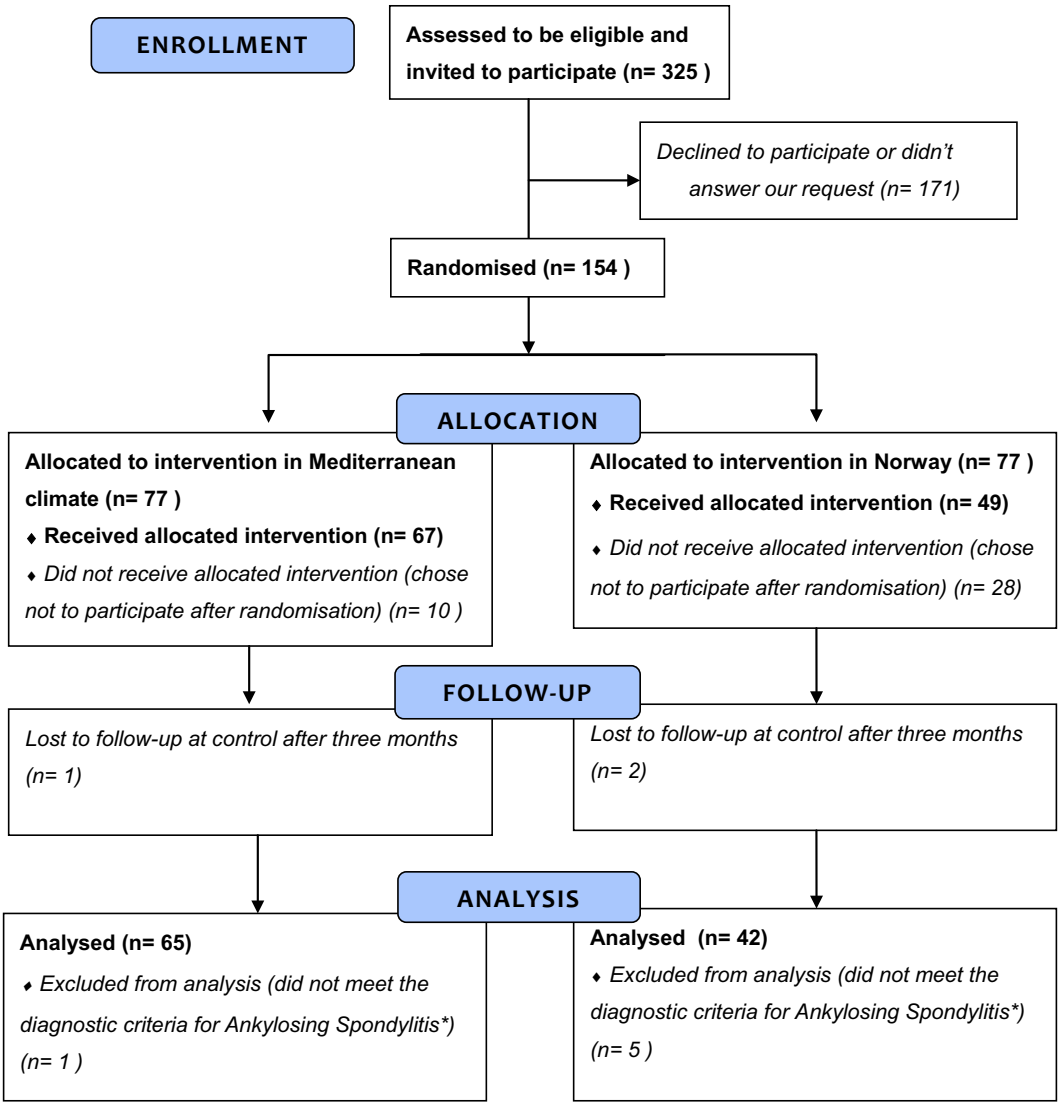
Figure 1. Summary of patient disposition in the rheumatoid arthritis patients, *non-participants in italics (n= 167+19+43).* * The patients excluded did not meet the American College of Rheumatology (ACR) classification criteria of RA (1987) at the first medical examination (2).




## FLOW OF THE PARTICIPANTS IN THE AS STUDY

The 107 AS patients were recruited from the applicants to a rehabilitation programme in a Mediterranean country, administered by the Section for Climate Therapy at Oslo University Hospital, Rikshospitalet or from the applicants to the North Norway Rehabilitation Centre (RNNK) in Tromsø.

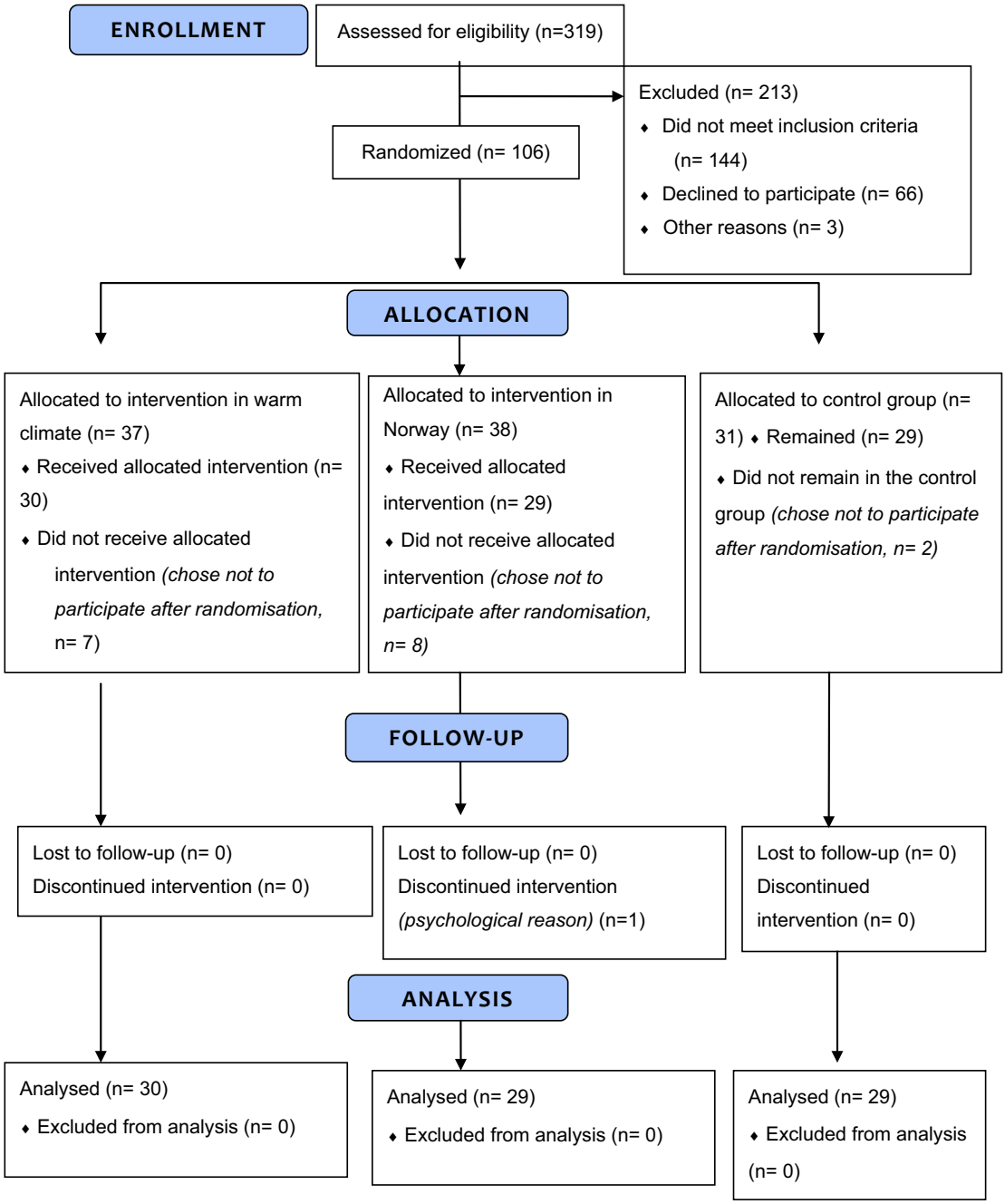
Figure 2. Summary of patient disposition in the ankylosing spondylitis patients, *non-participants in italics, n=218 (171+10+1+1+28+2+5).* * The patients excluded from the analysis did not meet the Modified New York Criteria for Ankylosing Spondylitis (1984) at the first medical examination (9).



# FLOW OF THE PARTICIPANTS IN THE PPS STUDY

The 88 PPS patients in this study were recruited from the previously registered patients with PPS at Sunnaas Rehabilitation Hospital.

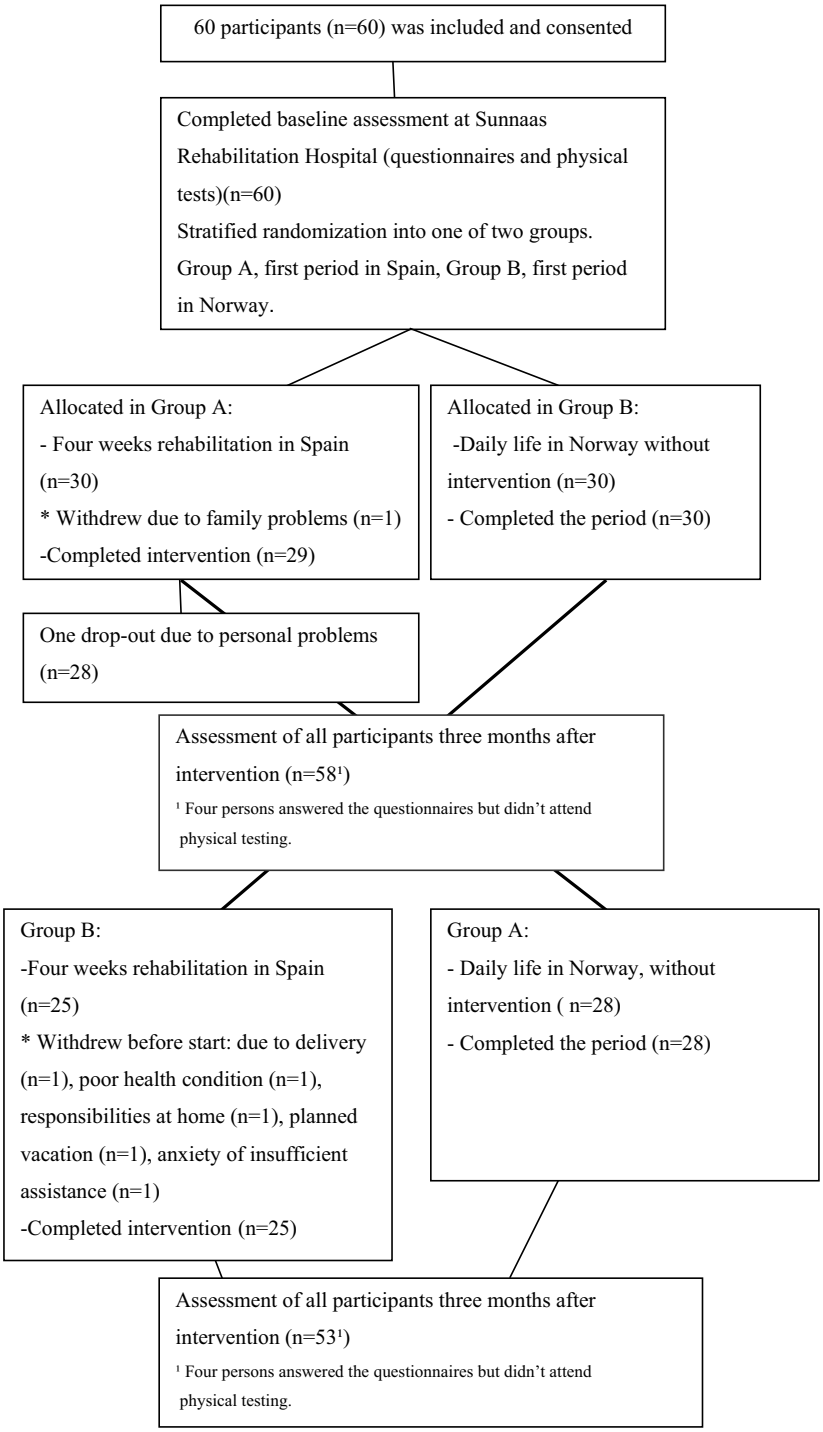
Figure 3. Summary of patient disposition in the PPS study.



# FLOW OF THE PARTICIPANTS IN THE NMD STUDY

The 60 participants of this study were recruited through advertisements in six daily newspapers and the Norwegian neuromuscular organization's newsletter, or through the local groups of the Norwegian neuromuscular organization or one of the two university hospitals in Norway with special units for neuromuscular diseases (Oslo University Hospital, Rikshospitalet and the University Hospital of North Norway).

Figure 4. Flow of the participants through each stage of the cross-over designed trial with patients having neuromuscular diseases.



# PATIENT CHARACTERISTICS

Number, female sex proportion and mean age of the participants in the RA, AS, PPS and NMD studies are given in Table 7.

**Table 7. Number, female sex proportion and mean age of the participants in the RA, AS, PPS and NMD studies**

| | **n** in warm climate/cold climate/control | **Female sex**, n (%) in warm/cold climate/control | **Age**, years, mean (SD) in warm/cold climate/control |
|---|---|---|---|
| RA | 72/52 | 56(78)/ 41(79) | 53(9)/ 53(10) |
| AS | 65/42 | 27(42)/ 19(45) | 48(10)/ 51(8) |
| PPS | 30/29/29 | 22(73)/ 20(69)/ 19(66) | 57(8)/57(8)/59(9) |
| NMD | 60 | 38(63) | 44(12) |

# INTERVENTION

## RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS STUDY

The participants followed the regular rehabilitation programme given to RA and AS patients at the four different centres attended (Table x). The main components of the therapy offered were individualised physiotherapy with exercises, group exercises, passive therapy, relaxation, and patient education.

***Active physiotherapy.*** This included both individualised physiotherapy with exercises and group exercises. The individualised physiotherapy was given once a day either on the couch, in the fitness department using specially constructed equipments, or in the pool. The group training (eight to 15 patients) was given twice a day, once in the gym and once in a temperature-controlled swimming pool. During one week, the patients had a total of 12-15 obligatory sessions, active physiotherapy of 20-45 minute duration in the Mediterranean climate and 15-16 sessions of 30-60 minute duration in Norway. The exercise therapy aimed at increasing endurance, mobility and strength. While the Norwegian programme included more endurance training, the Mediterranean programme had more focus on mobility. At all treatment centres, the patients had different opportunities for additional, voluntary, physical activities either in groups or individually.

***Passive therapy*** comprised of thermotherapy, massage and electrotherapy. At both rehabilitation centres in warm climate (thermo-)mineral water was used in the swimming pools, bubble baths and for underwater massage; hence balneotherapy was part of the programme. The mud is administered as warm packets or filled in a bath tub and mixed with mineral water. A wide range of electrotherapy was offered for local soft tissue pain and oedema. It was the doctor who prescribed the type and amount of passive therapy. At both rehabilitation centres in the Mediterranean climate, they usually prescribed two passive treatments of 10-15 minutes a day for each patient, whereas the patients in Norway only got passive therapy when they had a special need for it.

The different rehabilitation centres had different specialities, and this was especially reflected in the passive therapy offered. Balcova Thermal has two thermo mineral water springs which has been used in spa therapy since ancient times

("Agamemnon spring"). Institute Igalo has a mineral water spring as well and radioactive mud coming from the river of Sutorina which they use in therapy.

***Relaxation.*** The programme included classes in relaxation, organized as 30-45 minute supervised relaxation two to four times a week at Lillehammer, Tromsø and Balcova. At Institute Igalo, activities like yoga and tai chi were offered.

***Patient education.*** Disease-specific lectures about RA were given at all four centres focusing on diet, physical activity, self efficacy, coping techniques and advice related to general health.

***Voluntary physical activities.*** When the compulsory therapy of the day was finished, the patients had different opportunities for voluntary physical activities such as arranged hiking trips, ball games and self-training in the pool or fitness department. The programme varied across the different therapy centres, and the proportion of attending patients was higher at the Norwegian centres.

## POSTPOLIO STUDY

The three institutions involved offered their ordinary programmes adapted for PPS subjects during the intervention period. However, to ensure similar treatment at the three centres, professionals from Sunnaas Rehabilitation Hospital discussed and repeated the main principles for treatment of PPS subjects with the professionals at the involved rehabilitation centres. The main components of the therapy offered were active physiotherapy in groups, individualised physiotherapy with exercises and passive therapy, relaxation, patient education and occupational therapy advices.

***Active physiotherapy.*** This included group exercises which were given twice a day, once in the gym (sitting on a chair) and once in a temperature-controlled

swimming pool. Most subjects attended daily treatment in the swimming pool (45 minutes) and physiotherapy (30 minutes). In addition, each subject was prescribed an individually-adapted training program based on his or her functional level.

***Passive therapy.*** The individualised physiotherapy was given either on the couch or in the fitness department using specially constructed equipments. Apart from supervision in active exercises, this was a passive form of therapy: soft tissue treatment, stretching, thermotherapy, electrotherapy or acupuncture. A session was 30 minutes, five times a week at Clinica Vintersol, four times a week at Hokksund Kurbad, and three to five times a week at Vintersol Kurbad.

***Relaxation.*** The programmes included classes in relaxation, organized as supervised relaxation at Hokksund Kurbad and Clinica Vintersol, and as autogenic training at Vikersund Kurbad.

***Patient education*** focusing on physical activity, self efficacy, ergonomics and advice related to energy conservation was given once a week at Vikersund Kurbad. Focus group interviews were performed at Hokksund and Vintersol Kurbad one to two times a week and once in the third week for all patients by the study team.

***Occupational therapy*** advice was given when needed at Vikersund Kurbad and Clinica Vintersol and ergonomic group training for hand function were offered at Clinica Vintersol as well.

***Voluntary physical activities*** such as self-training in the pool or fitness department, arranged hiking trips or ball games were offered at all treatment centres.

## STUDY OF NEUROMUSCULAR DISEASES

The treatment programme comprised of strength and endurance training at low to moderate intensities, as well as exercises to improve stability, balance and

coordination. To be able to give an adapted level of training, the participants were divided into three different training groups based on the clinical evaluation of physical function by the physiotherapists.

***Active physiotherapy.*** This included group exercises that were given twice a day; in the gym (60 min) and in a temperature-controlled swimming pool (60 min). In addition, each patient was prescribed an individually adapted training program based on his or her functional level.

***Individualised physiotherapy*** was given on request. An average of four treatments was given to each participant during one week. This comprised both supervision in self-training and transfer techniques and more ***passive therapies*** like soft tissue treatment and stretching.

The programmes included one class in ***relaxation*** each week. ***Patient education*** was given focusing on the included diagnosis and corresponding treatment recommendations.

***Voluntary physical activities*** like Nordic Walking and ball games were arranged. The organisation of the daily programme gave the participants opportunity to recover  perform exercises or take a walk on their own according to their individual needs.

# CLIMATE

Apart from Clinica Vintersol at Tenerife, which is a Canary Island located on the west coast of Africa, all treatment centres in our studies were located by the Mediterranean Sea and are therefore supposed to have a Mediterranean climate. Institute Igalo is located at the Montenegrian coastline, Balcova Thermal Therapy

Centre in Izmir in Turkey and Reuma-Sol Centre on the coast of Spain (Costa Blanca).

In the RA and AS study, the patients living in the northern parts of Norway received their rehabilitation programme at RNNK in Tromsø, which is located on the Northern Norway coastline, while the patients living in the southern parts received their rehabilitation programme at Skogli in Lillehammer, which is located in the inland area. Norwegian treatment centres attended in the PPS study, Hokksund og Vikersund Kurbad, were located at the inland area of eastern Norway. Mean temperature and number of "rainy days" during each four week rehabilitation period at the sites of intervention in the RA, AS, PPS and NMD (111) studies are presented in Table 8.

**Table 8. Mean temperature and number of "rainy days" * during each 4-week rehabilitation period at the sites of intervention in the RA, AS, PPS and NMD studies**

| Diagnosis | Climate group | Centre | Mean temp °C | Rainy days* (n) |
|---|---|---|---|---|
| Rheumatoid Arthritis | Warm Climate | Igalo | 24 | 2 |
| | | Izmir | 20 | 1 |
| | Cold Climate | Lillehammer | 1 | 9 |
| | | Tromsø | 6 | 13 |
| Ankylosing Spondylitis | Warm Climate | Igalo | 24 | 2 |
| | | Izmir | 20 | 1 |
| | Cold Climate | Lillehammer | 2 | 8 |
| | | Tromsø | 3 | 12 |
| Postpolio Syndrome | Warm Climate | Tenerife | 25 | mostly dry and sunny |
| | Cold Climate/ Control | | 0 | mainly rainy or snowy |
| Neuromuscular Diseases | Warm Climate (1st period) | Spain | 25 | 4 |
| | (2nd period) | Spain | 24 | 3 |

* days with precipitation above 1.0mm

# OUTCOME MEASURES

The physiotherapy programmes offered to the different patient groups of our studies all aimed at improvement of, or prevention of, the deterioration in physical functioning. Thus, tests of physical capacity became appropriate and had common outcome measures. The Six Minute Walk Test (6MWT) was measured in all patient groups. In addition, questionnaires about physical function were also used in all patient groups. Modified Health Assessment Questionnaire (MHAQ) was measured in the RA patients, Bath Ankylosing Spondylitis Functional Index (BASFI) in the AS patients, and Sunnaas ADL index and Rivermead Mobility Index in the patients with PPS or NMD. MHAQ and BASFI are disease specific instruments designed for the typical problem areas in RA and AS patients, respectively, thus they are naturally not as comparable as a generic questionnaire or an endurance test would be.

Pain measured on a visual analogue scale (VAS) was another common parametre, reflecting pain as a common symptom in all patient groups described in this thesis.

## PREDEFINED IMPROVEMENT CRITERIAS

In rheumatology, predefined criteria are developed to measure disease activity and improvement. These criteria are defined by international accepted working groups, and are supposed to reflect common, clinical signs and complaints in the actual patient group. Thus, the outcome measures chosen to evaluate the efficacy of treatment in RA patients in our study were designed to fit into the 28-Joint Disease Activity Score (DAS28) -calculator of disease activity, and the American College of Rheumatology improvement criteria (ACR 20% or 50%). Similarly, the ASsessments

in Ankylosing Spondylitis working group's Improvement Criteria (ASAS-IC) were used to measure treatment response in the AS patients (107). In addition, spinal mobility tests were taken to concur with the ASAS international working group's core set for physical therapy (PT) interventions, which includes tests of spinal mobility in addition to the ASAS-IC parametres (Figure 5) (53).

Figure 5. The ASAS international working group's core set for physical therapy (PT) interventions used for patients with ankylosing spondylitis.

**Table 7** ASAS core sets

| Domain | Core set CR | SMARD/PT | DC-ART | Instruments |
|---|---|---|---|---|
| Physical function | x | x | x | Bath Ankylosing Spondylitis Functional Index (BASFI) or Dougados Functional Index |
| Pain | x | x | x | VAS in the past week, spine at night, due to AS *and* VAS in the past week, spine due to AS |
| Spinal mobility | x | x | x | Chest expansion *and* modified Schober *and* occiput to wall distance *and* (BASMI or lateral side flexion) |
| Patient's global assessment | x | x | x | VAS in the past week |
| Stiffness | x | x | x | Morning stiffness |
| Peripheral joints and entheses | x | | x | Number of swollen joints and assessment of painful entheses |
| Acute phase reactants | x | | x | ESR |
| Fatigue | | | x | VAS question on fatigue from BASDAI |
| Imaging | | | x | AP and lateral x ray examination of the lumbar spine, lateral cervical spine, AP pelvis (SI and hip joints) |

CR, clinical record keeping; SMARD, symptom modifying antirheumatic drug; PT, physical therapy; DC-ART, disease controlling antirheumatic treatment; VAS, visual analogue scale; BASMI, Bath Ankylosing Spondylitis metrology Index; ESR, erythrocyte sedimentation rate; AP, anteroposterior; SI, sacroiliac.

## DAS28 AND ACR CRITERIA

For RA patients, the 28-Joint Disease Activity Score (DAS28) was calculated from the following formula using the patient's assessment of disease activity (100mm VAS) instead of general health (GH): DAS28 = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR) + 0.014 * GH (112) das-score.nl .

ACR20 and ACR50 responses were calculated based on changes in the components of the ACR-core set. To fulfil the ACR20 improvement criteria, a RA patient has to achieve greater than or equal to 20% improvement in tender joint

counts (TJC) and swollen joint counts (SJC) and greater than or equal to 20% improvement in at least three of the following five ACR core set measures: pain, patient and physician global assessments, self-assessed physical disability, and acutephase reactant. An ACR50 response reflects a 50% improvement in the same parametres (106).

### ASAS IMPROVEMENT CRITERIA AND ASAS CORE SETS

To attain an ASAS20 improvement, an AS patient has to achieve ≥20% relative improvement and an absolute improvement of ≥1 unit (on a scale of 0-10) in three or more of the following four domains: patient's global assessment, patient's perception of pain (question two of the BASDAI), inflammation (mean of questions five and six of the BASDAI), and function (BASFI), with no worsening by ≥20% and ≥1 unit in the remaining domain (107). ASAS40 improvement was defined as attaining a ≥40% relative improvement and an absolute improvement of ≥2 units in three or more of the four domains, with no deterioration from the baseline in the remaining domain (113).

## THE ICF PERSPECTIVE

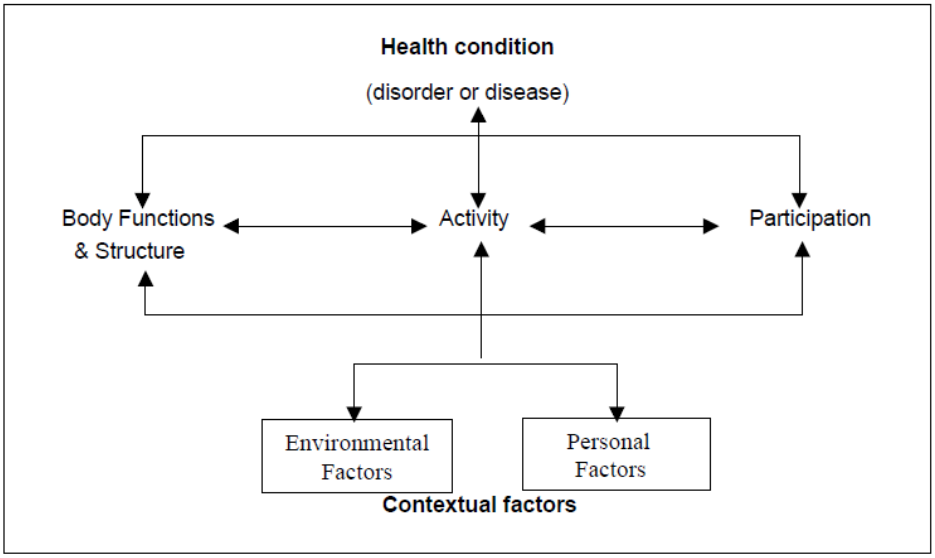
The studies of postpolio syndrome and neuromuscular diseases were designed at Sunnaas Rehabilitation Hospital (SunRH), thus the rehabilitation aspect leads to a selection of outcome measures in an "International Classification of Functioning, Disability and Health" (ICF) perspective. The ICF is a classification of health and health-related domains. These domains are classified from body, individual and societal perspectives by means of two lists: a list of body functions and structure, and a list of domains of activity and participation. Since an individual's functioning

and disability occurs in a context, the ICF also includes a list of environmental factors."(Figure 6) http://www.who.int/classifications/icf/en/

ICF belongs to the WHO family of international classifications, the best known member of which is the ICD-10 (the International Statistical Classification of Diseases and Related Health Problems). ICD-10 gives users an etiological framework for the classification, by diagnosis, of diseases, disorders and other health conditions. By contrast, ICF classifies functioning and disability associated with health conditions. The ICD-10 and ICF are therefore complementary, and users are encouraged to use them together to create a broader and more meaningful picture of the experience of health of individuals and populations. (114;115)

Figure 6:

The International Classification of Functioning, Disability and Health (ICF)



In Table 9, the outcome measures used in the two studies of neurological diseases are coded in an ICF perspective. Some multidimensional outcome measures might cover more than one dimension of health, and then the dimension that has been focused on in our setting is chosen.

**Table 9. Outcome measures in a ICF perspective**

| **Variables** | **ICF code** | **PPS** | **NM** |
|---|---|---|---|
| **Body functions and structures** | | | |
| **Pain**<br>10cm or 100mmVAS (116)<br>1-6 Likert scale | b280 Sensation of pain | X<br>X | X |
| **Fatigue**<br>Fatigue Severity Scale (117;118) | b130 Energy and drive functions | X | X |
| **Subjective health complaints (SHC)**, (=Ursin Holger Inventorium) (119) | Chapter b2 More sensory functions and pain | X | X |
| **Handgrip strength**<br>Grippit Deluxe Hand Dynano-meter Jamar Limited (120) | b730 Muscle power | X | |
| **Lung function**<br>Micro Plus Spirometer (121) | b440 Respiration functions | X | |
| | | | |
| **Activity** | | | |
| **Walking endurance**<br>Six Minute Walk Test (6MWT) (122;123) | b4550 General physical endurance and<br>d450 Walking | X | X |
| **Fast walking** (measured by a 20 m walking test) (122;123) | b770 Gait pattern functions and<br>d450 Walking | X | X |
| **Mobility/ balance**<br>Timed Up and Go (TUG) (124) | d420 Transferring oneself, d450 Walking | X | X |

| | | | |
|---|---|---|---|
| **Rivermead Mobility Index** (125) (122) | d410 Changing basic body position | X | X |
| **Activities of daily life**<br>Sunnaas ADL index (126) | b620 Urinary function<br>d455 Moving around<br>d510 Washing oneself<br>d520 Toileting<br>d540 Dressing<br>d550 Eating<br>d560 Drinking<br>d630 Preparing meals<br>d640 Doing housework and d399 Communication, unspecified | X | |
| | | | |
| **Participation** | | | |
| **Quality of life**<br>Life Satisfaction Scale (LSS) (127;128) | d750 Informal, social relationship<br>d760 Family relationship<br>d770 Intimate relationship d870 Economic self-sufficiency d859 Work and employment | X | X |
| **Mood**<br>Profile of Mood States (POMS) (129) | b152 Emotional functions<br>b1263 Psychic stability | | X |
| **Depression**<br>Beck's Depression Inventory (BDI) (130) | B152 Emotional functions, b180 Experience of self and time functions | X | |
| From the ICF checklist: b= Impairments are problems in body function as a significant deviation or loss, d= Activity limitations are difficulties an individual may have in executing activities. Participation restrictions are problems an individual may have in involvement in life situations. | | | |

ICF core sets for rheumatoid arthritis have been defined (131) and tested for reliability (132). Stucki et al. focus on ICF's value and application in rehabilitation medicine (133), stating that its success will depend on the compatibility with current measures used in rehabilitation medicine (133). The outcome measures used in the RA and AS study of this thesis could be coded into an ICF perspective as well. But

since the results in these patients have been presented according to the predefined improvement criteria, we chose to hold on to that disposition.

# STATISTICAL ANALYSES

Statistical analyses were undertaken with the SPSS (Statistical Package for Social Sciences) program, versions 13.0 (RA and AS), 12.0 (NMD) and 7.5 (PPS). Continual data was presented as mean and standard deviation (SD) or median and $25^{th}$, $75^{th}$ centiles (quartiles) according to whether the observations showed normal distribution. Number of patients and percentage of total number were given for the categorical data.

In all studies of this thesis, we did statistical analysis for the comparison of two groups. To compare the non-participants with the participants and the different treatment or control groups, we used the Pearson Chi-Square Test if the observations were of categorical nature and Fisher's Exact Test if expected frequency was below five in more than 25% of the cells. If the observations were of continual nature, we used the Independent Samples T-Test for observations with normal distribution and presented the results given for equal variances not assumed if $p<0.05$ at Levene's Test for Equality of Variances. The Mann Whitney U-Test was done if the continual observations did not show normal distribution.

In the RA, AS and NMD studies, the clinical response was given as the mean difference from baseline with corresponding SD, or median difference from baseline with corresponding quartiles according to whether the differences showed normal distribution or not (Papers 1, 2 and 4). In the PPS study, the values at each time point were presented (Paper 3). In the NMD study, the 95% confidence intervals were

given for the differences in changes from baseline between the groups (Table II, Paper 4).

For the normal distributed mean or mean difference, Paired Samples T-Test and Independent Samples T-Test were used for within group and between groups analysis, respectively. When the median or the median difference have been presented, the Wilcoxon Signed Rank test and Mann-Whitney U-test have been used for within group and between groups analysis, respectively.

The data from the cross-over study (NMD) were analysed as described in *Altman; practical statistics for medical research ( page 467-471)* (134). No significant period or carry-over effects were found for the changes, and the analyses were therefore performed on the material as a whole, not regarding the order in which intervention was given (Paper 4).

The chosen level of significance was probability (p) values $\leq 0.05$.

In the thesis, we calculated the effect sizes (ES) of the attained improvements in the 6MWT and pain (VAS) parametres in order to achieve a standardised measure of the amount of change. An effect size is the size of the relationship between two variables and is usually defined as the difference in mean outcomes between a treatment and a placebo group. Cohen defined *d* as the difference between the means, M1 - M2, divided by the standard deviation of either group (when the variances of the two groups are homogeneous).

$$\frac{\Delta\text{treatment} - \Delta\text{placebo}}{\text{SD (mean baseline value of the treatment or placebo group)}}$$

This ES calculations are described at http://www.researchconsultation.com/effect-size-calculation-help.asp , and by Fan and Konold (135). In this thesis, the effect size was calculated for each group as well by the formula:

$$\frac{\text{mean week16 value} - \text{mean baseline value}}{\text{SD (mean baseline value)}}$$

Effect sizes are generally defined as small ($d = .2$), medium ($d = .5$), and large ($d = .8$).

# ETHICAL ASPECTS

Written, informed consent was obtained from all participating patients. They were informed that they could withdraw from the study at any time. The Regional Committee of Medical Research Ethics of Norway gave ethical consent for the RA, AS and PPS studies. The NMD study was approved by the internal ethical committee at the Sunnaas Rehabilitation Hospital, University of Oslo, based upon the fact that the almost identical study on patients with postpolio syndrome was approved by the Regional Ethical Committee the year before. Furthermore, The Norwegian Social Science Services/ Data Inspectorate approved the collection, processing and storage of personal information attained in the RA and AS study.

# SUMMARY OF RESULTS

## PAPER 1 -RA

### THE EFFICACY OF REHABILITATION FOR PATIENTS WITH RHEUMATOID ARTHRITIS: COMPARISON BETWEEN A 4-WEEK REHABILITATION PROGRAMME IN A WARM AND A COLD CLIMATE

This study was designed as a randomised, controlled, parallel group trial to compare the effects of therapy given in a Mediterranean climate versus in a Norwegian climate. The 124 RA patients applying for rehabilitation were randomized to a rehabilitation programme either in Norway or in a Mediterranean climate. The participants were examined clinically immediately before (week 0) and after (week 4), as well as three months after (week 16) the rehabilitation period. They also answered a mailed questionnaire after six months (week 28). Long-term effect was defined as a sustained effect for at least three months. The 28-Joint Disease Activity Score (DAS28), the American College of Rheumatology (ACR) response, and physical tests were used to measure clinical response.

We found that the baseline DAS28 value 4.45(1.16) was reduced by -0.95 (1.05) in the Mediterranean climate and the baseline DAS28 value 4.18 (1.17) was reduced by -0.37(0.92) in the Norwegian climate at week 16 (p=0.003). An ACR20 improvement was achieved in 25% of the patients treated in the Mediterranean

climate and 15% of those treated in the Norwegian climate. Sustained improvement in all ACR core components at week 16 and in patient's assessment of health status at week 28 was found in the patients treated in the Mediterranean climate only. Tests of physical function, the Six Minute Walk Test (6MWT) and the Timed Up and Go (TUG) showed comparable improvements in patients treated in both climates.

In short, we found that RA patients had positive immediate effects on disease activity, physical function, and symptoms during a four week rehabilitation programme. The effects on disease activity and symptoms were greater and better maintained at least three months after rehabilitation in a warm than in a cold climate, while the effects on physical function were comparable in the patients treated in both climates three months after the rehabilitation period.

# PAPER 2 -AS

## THE EFFICACY OF REHABILITATION FOR PATIENTS WITH ANKYLOSING SPONDYLITIS: COMPARISON BETWEEN A 4-WEEK REHABILITATION PROGRAMME IN A WARM AND A COLD CLIMATE

The 107 AS patients in this study were part of the randomised, controlled, parallel group trial described for the RA patients. They were randomised to a four week in-patient rehabilitation programme in Norway or in a Mediterranean country and evaluated at the same time points. The ASsessments in Ankylosing Spondylitis working group's Improvement Criteria (ASAS-IC), and tests of spinal mobility and physical capacity were used to measure treatment response.

In these patients, we calculated the proportions of patients who fulfilled the pre-defined improvement criteria at week 16. For the ASAS20 and ASAS40

improvement criteria, we found improvement in 50% and 29% of the participants in the Mediterranean group and 23% and 10% of the participants in the Norwegian group. The proportion of patients who achieved a 20% and 40% improvement in Schober's test was 43% and 29% in the Mediterranean group and 25% and 10% in the Norwegian group. In addition, the proportion of patients with 20% and 40% improvement in lateral flexion was 91% and 75% in the Mediterranean and 54% and 39% in the Norwegian group.

This study showed that AS patients had a sustained positive effect of a four week rehabilitation programme both in a Mediterranean climate and in a Norwegian climate. Nearly all disease variables were still improved both in the Mediterranean climate and the Norwegian climate groups at week 16. While the improvements in physical capacity were comparable, the improvements in the patient's assessments of health status and spinal mobility measures were greater and better maintained at least three months after rehabilitation in a Mediterranean climate.

# PAPER 3 -PPS

## TREATMENT OF PATIENTS WITH POSTPOLIO SYNDROME IN WARM CLIMATE

In this study, 88 patients with postpolio syndrome were randomised into three groups. One group underwent a four week physiotherapy programme at Tenerife, a second group received a similar treatment in Norway, while the participants in the third group followed their ordinary health care programme (control group). All patients were tested at the start of study, and three and six months later, and the patients in the intervention groups were tested after the rehabilitation period as well.

The aim of the outcome measures was to cover the three levels of WHO's defined consequences of disease; impairment, disability and handicap, including physical tests and several questionnaires.

In short, we found that PPS patients had positive sustained effects on both symptoms and physical function three months after a rehabilitation programme in a warm climate, but on physical function only after a rehabilitation programme in a cold climate. Effects on depression measured by Beck's Depression Inventory were seen in both the control and the warm climate group. A summary of the results in the chosen outcome measures of this study is given in Table 10, the parametres still significantly improved at week 16 are highlighted (136).

**Table 10. Summary of results from the PPS and NMD studies in an ICF perspective. Sustained improvements three months after the intervention (week 16) are highlighted.**

| **Variables** | **ICF code** | **PPS** | | | **NM** | |
|---|---|---|---|---|---|---|
| **Body functions and structures** | | wc | cc | control | wc | control |
| **Pain**<br>10cm or 100mmVAS (116)<br>1-6 Likert scale | b280 Sensation of pain | **<br>** | | | **<br>x | x |
| **Fatigue**<br>Fatigue Severity Scale (117;118) | b130 Energy and drive functions | *** | | | *** | |
| **Subjective health complaints (SHC)**, (=Ursin Holger Inventorium) (119) | Chapter b2 More sensory functions and pain | *** | | | ** | |
| **Handgrip strength**<br>Grippit Deluxe Hand Dynano-meter Jamar Limited (120) | b730 Muscle power | *** | *** | * | x | x |
| **Lung function**<br>Micro Plus Spirometer (121) | b440 Respiration functions | | | | x | x |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Activity** | | | | | | |
| **Walking endurance**<br>Six Minute Walk Test (6MWT) (122;123) | b4550 General physical endurance and<br>d450 Walking | *** | ** | | *** | |
| **Fast walking** (measured by a 20 m walking test) (122;123) | b770 Gait pattern functions and d450 Walking | *** | | | ** | |
| **Mobility/ balance**<br>Timed Up and Go (TUG) (124) | d420 Transferring oneself and d450 Walking | *** | * | | *** | |
| **Rivermead Mobility Index** (125) (122) | d410 Changing basic body position | | | | | |
| **Activities of daily life**<br>Sunnaas ADL index (126) | b620 Urinary function<br>d455 Moving around<br>d510 Washing oneself<br>d520 Toileting<br>d540 Dressing<br>d550 Eating<br>d560 Drinking<br>d630 Preparing meals<br>d640 Doing housework and<br>d399 Communication, unspecified | | | | x | x |
| | | | | | | |
| **Participation** | | | | | | |
| **Quality of life**<br>Life Satisfaction Scale (127;128) | d750 Informal, social relationship,<br>d760 Family relationship<br>d770 Intimate relationship<br>d870 Economic self-sufficiency d859 Work and employment | | | | | ** |
| **Mood**<br>Profile of Mood States (POMS) (129) | b152 Emotional functions<br>b1263 Psychic stability | x | x | x | *** | |
| **Depression**<br>Beck's Depression Inventory (BDI) (130) | B152 Emotional functions,<br>b180 Experience of self and time functions | *** | | * | x | x |
| Significant improvement from baseline: *=p<=0.05, **=p<=0.01, ***=p<=0.001. wc=warm climate, cc=cold climate, x= parametre not used in this study | | | | | | |

# PAPER 4 -NMD

## PATIENTS WITH NEUROMUSCULAR DISEASES BENEFIT FROM TREATMENT IN WARM CLIMATE

The aim of this study was to explore if a four week rehabilitation programme in a warm climate influenced health for patients with neuromuscular diseases. We chose a RCT with crossover design, thus all the participants were followed through one period of intervention and one period of "life as usual." Randomisation was performed after the first baseline examinations. Long-term effects were defined as changes in physical and psychological functions persisting after three months (week 16) and several scales according to WHO's classification of functioning were used. Primary and secondary outcome measures were defined prior to study start, thus, we could improve the statistical conditions, and still cover the large variety of symptoms and complaints in these patients.

We found sustained improvements on symptoms, tests of physical function and the Profile of Mood States (POMS) three months (week 16) after the rehabilitation programme in a warm climate. Basic ADL functions (Rivermead Mobility Index) remained unchanged, and there was a reduction in the Life Satisfaction Scale during the control period. A summary of results in the chosen outcome measures of this study is given in Table 10 and the parametres still significantly improved at week 16 are highlighted.

This study shows positive long-term effects on the body functions and structures, the activity and the participation dimensions of health after a four week rehabilitation program in a warm climate for patients with neuromuscular diseases. This effect might be due either to the program or to the warm climate or to a combination of these.

# GENERAL DISCUSSION

# METHODOLOGICAL CONSIDERATIONS

## OVERALL DESIGN OF THE STUDIES

The three studies of this thesis are designed as randomised controlled trials (RCTs). The objective of a RCT design is to sort out how one single factor influences the results of an intervention. When implementing RCTs in rehabilitation medicine, you meet some challenges. Rehabilitation implies a multifactorial approach to a problem, or more often, a complexity of problems associated with a disease or a trauma. Thus, isolating climate as the only differing factor in the treatment programmes offered in warm versus cold climates might be a difficult task.

Blinding, another important principle in the "gold standard RCT," has been impossible to implement in this study. Both the patients and the therapists have been fully aware of being in Norway or in a warmer climate.

Paul Dieppe has focused on the problems of implementing RCTs in complex interventions, such as in a physical therapy trial. Not surprisingly, this concurs with the methodological challenges of our studies. He pinpoints the difficulty that arises when an improvement is gained. The RCT will not allow you to find out how or why the intervention has worked—it does not allow us to dissect the effects of, for

instance, the therapists and their personalities from the exercises they recommended. Thus, the attained improvement may not have helped in an understanding of what is going on after all (137).

The NMD study was designed as a crossover RCT. In this design, the participants followed both intervention periods, which reduces the inter patient variation in the obtained data. The fact that only one of the periods included treatment, while the other was a control period only, ascertains the efficacy of rehabilitation in warm climate only, which has weakened the impact of this study.

## STANDARDISATION OF TREATMENT?

The intervention given in the studies of this thesis fulfil the definition of comprehensive rehabilitation given in the introduction, apart from the fact that the occupational therapy might be somewhat scanty and that the self-management programme might differ in quality at some of the rehabilitation centres.

In the postpolio study, the physiotherapists in our study group attempted to isolate climate as the only differing factor by standardising the physiotherapy programme at each rehabilitation centre before the first patient group arrived. This made us able to conclude about a possible difference in efficacy of a physiotherapy programme when given in a warm or in a cold climate setting.

The design of the study of neuromuscular diseases did not include an intervention group in Norway, but had a crossover design comparing treatment in a warm climate with no extra intervention (control group). This made us able to conclude whether the intervention in warmer climate was better than no intervention.

In the RA and AS study, we focused more on evaluating “the existing” treatment than on exploring the climatic influence only. Thus, the physiotherapy

programmes were comparable, but not identical. The main difference was the passive therapy including balneotherapy given in the Mediterranean climate centres only. A consequence of this design was that each centre had the opportunity to use their specialty in their treatment. This might give a better result for the individual patient, but in a scientific view, it weakens the validity of a conclusion about the difference in efficacy when a four week rehabilitation programme is given in a warm climate versus a cold climate. However, our results might indicate from which of the existing treatments the patients benefit most. This might in turn be the most interesting fact to know for the patients, their medical therapists, and in a health economic view.

## CONFOUNDING VARIABLES

For the interventions, more than the climatic conditions differed between the programmes offered in a cold and a warm climate setting. Daily light exposure differs between the centres attended, and this might influence disease activity in RA patients according to some studies (92;138;139). Factors that come with the change in environment and being far away from home and daily duties might also be of importance. Furthermore, the positive psychosocial effects of spending time together with other people and participating in a social life might be of importance for the total experience of wellbeing. These confounding variables are hard to control for, and imply that we have to be careful with our conclusions about climatic influence.

## INCLUSION AND REPRESENTATIVENESS

To what degree that our results are generalisable might be affected by the different inclusion procedures used to gain participants in the three different studies. Hence, it

is appropriate to discuss whether the study participants were representative of the actual patient population. The participants in the RA and AS study were recruited from the applicants to a rehabilitation programme in a Mediterranean country, administered by the Section for Climate Therapy or from the applicants to the North Norway Rehabilitation Centre (RNNK) in Tromsø. Accordingly, these patients are likely to be more motivated to participate in a four week rehabilitation programme than other patients might be. Many of them were supposed to have earlier experience with, and expectations for, the warm climate treatment programme.

There is an aspect of self-selection in the participants of the NMD study, as well. They were recruited by an advertisement in six large newspapers as well as in the magazine of the Norwegian association of patients with muscular diseases. In addition, information from this study was given to the Norwegian association of patients with muscular diseases and to two different departments of neurology that treat patients with neuromuscular diseases. Not surprisingly, a large proportion of the participants were members of the Norwegian Association of Patients with Muscular Diseases. This might bias the selection towards the more informed part of this patient population, which might have a higher degree of disease acceptance than other patients.

In the PPS study, we invited patients that had once been at Sunnaas Rehabilitation Hospital (SunRH). Therefore, the patient population was selected according to specific criteria from the information available in a hospital journal. A "hospital population" of patients might have a more severe manifestation of the disease than other patients with the same diagnosis.

The inclusion and exclusion criteria of a study are likely to cause a selection bias. Because of practical and economical considerations, all participants should be

able to handle primary activities of daily living without assistance. Therefore, the persons with severely reduced physical function were not included in any of our studies, and our conclusions are not directly generalisable to be valid for these patients.

## DIAGNOSIS AND VALIDITY

The most important inclusion criterion in all these studies was that the actual diagnosis had to be verified by a specialist according to specific diagnostic criteria. This was assured by information in hospital journals in the PPS patients, and by medical records enclosed in the doctor's application in the RA, AS and NMD patients. In the RA and AS study, we had to exclude some of the study participants from the analysis because of uncertainty about the diagnosis based on our own medical examination at baseline. This is likely to increase the validity of our results in the sense that we have included the patients we intended to.

## DROPOUT RATE AND VALIDITY

A selection of patients prior to study start might affect the generalisability of the study result. When the participants drop out during the study period, the selection bias might affect the intern validity of the study findings. To evaluate the harm of a high dropout rate, it is essential to know why the patients dropped out of the study. The reasons could indicate whether the patient selection is likely to bias the results or not.

When counting the dropouts of our studies, we find some typical patterns. A not negligible percentage of the participants withdrew immediately after

randomisation. This occurred in both the PPS, RA and AS studies, but not in the NMD study that had a crossover design which means that all participants received intervention in both a warm climate and a control period. If withdrawal occurs as a consequence of disappointment with the randomisation result, a selection bias might influence the study results. However, Mouffett et al. asked the patients in their RCT about which therapy they would prefer before randomisation, and demonstrated that the patient preference did not significantly affect response to treatment (140).

In the RA and AS study, more patients dropped out after randomisation in the Norwegian group than in the Mediterranean group, even though we included the subjects who were willing to be randomised to both climate groups only. Because these persons basically had applied for rehabilitation in a warm climate, the Section for Climate Therapy guaranteed rehabilitation in a warm climate the next year for the patients who agreed to stay in the study even though they were randomised to rehabilitation in Norway. This might have reduced the number of dropouts somewhat.

The reasons for withdrawal after randomisation in the RA and AS patients are given in Table x. More subjects specify dissatisfaction with the randomisation result as their reason for withdrawal after randomisation in the Norwegian than in the Mediterranean climate group, but this number of patients is quite small. Unfortunately, many of the participants did not give any reason why they chose to withdraw from the study, thus we are left to speculate.

The only variables available in the persons who discontinued after randomisation were the stratification variables age, sex, the use of disease modifying anti-rheumatic drugs (DMARDs) in the RA patients, and the type of articular involvement (axial/peripheral) in the AS patients. The last mentioned variables were chosen to

reflect the severity of RA/AS. In these variables, the dropouts were comparable to the completers in both the RA and the AS part of the study. The reasons for dropout after randomisation before intervention in the RA and AS study are given in Table 11a.

**Table 11a. The reasons for dropout after randomisation before intervention in the RA and AS study, sorted by frequency**

| **Reasons for dropout after randomisation** | **Number of RA patients** | | **Number of AS patients** | |
|---|---|---|---|---|
| | *Mediterranean climate* | *Norway* | *Mediterranean climate* | *Norway* |
| Practical consideration | 1 | 5 | 2 | 7 |
| Dissatisfaction with the randomisation result | 1 | 4 | 1 | 3 |
| Acute trauma/ hospitalisation | | 4 | | 3 |
| Responsibility at home | 2 | 2 | 2 | |
| Elective therapy (drug infusion, surgery) | 1 | 2 | | |
| Economical reason | 2 | 1 | | |
| No need for rehabilitation (improved health status) | | | | 2 |
| Did not meet at the rehabilitation centre | | 2 | | |
| Unknown reason | 5 | 9 | 5 | 13 |
| **Total** | **12** | **29** | **10** | **28** |

In the PPS study, we had a significantly better baseline values in the control group compared to the intervention groups in the mobility and walking tests. This bias in physical function might be a result of the fact that more patients dropped out

from the intervention groups (n=7+8) than from the control group (n=2) (Figure 3-pps flow chart). Did the drop-outs of the intervention groups have physical function lower than the mean? The given reasons for dropout after randomisation do not support this theory (Table 11b); nevertheless, there are more factors that could influence the obtained baseline data.

**Table 11 b The reasons for dropout after randomisation before intervention in the PPS study, the known reasons sorted by frequency**

| **Reasons for dropout after randomisation** | **Number of PPS patients** | | |
|---|---|---|---|
| | *Tenerife* | *Norway* | *Control* |
| Responsibility at home (work, family situations) | 4 | 2 | |
| Holiday in warm climate (Dissatisfaction with the randomisation result?) | 1 | 3 | |
| Medical reasons | 2 | | |
| Practical reasons (long distance to travel) | | | 2 |
| Economical reasons | | 1 | |
| Unknown reasons | | 2 | |
| **Total** | **7** | **8** | **2** |

The number of dropouts after the initiation of intervention were rather low in all of our studies; this is supposed to affect the validity in a positive direction.

# PATIENT EXAMINATIONS AND RELIABILITY

The reliability of a study depends upon which outcome measures you choose to measure the patients' health status, as well as how you perform these measurements and tests. The selection of outcome measures in our studies aimed at internationally accepted instruments and core sets that had been tested for reliability and validity. We aimed to use outcome measures that reflected the actual patients' problems and were responsive to physiotherapy interventions.

The main challenge in our studies was the performance of the physical tests and the doctors' examinations. Ideally, all patient evaluations should have been performed by the same investigator. However, when the patients stayed at different rehabilitation centres across the world at the same time, we had a logistical problem. In the PPS and NMD studies, two physiotherapists managed to do all of the physical tests at all treatment centres. In the RA and AS studies, two physiotherapists and one nurse did the physical tests, and four physicians did the doctors' examinations, two in each climate group. Apart from a few exceptions, each study patient was examined by the same physiotherapist, nurse or doctor at all controls.

It has been shown that are wide variations among observers for joint counts(132;141). Thus, the inter-rater variation is supposed to reduce the reliability of our study results. The fact that each study patient was examined by the same investigator at all controls reduces the impact on this variation within group analyses. Therefore, the measured improvements within each group might be more reliable than the between group comparisons, particularly in the joint count analysis of the RA study.

# STATISTICAL ANALYSIS

In all studies of this thesis, we have performed statistical analysis for two group comparisons. Since we had four different examination points, we considered whether a General Linear Model of Repeated Measures analysis would be a better choice. This statistical method analyses the variation in a variable in the course of time, and whether this course differs between two or more groups. This method is perfect for the analysis of growth curves in children, for instance. However, in our studies, we expect a peak effect immediately after the intervention and not only variation during time, thus we ended up with simple two group comparisons after all.

Rehabilitation implies a multifactorial approach to a problem, or more often a complexity of problems associated with a disease or a trauma. This complexity of both patient problems and types of intervention has resulted in more outcome measures in our studies than recommended in a statistical view. In the theory, every $20^{th}$ parametre is supposed to show a significant change by chance when the chosen level of significance is set to be 0.05. Thus, we considered performing adjustments due to multiple testing in our studies. However, the fact that Bonferroni's correction of multiple comparisons presumes independency between the variables tested and the tests in our studies were on the same subjects using highly correlated variables, Bonferroni's correction was judged to be too conservative (142).

Even though we had three different groups in the PPS study, we did not use the One-way analysis of variance (ANOVA), but two group comparisons only. In the NMD study, we selected five primary and four secondary outcome measures prior to study start in order to reduce the statistical problem of multiple comparison.

# GENERAL DISCUSSION OF MAIN RESULTS

## EFFICACY IN THE DIFFERENT PATIENT GROUPS

### EFFICACY IN PATIENTS WITH RHEUMATOID ARTHRITIS

In this study, RA patients had an improved physical function and exercise capacity lasting for at least three months after a four week rehabilitation programme both in the Mediterranean and Norwegian climates. The changes in physical tests were comparable, while improvements in DAS28 score, ESR, physician's global assessment of disease activity and patient's assessments of health status were greater in warm than in cold climates. The patient evaluations of health status remained improved after three and six months in the patients that were treated in the Mediterranean climate only.

Johansson and Sullivan found an immediately better effect of physiotherapy in a warm climate compared with outpatient treatment in Sweden (100). Our study confirms that there is also a difference in long-term efficacy, measured by the DAS28 score, ESR, physician and patient evaluations of disease activity which showed greater improvements after therapy in a warm than in a cold climate.

#### *DISEASE ACTIVITY REDUCTION?*

Potentially detrimental effects on disease activity have been the focus of earlier research of exercise therapy in RA patients. Some earlier studies and two reviews agree on the lack of detrimental effects as mentioned in the introduction (31;33;38;40). However, do we have any evidence for a reduction in disease activity

after an exercise or an in-patient rehabilitation programme in RA patients? This might be an interesting matter of discussion.

In our study, the baseline DAS28 value 4.45(1.16) was reduced by -1.14(0.80) after the four week physiotherapy programme, and by -0.95 (1.05) at the three month check-up (week 16) in the Mediterranean climate group. The corresponding values in the Norwegian climate group were 4.18 (1.17), -0.57(0.76) and -0.37(0.92). Häkkinen et al. used the DAS28 as a measure of disease activity as well. They compared strengthening exercises with range of motion (ROM) and stretching exercises performed for 45 minutes twice a week for a two year period (40). The mean (SD) DAS28 decreased significantly from 4.4 (1.2) to 2.2 (1.2) in the strength exercise group and from 4.9 (1.1) to 2.7 (1.2) in the ROM exercise group during a two year training period in their study. After the two year measurements, all subjects were instructed to carry out the strength training programme and aerobic exercises two to three times a week. At the five year check-up visit, the corresponding DAS indices were 2.3 (1.0) in the strength exercise and 3.0 (1.2) in the ROM exercise group (41). This reveals a decrease in disease activity in a long-term aspect.

Our four week study with three month follow-up had comparable baseline DAS28 values at moderate disease activity, but demonstrated a numerical lower reduction in this disease activity score. However, the subjects of our study had a median disease duration of nine to ten years and the study of Häkkinen et al. included only early arthritis patients (disease duration <24 months at inclusion). The fact that DMARD therapy was initiated in all patients after the baseline measurements is supposed to be a serious confounder with respect to the attained DAS28 reduction in their study. However, they demonstrated a significant between

group difference between -0.5 and -1.0 for all follow-up controls in favour of the strength training group. The maintenance of the attained improvement is supposed to be dependent on the subjects' continuation of exercising during the follow-up time.

*SJC*

Van den Ende et al. investigated the benefit of intensive dynamic exercises in comparison to range of motion (ROM) and isometric exercises in rheumatoid arthritis in 1996. The participants of this RCT had a mean disease duration of 8,4-11,5 years and unchanged medication during the exercise period. Therefore, they are considered to be comparable to the participants in our study. The SJC in the patients of the high intensity exercise

programme decreased significantly by -1.7 from 5.2 at the check-up after 12 weeks with a high intensity exercise programme. Still, the overall conclusion was that the disease activity remained unchanged during the exercise period (35).

This was supported by Minor et al. in a similar study of aerobic versus nonaerobic exercise, demonstrating the efficacy of aerobic exercises in physical capacity, depression and anxiety, but finding no significant between-group differences in flexibility, number of clinically active joints, duration of morning stiffness, or grip strength (34). = Minor 1989

In a dance-based aerobic exercise for rheumatoid arthritis study of Pearlman et al., analyses of pretest to posttest changes after a 16-week program (twice weekly for two hours) indicated no deleterious effects on disease activity. In fact, physician-assessed articular pain and swelling decreased significantly (143).

Lyngberg et al. focused on disease activity in their crossover study of 18 RA patients comparing aerobic conditioning and strength exercises over an eight week period. They demonstrated that training of the muscles acting over the swollen joints

resulted in more than a 35% decrease in the number of swollen joints. The hemoglobin level increased significantly after the training period, while the erythrocyte sedimentation rate, the complement factor C3d, and the number of sore joints remained unchanged. Their conclusion was that rheumatoid arthritis activity decreased with fewer swollen joints and higher hemoglobin level after training, and that RA-patients with some activity are trainable without aggravating the disease, even in the chronically swollen joints (144). This is interesting in the context of our findings of a persisting reduction in SJC at week 16 of 30% and 40% in the cold and warm climate group, respectively. Numerically, it concurs with the 33% decrease of the SJC in the 68 joint count status of the Lyngberg study and a 33% reduction in the high intensity exercise group of van den Ende et al. as well (35).

*ESR*

The median, baseline ESR in our study was 20 mm and 17 mm in the warm and cold climate group, respectively. We found some small changes at week four, but a greater ESR reduction in the warm climate group at week 16. A similar ESR reduction pattern was seen in the AS patients attending the same study. In the RA patients treated in a warm climate, the mean reduction was -8.9 mm which constitutes a 45% reduction. Whether this could be an indication of a delayed reduction in disease activity might be an object of discussion.

However, the number of patients affected by diseases that might influence the outcome of our study was registered. Significantly more participants experienced intercurrent diseases during the warm climate intervention than during the cold climate intervention, 19% and 6%, respectively. The corresponding values were 10% and 8% for the follow-up period (week four to week 16). This is supposed to reflect

the higher risk of infectious diseases when visiting a foreign country, and might interact with a potential anti-inflammatory effect of a rehabilitation programme in warm climate.

Some other studies of exercise therapy have used ESR as an outcome measure with varying results. Lyngberg et al. found no significant changes in ESR in their eight week study of physical training (144). Neuberger et al. report positive effects of 12 weeks of low-impact aerobic exercise on fatigue, aerobic fitness, without worsening their arthritis, based upon no significant increases in joint count or ESR. Looking closer to the results of this study, they report a significant decrease in mean ESR from end of treatment to follow up 15 weeks after completion of the exercise programme. This decrease was from 30.0 mm to 16.2 mm, which constitutes a 54% reduction from the end of treatment value, which is comparable to the 45% reduction in the ESR value in the similar period of the RA patients of our study of treatment in a warm climate (29).

In 2007, Neuberger et al. present a new and more comprehensive RCT of 220 RA patients participating in either a class exercise, home exercise or a control group, measuring disease activity variables as total joint count, ESR and CRP. These variables appeared to be strikingly stable during the 12 weeks of exercise, supporting the conclusion on no significant increases in measures of disease activity (145), and perhaps answering the question about reduction in disease activity as well.

*THE WARM CLIMATE EFFECT*

The DAS28 improvement attained in the subjects of our study of treatment in a Mediterranean climate was clinically significant after three months according to the EULAR response criteria's definition of moderate improvement: $> 0.6$ when moderate disease activity ( 3.2-5.1) at baseline (146). The intervention given to this

group of patients consisted of more than just exercise therapy. To what extent do the "sunny, warm, dry and stable climatic conditions" play a role in the differences in attained improvements in this disease activity score? A regression analysis could have made us more capable of ruling out climate as an explanatory variable for the differences in improvements between the warm and cold climate intervention. The study setting might be too complex to be able to ascertain this as a cause and effect relationship; however, there is some rationale for the fact that factors in the Mediterranean climate, such as more UV-radiation (147;148) and daylight time (138;139), may affect disease activity in RA patients. This might be supported by the study of Drosos et al. demonstrating a clinical, radiologic, and serologic more severe disease of RA patients in Britain versus Greece (88), concluding that both genetic and environmental factors may be responsible for the differences in disease expression.

Hashkes demonstrated an immediate ACR20 improvement in 57% of the RA patients of his uncontrolled study of climatic therapy, concluding that the "short term effect of climatic therapy are not less than for most new medications" (104). In our study, an immediate ACR20 improvement was achieved in 38% of the patients in the Mediterranean group and 21% in the Norwegian group. This proportion of responders is lower than shown in Hashkes' study. However, more patients with low levels of SJC and TJC at baseline were included in our study, and a high proportion of patients with zero values made improvements according to the ACR criterion difficult to obtain. Shorter disease duration and more active disease were associated with a greater response in RA patients according to Hashkes. The patients of our study had median disease duration of 9-10 years, and the baseline DAS28 score

indicated a moderate disease activity (146). Thus, ACR improvement might not be the most appropriate response criterion in our study.

### *THE EFFECTIVENESS OF A SUPPLEMENTARY INTERVENTION*

Reviewing the effectiveness of comprehensive rehabilitation programs, Uhlig et al. found only a modest effect on measured outcomes after comprehensive rehabilitation in rheumatologic conditions (52). They pinpoint the fact that the patients with access to qualified care are supposed to also have undergone drug therapy earlier, and often in conjunction with a rehabilitation programme. Thus, comprehensive rehabilitation is supposed to be supplementary to at least regular medical care. This poses a difficulty in generating significant or clinically important changes in outcome measures, because improvements caused by pharmacological interventions may exceed rehabilitative effects (52). Thus, the moderate number of patients attaining an ACR20 improvement in our study might be better understood in this context.

### *REHABILIATION IN WARM CLIMATE REVIEWED*

Recently, a systematic review collecting the evidence for the efficacy of comprehensive rehabilitation in a warm climate of patients with a wide variety of rheumatic diseases has been presented online (149). Our study was one of the six studies that met the inclusion criteria and the only one assessed to be of moderate quality of evidence according to the GRADE approach (150). For patients with rheumatoid arthritis, moderate evidence was found for reduction of disease activity, pain, fatigue, and global disease impact. The evidence was also moderate that comprehensive rehabilitation in a warm climate did not improve fitness or reduce activity limitation beyond levels reached by rehabilitation in Scandinavia.

The main goal of rehabilitation in RA patients is to improve the patients' functional capacity and prevent further deterioration (99). Consequently, the obtained positive effects at the functional level are of importance.

## EFFICACY IN PATIENTS WITH ANKYLOSING SPONDYLITIS

### *ASAS20 RESPONSE*

Seventy-nine percent of the AS patients treated in a warm climate compared to 44% of the AS patients treated in a cold climate were immediate responders according to the ASAS20 response definition in our study. In 2002, Hashkes evaluated the efficacy of a comparable four week in-patient rehabilitation programme in Israel, demonstrating an immediate ASAS20 response in 60% of the AS patients. However, this number is supposed to be underestimated since they did not measure more than three of the four separate ASAS items defined, and thus their criteria for improvement became more stringent (107). The number of responders after rehabilitation in a warm climate was similar to that of anti-TNFα therapy previously found for AS patients (151).

However, the obtained effects of the rehabilitation programme decline with time in contrast to the continuous anti-TNFα therapy. This concurs with the uncontrolled study of Lubrano et al., evaluating 52 active AS patients consecutively admitted to a rehabilitation inpatient clinic in Italy, demonstrating improvement by the ASAS response criteria (152). The number of ASAS20 responders in their study was 89% at the end of the rehabilitation, 60% 6 weeks, and 33% 12 weeks after the end of therapy. In our study, 50% and 23% had persisting ASAS20 improvement 16 weeks after the initiation of the four week rehabilitation programme in warm and cold climate, respectively.

*SUSTAINED IMPROVEMENT OF SPINAL MOBILITY*

The baseline Schober at 3.3cm improved to 4.0cm after intervention and 3.8cm 16 weeks after initiation of intervention in a warm climate. The corresponding values were from 3.2cm to 3.3cm and 3.4cm in a cold climate. Different exercise programmes for AS patients have shown improvements similar to the warm climate intervention. Viitanen et al. demonstrated a baseline Schober at 3.3cm, improved to 3.6cm immediately after the three to four week in-patient rehabilitation, but reduced to 3.2cm at the 15 months follow-up (60). The patients had been encouraged to continue exercises at home, but had not been offered any group or follow-up regime. In the study of Altan et al., Schober improved from 3.19cm to 3.65cm after three weeks of intensive treatment, including daily balneotherapy and home exercises. This intervention was followed by a 30-min home exercise program for six months, improving the mean Schober value to 4.12cm in the intervention group (153). This pinpoints the value of continuation of an exercise programme subsequent to an intensive physiotherapy programme. Analay et al. compared home exercises to supervised group exercises, finding that group exercises improve movement in the spine more than home exercises. In the intervention group of their study, a baseline Schober at 4.38cm was improved to 5.26 after six weeks of intervention (58). The participants of this study were aged 18 to 55 years and the criteria for inclusion might have resulted in a selection of the less affected patients with a baseline Schober close to normal. However, none of these studies show improvements above a 10mm level; this concurs with Viitanen et al.'s clinical assessment of spinal mobility measurements in ankylosing spondylitis, evaluating the Schober test to be both a valid and reliable measurement, but not very sensitive to change (154;155).

However, the obtained improvements in spinal mobility seem to be more stable than the ASAS improvements in our study. Lateral lumbar flexion is a responsive measure judged by a high standardised response mean (SRM) (0.84), and has been recommended among the spinal mobility measures (113). The number of patients having 20%/ 40% improvement in lateral flexion remained high even three months after the four week rehabilitation programme (week 16): 91/75 in the Mediterranean group and 54/39 in the Norway group. Thus, our study supports the poor-quality evidence for long-term effects on improved mobility following an inpatient physiotherapy programme for AS patients (59;60). Warm and stable climatic conditions may enhance rheumatic patients' capacity to perform physical exercise (105); this might explain why the improvements in our study were greater when the rehabilitation was performed in a Mediterranean climate.

*SPA-EXERCISE THERAPY*

The patient's assessments of symptoms like pain, global health, morning stiffness and fatigue showed a remarkable reduction immediately after the intervention in our study. The improvements persisted for 16 weeks after intervention in a cold climate and for 28 weeks after a rehabilitation programme in a warm climate. This concurs with the study of van Tubergen et al. demonstrating a spa-exercise therapy to improve pain and overall well-being more than a weekly group exercises programme alone (61), and that the beneficial effects may last for at least 40 weeks. The standardized spa exercise therapy of three weeks' duration consisted of group physical therapy, walking, correction therapy (lying supine on a bed), hydrotherapy, sports and visits to either the Gasteiner Heilstollen in Austria or to the sauna in The Netherlands in their study. This combination of spa and exercise therapy is comparable to the complexity of the intervention in warm climate given in our study.

The fact that there is a huge variation in the content and duration of in-patient programmes described in literature poses a methodological problem, as types of programs vary enormously, and many confounders are difficult to address.

*PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENTS*

According to Lubrano et al., rehabilitation was superior to anti- TNFα therapy for improvements in anthropometric measures (156). Yurtkuran *et al.* conducted an RCT comparing spa therapy to non-steroidal anti-inflammatory drug (NSAID) therapy and a combination of both (157). It was found that spa therapy was more effective in relieving symptoms and improving spine mobility than NSAIDs alone, with the effect lasting up to six months. Thus, physiotherapy and physical exercise and/or spa therapy may be a substantial supplement to medical treatment in order to improve mobility AS patients.

Consensus has been obtained for the ASAS/EULAR recommendations that non-pharmacological and pharmacological treatments are complementary and that both are of value in the initial and continuing treatment of patients with AS (53).

*REHABILIATION IN WARM CLIMATE REVIEWED*

The systematic review summarising the evidence of the efficacy of comprehensive rehabilitation in a warm climate of patients with a wide variety of rheumatic diseases found low evidence for reduction of disease activity, pain, joint range of motion, activity limitation, and global disease impact among patients with ankylosing spondylitis (149). The level of evidence may have been increased if the paper about the AS patients in our study had been published prior to this systematic review.

Our study indicates significant health effects in PPS patients after a four week rehabilitation programme both in Norway and in Tenerife. The attained improvements were greater and longer lasting when treatment was given in a warm climate.

In 2006, the European Federation of Neurological Societies (EFNS) developed an evidence-based guideline for the diagnosis and management of postpolio syndrome. Our study was reported as high class (Class I) evidence for the efficacy of treatment both in a warm and in a cold climate. No other studies of in-patient rehabilitation programmes were referred (158).

In 2009, Davidson et al. reported prolonged benefits for physical, psychological and functional outcomes after comprehensive rehabilitation in PPS patients (159). The 27 patients who completed this uncontrolled study were comparable to the patients in our study concerning mean age, mean age of polio onset and PPS symptom onset, but in contrast to our study, more men than women were included. In this rehabilitation study, significant improvements were recorded for exercise endurance, depression and levels of fatigue, but there was no significant change at six months for muscle strength or anxiety. These patients were treated in London and were thus comparable to the cold climate group of patients in our study. In comparison, we found improvements in endurance, but also handgrip strength and mobility in both climate groups. The improvements in fatigue, depression and pain were sustained in the warm climate group only.

Evidence based recommendations of physiotherapy, physical activity and muscle training in PPS patients are given in a recent review (2010) about the management of postpolio syndrome by Gonzalez et al. (160). Even though an

intensive rehabilitation programme is not mentioned as a recommendation, the main components of a rehabilitation programme given in our study are recommended. Aquatic exercise being an important part of the programme (161). Furthermore, it is claimed that the training programmes should be carefully customised and planned by physiotherapists to avoid both overuse and disuse, and the level of physical activity modified to decrease pain (160), which is supposed to be easier to realise in an in-patient rehabilitation context.

## EFFICACY IN PATIENTS WITH NEUROMUSCULAR DISEASES

Our study showed positive effects on different dimensions of health with at least three months' duration following a four week rehabilitation program in a warm climate for patients with neuromuscular diseases. Statistical significant improvements were revealed in the primary outcome measure for pain (VAS scale), endurance (six minute walking test), fatigue (Fatigue Severity Scale), and mobility (Timed up and go).

Dahl et al. evaluate the effect of a four week rehabilitation programme for patients with hereditary, congenital neuromuscular diseases similar to those included in our study (109;110). This trial had a RCT design with 20 patients being treated in a warm climate and 20 patients in a cold climate. Apart from this study, no comparable study of any intensive physiotherapy programmes for patients with hereditary, congenital neuromuscular diseases was found in medical databases. But a systematic review of Cup et al. in 2007 concludes with level II evidence (likely to be effective) for strengthening exercises in combination with aerobic exercises for patients with muscle disorders, and that most studies reported the absence of adverse effects (162).

The improvement in exercise capacity demonstrated in our study was an increase of 54 m during six minutes walking persisting three months after treatment in a warm climate. Dahl et al. demonstrated an improvement of 60m (from 343(87)m to 403(104)m) in the Mediterranean climate and 53m (from 384(117)m to 437(130)m) in the Norwegian climate group. In this study, no significant difference was found between the two climate groups.

In 2009, Albresch et al. summarized the current knowledge regarding the effect of exercise on individuals with NMDs concluding that there is inadequate evidence from randomized controlled trials with sufficient sample size to make recommendations (163). In a "rehabilitation in practice" article of 2010, Gita M Ramdharry focuses on weakness as a primary impairment of neuromuscular diseases. She concludes that research to date has helped to dispel the old practice of exercise avoidance in neuromuscular conditions and that exercise trials are starting to answer some questions found in muscle disease, poliomyelitis and hereditary neuropathy (16). Both Albresch and Ramdharry agree that results from the aerobic studies performed almost uniformly show that individuals who are mildly affected by the disease or who are early on in the course of their disease demonstrate short-term cardiopulmonary improvements that are similar to those seen in persons without NMDs, but the level of training and kind of training depends on the type, stage, and severity of the disease (16;163).

The baselineVAS pain score was 25 in our study and 26 for both climate groups in the study of Dahl et al. (109;110). A statistically significant improvement of nine (22) was revealed in our study. It might be a matter of discussion whether this improvement is of clinical importance. Dahl et al. revealed an immediate relief from

pain after intervention in the warm climate only, but this change did not persist three months after intervention.

When exercise can improve cardiovascular fitness, it may help to reduce experienced fatigue (16). A statistically significant reduction in fatigue measured by the Fatigue Severity Scale (FSS) was found to persist even three months after the intervention in our study. A median baseline score at 4.7(4.0-5.5) was reduced by 0.5 (-0.2-1.6). Dahl et al. demonstrated an immediate improvement from mean 4.8(1.5) to 3.9 (1.5) in FSS in the warm climate group of his study, but this improvement did not persist after three months. Robert Miller has reviewed recent studies of fatigue in common neurological conditions, discussing therapeutic interventions (164). He states that fatigue is one of the most common causes of disability in patients with neurological disease. Peripheral and central fatigue mechanisms often coexist. Several groups have demonstrated benefits from therapeutic exercise, although the mechanisms of action are poorly understood and may not be specific (164).

In conclusion, the improvements attained at the activity level in our study are found to be probable and seem to be rather persistent. Thus, our randomised, controlled trial supports an effect of an intensive physiotherapy programme maintained for at least three months. The improvements in symptoms like pain and fatigue are essential for the group of patients with NMDs. According to Dahl et al., the improvements in these symptoms might be more transient and may differ according to which climate the physiotherapy programme was given. The study of Dahl et al. is considered to be comparable to our study including similar diagnosis and outcome measures. It is striking how similar the baseline values and attained improvements are in these studies. This is considered to support our findings, and introduces the aspect of different climate settings not ascertained in our study.

# 6MWT IMPROVEMENTS ACROSS DIAGNOSIS

The Six Minute Walk Test (6MWT) measures how many metres you manage to walk in six minutes and it is widely used in different patient groups. The performance of this test depends on multiple health factors and is supposed to reflect functional capacity (165). Walking few metres might indicate a deconditioned state, or immobility in the lower limbs according to pain or paresis. Especially in older people, the 6MWD appears to provide a measure of overall mobility and physical functioning rather than a specific measure of cardiovascular fitness (166). This physical test was an important outcome measure of all studies included in this thesis. An overview of the mean responses obtained in this parametre in the different diagnosis at week 16 are presented in Table 12; effect sizes above medium level are coloured. This may form the basis for some interesting comparisons.

| Table 12. An overview of the sustained mean responses in the Six Minute Walk Test (6MWT), metre, at week 16 in the different diagnosis, with corresponding effect sizes | n | | Changes from baseline | | |
|---|---|---|---|---|---|
| | | Baseline values | Week 16 | p value | Effect Size (ES) |
| **Rheumatoid arthritis** | | | | | |
| Mediterranean group | 72 | 550(86) | 58(52) | 0.001 | 0.67 |
| Norwegian group | 52 | 547(85) | 64(53) | 0.001 | 0.75 |
| Diff between the groups | | | | 0.559 | 0.07 |
| **Ankylosing spondylitis** | | | | | |
| Mediterranean group | 65 | 559 (84) | 68 (65) | 0.001 | 0.81 |
| Norwegian group | 42 | 566 (99) | 59 (54) | 0.001 | 0.60 |
| Diff between the groups | | | | 0.470 | 0.11 |
| **Postpolio syndrome** | | | | | |
| Mediterranean group | 27 | 347(119) | 84(45) | 0.001 | 0.71 |
| Norwegian group | 23 | 316(149) | 40(62) | 0.003 | 0.27 |
| Control group | 26 | 414(120) | -4(49) | 0.536 | 0.03 |
| Diff between MC-Nor | | | | 0.005 | 0.37 |
| Diff between MC-Control | | | | <0.001 | 0.74 |
| Diff between Nor-Control | | | | 0.003 | 0.30 |
| **Neuromuscular diseases** | | | | | |
| Mediterranean group | 44 | 387(85) | 54(65) | 0.001 | 0.64 |
| Control group | 44 | 387(85) | 2(38) | 0.62 | 0.02 |
| Diff between the groups | | | | <0.01 | 0.61 |

Baseline values are shown as mean (SD), and changes from baseline are shown as mean difference from baseline (SD). ES= Effect size= Change from baseline(∆)/SD(mean baseline). Effect sizes are generally defined as small (*d* =0 .2), medium (*d* = 0.5), and large (*d* = 0.8), all medium or large effects are coloured. Diff=difference.

The normal values of this test may be computed according to the reference equations presented by Enright and Sherrill in 1998 (167). They administered the standardized Six Minute Walk Test to 290 healthy adults, aged 40 to 80 years, and measured median distance walked to be 576 m for men and 494 m for women. Thus, the RA

and AS patients included in our study had a baseline value comparable to healthy subjects, while the baseline values were moderately reduced in the subjects with neurological diseases. The strikingly large SD of the PPS patients' baseline values indicate a greater variation in their walking speed than among the other patient groups.

Technical aids like crutches and manual wheelchairs in the performance of this test were allowed. None of the participants in the RA and AS study used wheelchairs. In the postpolio study, 11 patients used manual wheelchairs and 17 used powered wheelchairs, some permanently and others occasionally. The corresponding number was 12 manual and 18 powered wheelchairs in the neuromuscular study. Those who were completely dependent on a powered wheelchair were excluded from the test, while those who were dependent on a manual wheelchair performed the test with their wheelchair.

In the original postpolio article, the mean value was given for week 16 (three months' control) while the mean difference from baseline has been given in the other studies. The between group comparisons presented in the original postpolio study compare the mean values at week 16, independent of the baseline value. In hindsight, it would have probably been a better idea to compare the mean difference from the baseline as has been done in the other studies. This would have given a more correct presentation of the real differences in improvement between the groups as presented in Tables 2, 3 and 4 in the 3rd paper of this thesis.

Effect sizes are generally defined as small ($d$ = .2), medium ($d$ = .5), and large ($d$ = .8). It is striking that all included patients showed a sustained improvement of medium or large effect size after treatment in a Mediterranean climate, no matter the diagnosis. While the rheumatic patients had a similar improvement after treatment in

a Norwegian climate and in a Mediterranean climate, the size of effect was small after treatment in a Norwegian climate for the PPS patients. The control groups showed no significant improvements at all.

Studies using the Six Minute Walk Test (6MWT) as an outcome measure differ in their definition of minimal clinically significant difference (MCSD) from 30 and 56 metres (168;169). Paul L. Enright reports that a 12-40% mean improvement from baseline values has been published for various interventions (170). It is important to bear in mind that these studies involve patients with pulmonary diseases, which might limit the transfer value of the results. However, the definition of MCSD corresponds well to the fact that all attained improvements calculated to have medium or large effect size (above 0.5) in our studies, have an improvement of 54 metres or greater.

## VAS PAIN IMPROVEMENTS ACROSS DIAGNOSES

Pain is described as a common complaint in all four patient groups included in this thesis. We have used the 100mm VAS scale for a subjective rating of the intensity of pain in all patient groups. The baseline values and change from baseline 16 weeks after initiation of intervention (three month control) are presented in Table 13, effect sizes above a medium level are coloured. This may form the basis for some interesting comparisons.

| Table 13<br>An overview of the sustained mean responses in VAS pain (0-100) at week 16 in the different diagnoses, with corresponding effect sizes | n | | Changes from baseline | | |
|---|---|---|---|---|---|
| | | Baseline values | Week 16 | p value | Effect Size (ES) |
| **Rheumatoid arthritis** | | | | | |
| Mediterranean group | 72 | 42 (22) | -16 (24) | 0.001 | 0.73 |
| Norwegian group | 52 | 44 (22) | -4 (22) | 0.197 | 0.18 |
| Diff between the groups | | | | 0.005 | 0.55 |
| **Ankylosing Spondylitis** | | | | | |
| Mediterranean group | 62 | 53 (21) | -20 (32) | 0.001 | 0.95 |
| Norwegian group | 42 | 49 (19) | -13 (21) | 0.001 | 0.68 |
| Diff between the groups | | | | 0.180 | 0.33 |
| **Postpolio syndrome** | | | | | |
| Mediterranean group | 29 | 42 (22) | -14 (24) | 0.003 | 0.64 |
| Norwegian group | 26 | 43 (24) | 1 (14) | 0.969 | 0.04 |
| Control group | 29 | 40 (19) | -7 (21) | 0.063 | 0.37 |
| Diff between MC-Nor | | | | 0.006 | 0.68 |
| Diff between MC-Control | | | | 0.241 | 0.32 |
| Diff between Nor-Control | | | | 0.112 | 0.33 |
| **Neuromuscular diseases** | | | | | |
| Mediterranean group | 51 | 25 (25) | -9 (22)* | <0.01 | 0.36 |
| Control group | 51 | 25 (25) | 0 (15) | 0.90 | <0.01 |
| Diff between the groups | | | | 0.03 | 0.36 |

Baseline values are shown as mean (SD), and changes from baseline are shown as mean difference from baseline (SD). *Changed to negative after consultation with Petra A. Nordby, who analysed the original data. Diff= difference. ES= Effect size= Change from baseline(∆)/SD(mean baseline). Effect sizes are generally defined as small (*d* =0 .2), medium (*d* = 0.5), and large (*d* = 0.8), all medium or large effects are coloured.

The ankylosing spondylitis patients had the highest and the neuromuscular patients had the lowest baseline pain scores. We found persistent improvements at week 16 in

all patient groups after rehabilitation in a Mediterranean climate. Effect sizes are generally defined as small ($d = .2$), medium ($d = .5$), and large ($d = .8$). The measures effect size (ES) was relatively high (0.64-0.95), except for the patients with neuromuscular diseases having ES below 0,5. Only the ankylosing spondylitis patients had statistically significant reduced pain 16 weeks after rehabilitation in Norway, and in the rheumatoid arthritis and postpolio patients, we found a statistically significant difference in efficacy between the Mediterranean climate and the Norwegian climate groups. For the neuromuscular patients, there was a significant difference between the intervention and control group at week 16; this was not the case for the patients with postpolio syndrome, which might question how valuable the within-patient improvements in this patient group really are. However, it is important to bear in mind the seasonal variation in Norway, affecting all groups being tested during spring time.

Whether the sustained improvements in VAS pain are of clinical significance might be a matter of discussion. In a study on acute pain in emergency medicine (171), the minimal clinically significant difference (MCSD) in the VAS pain score was determined to be 12 mm (95%CI: 9mm to 15mm). This study concludes that the MCSD in the VAS pain score did not differ according to the severity of pain being experienced. Another study of patients with both traumatic and non-traumatic pain found the MCSD in the VAS pain score to be 9 mm (95%CI: 6mm to 13mm), and that the MCSD did not differ significantly according to age, sex and cause of pain (172). This corresponds well to the fact that all attained improvements in our studies which are calculated to have a medium or large effect size (above 0.5), have an improvement greater than 12 mm.

# POTENTIAL MECHANISMS OF IMPROVEMENT

According to Hafström and Hallengren (105), the benefits of a physiotherapy programme could be due partly to the climate and partly to the change in environment, as well as to the intense coordinated physiotherapy. The most afflicted patients have been shown to improve most after a physiotherapy programme in a warm climate (100;101). Johansson og Sullivan analysed the correlation between background variables and the efficacy of physiotherapy in a warm climate (100). How the patients reported their symptoms were more highly correlated to disease activity measures than to personality traits, measured by Edwards' personality inventory. Furthermore, they demonstrated that emotional or psychosocial problems at baseline had a negative influence on the outcome of this intervention. Thus, we have some signs that might support a mechanism of improvement at an objective level.

It is important to bear in mind that there are differences in the nature of the neurological and the rheumatic diseases included in this thesis. The neuromuscular diseases are slowly progressive; the postpolio syndrome might be better characterised as a sequelae state, even though there is a component of progression in this disease as well. The fluctuating state of disease activity is an important aspect of the rheumatic diagnosis studied.

# ANTI-INFLAMMATORY EFFECT?

## DO THE ESR CHANGES REFLECT A DISEASE ACTIVITY REDUCTION IN THE RA AND AS STUDY?

The acute phase reactants are not increased in all AS patients, and the value of an acute phase reactant to measure disease activity is uncertain (173). The baseline ESR in the AS patients of our study was on the upper border of normality. We found some small changes at week four, but a greater ESR reduction in the Mediterranean climate at week 16. A similar ESR reduction pattern was seen in the RA attending the same study. Are these reductions of clinical importance? In the AS patients treated in a warm climate, the mean reduction was -8.3mm from a baseline median value at 17.0mm, which constitutes a 49% reduction. In the RA patients, we found a 45% reduction at -8.9mm from a median baseline at 20.0mm. Whether this could be an indication of a delayed reduction in disease activity might be an object of discussion.

## SUN EXPOSURE INDUCES RAPID IMMUNOLOGICAL CHANGES IN SKIN AND PERIPHERAL BLOOD IN PSORIASIS PATIENTS

An induction of rapid immunological changes in skin and peripheral blood in psoriasis patients after sun exposure has been demonstrated by Søyland and Heier et al. This very interesting finding is described in a submitted article (174) and is included in the doctoral thesis of Ingvild Heier (175). This study group examined immunological parametres in 20 psoriasis patients who underwent heliotherapy for 16 days on Gran Canaria. In addition to local immunmodulatory effects in both lesional and non-lesional skin, they revealed immunmodulatory changes in peripheral blood. The number of cutaneous lymphocyte antigen (CLA)+T cells was significantly decreased in peripheral blood after only one day in the sun and remained reduced at day 16. At day 16, phytohaemagglutinin (PHA) -stimulated

peripheral blood mononuclear cells (PBMCs) released significantly reduced levels of the following pro-inflammatory cytokines: interferon (IFN)-γ, interleukin (IL)-17, tumour necrosis factor (TNF)-α and interleukin (IL)-10 compared to baseline levels. On this basis, they conclude that sun treatment had a systemic effect. A systemic effect of sun treatment in psoriasis patients opens for similar immunological changes in other persons with other diseases.

## IMMUNOLOGICAL FACTORS AND CHRONIC INFLAMMATION IN PPS PATIENTS

Increasing interest in recent years has been devoted to the immunological process underlying postpolio syndrome. Concentrations of several cytokines, mainly those with proinflammatory actions (e.g., interferon-γ and tumour necrosis factor [TNF]), are high in the CSF of PPS patients (176). These findings probably reflect chronic inflammation in the spinal cord parenchyma, with potential damage to motor neurons. Potential causes of this chronic inflammation include a late aberrant immune response to the original infection, a late autoimmune complication of the original infection, and an immune response secondary to ongoing neurodegeneration caused by other factors. If the neurodegeneration in postpolio syndrome is an ongoing process caused by chronic inflammation, treatment of the disorder with drugs that modify the immune response should be possible. A randomised controlled trial of intravenous immunoglobulin in PPS patients has shown efficacy in muscle strength, vitality and physical activity in the treatment group; however, many of the parametres did not differ from the placebo group (177). Notwithstanding, this is an interesting finding in the context of potential anti-inflammatory effects of climate therapy.

## UV-RADIATION

High doses of ultraviolet radiation may induce immunosuppression (147;148;178). Ullrich et al. have discussed the role of immunosuppression in phototherapy and have argued that the pathology of diseases such as vitiligo, alopecia and lichen planus are thought to involve immune mechanisms; thus, the beneficial effect of PUVA may be due to immunosuppression. Furthermore, phototherapy may then be beneficial in the treatment of autoimmune disease and allergic reactions (147). Weichenthal and Schwarz have continued to study the mechanism of UV- radiation in phototherapy and conclude that many of the effects certainly are mediated via induction of apoptotic cell death, and that another major mechanism is the induction of immunosuppression (148).

In 1991, Urbach discussed the increase in biologically effective ultraviolet radiation due to the decline of stratospheric ozone concentration over the Northern Hemisphere in the past 20 years. He predicts the effects on human health to consist of increases in nonmelanoma skin cancer and malignant melanoma of the skin, possible alterations of immune response, and development of lens cataracts (178).

## DAILY LIGHT EXPOSURE

Cutolo et al. studied the circadian rhythms of serum melatonin, cortisol, and proinflammatory cytokines (TNFα, IL6) in RA patients and found that differences in daily light exposure might influence the circadian rhythms of these hormones and cytokines. Reduced daily light exposure as observed in northern Europe (Estonia), at least during the winter, might explain the higher and more prolonged serum melatonin concentrations that were observed in northern RA patients, as well as

some epidemiological features versus southern Europe patients (138). The fact that the production of proinflammatory cytokine TNFα is related to melatonin stimulation might in turn increase the disease activity in these RA patients. In another paper, Cutolo et al. present a northern and southern Europe comparison, stating that melatonin and TNFα (proinflammatory) were significantly higher in rheumatoid patients from a northern European country with reduced daily light exposure than in matched controls or in rheumatoid patients from a southern European country (139). Thus, the potential explanation of some differences in the epidemiological features in northern versus southern European patients might be the difference in daily light exposure. In addition, the efficacy of a rehabilitation programme might be influenced by the geographic position of the rehabilitation centre, especially in patients with an inflammatory disease.

## VITAMIN D PRODUCTION

Turner et al. studied the serum 25-hydroxyvitamin D, opioid intake and Short Form-36 Health Status Questionnaire in 267 chronic pain patients at admission to a pain rehabilitation center. They demonstrated vitamin D inadequacy in 26% of the patients using opioids, needing a higher mean morphine equivalent dose for a longer time period than the vitamin D adequate group. Opioid users with inadequate vitamin D levels reported worse physical functioning and health perception than opioid users with adequate levels. This might provide the basis for the assertion that vitamin D inadequacy may represent an under-recognized source of nociception and impaired neuromuscular functioning among patients with chronic pain (179).

According to Shinchuk and Holicks' review about Vitamin D and rehabilitation, Vitamin D inadequacy is pandemic among rehabilitation patients in both inpatient and outpatient settings. Vitamin D deficiency causes osteopenia, precipitates and exacerbates osteoporosis, causes the painful bone disease osteomalacia, and worsens proximal muscle strength and postural sway. Vitamin D deficiency and osteomalacia should be considered in the differential diagnosis of patients with musculoskeletal pain, fibromyalgia, chronic fatigue syndrome, or myositis. Vitamin D inadequacy can be prevented by sensible sun exposure and adequate dietary intake with supplementation (180).

## BALNEOTHERAPY EFFECT?

It is not known whether the minerals of mineral water penetrate the body surface, but they are known to cause a so-called spa or mineral water reaction (181). The mineral water reaction includes tiredness and fatigue especially after 5–8 baths with an associated rise in the leukocyte count and erythrocyte sedimentation rate even within the normal range. The mineral water reaction passes away after 5–10 baths, and the optimal "taking the waters" is a total of 15–22 baths taken daily (82).

## SPINAL MOBILITY

The obtained improvements in spinal mobility seem to be more stable than the ASAS improvements in the AS patients. This might indicate that an intensive rehabilitation programme could postpone the stiffening process in the columna of AS patients. According to Lubrano et al. , rehabilitation was superior to anti- TNFα therapy for improvements in anthropometric measures (156). Thus, physiotherapy and physical

exercise may be a substantial supplement to medical treatment in order to improve mobility AS patients. Warm and stable climatic conditions may enhance rheumatic patients' capacity to perform physical exercise (105), and this might explain why the improvements were greater when the rehabilitation was performed in a Mediterranean climate.

## QUALITY OF LIFE AND "RESPONSE SHIFT"

Most of the study patients appreciated that the rehabilitation was given for a group of patients with similar diagnosis. Many of the participants experience social isolation at home due to their physical limitations. To meet other persons with the same types of diagnoses can be valuable in terms of handling the stress that may derive from loss of abilities regarded as valuable (182). The quality of life measured by the questionnaire, Life Satisfaction Scale, in the neuromuscular study did not show any long-term effect. This is in contrast to the impression based on the participants' statements. A potential explanation can be that this questionnaire focused on satisfaction with life in general and everyday life and might not be sensitive to possible changes in aspects such as coping and self-esteem. Scott and Garrood have noted that quality of life instruments are only moderately sensitive to changes induced by rehabilitation therapy (183).

The notion "response shift" describes how an individual may change self understanding either through internal standards, values and/or quality of life (184). This is not unlikely to be an effect of a treatment in warm climate in a group of people with a similar diagnosis and everyday problems. Thus, the aspect of life quality might both have a positive, but also a negative effect in these kinds of studies.

In the postpolio study, we used the Beck's Depression Inventory (BDI, 0-63) (130), which measures depression as a phenomena more than quality of life. 55% of the participants reported cases of depression, i.e. a score above nine on the BDI at baseline, reflecting that depression is rather common among patients with postpolio syndrome. Furthermore, we found a significant reduction in mean BDI three months after intervention. In hindsight, we might have found a better instrument to measure life satisfaction in a population with presumably normal mental health.

## WHICH ASPECTS OF THE COMPREHENSIVE REHABILITATION ARE THE MOST APPRECIATED AND WHICH ARE WELL DOCUMENTED?

The "National clinical guideline for management and treatment in adults with rheumatoid arthritis" is prepared by The National Collaborating Centre for Chronic Conditions (NCC-CC) funded to produce guidelines for the National Institute for Health and Clinical Excellence (NICE). This evidence-based European treatment guideline is presented by the Best Practice database and defines the components of physiotherapy interventions to include:

- Exercise therapy: on land and in water (hydrotherapy/aquatic physiotherapy) and includes aerobic activities, flexibility and muscle-strengthening exercises, core stability exercise, balance rehabilitation, and promotion of lifestyle physical activity.
- Patient education and self-management: joint protection strategies, energy conservation/fatigue management, sleep hygiene training, management of flare, pain relief strategies, relaxation training, exercise and physical activity recommendations.

- Thermotherapy: hot/cold packs, paraffin/wax baths and infrared.
- Electrotherapy: Transcutaneous Electrical Nerve Stimulation (TENS), Ultrasound, Pulsed Electromagnetic Energy (PEME), Interferential therapy (IFT) and Laser.
- Occupational therapy: Provision and education of use of assistive devices: walking aids, splints, orthoses, and insoles.
- Manual therapy: includes mobilisation, manipulation, myofascial release, trigger point therapy, acupuncture and massage.

These components of physiotherapy interventions might be appropriate in the rehabilitation of more patients than simply those with rheumatoid arthritis. Apart from the fact that electrotherapy was mainly given in the rheumatic patients treated in warm climate, and occupational therapy was offered to a wider extent in the rehabilitation of the neurological patients, these main components were included in the physiotherapy programme given in our studies.

Van den Berg et al. have done a survey of a random sample of people with rheumatoid arthritis to investigate their attitude towards physical activity or exercise. Supervised group exercise and unsupervised individual physical activity were reported as the favourite activities. Furthermore, more people preferred being physically active under expert supervision than without supervision and preferred water-based over land-based activities. The most frequently-mentioned barriers were lack of energy, presence of pain, lack of motivation, lack of information, and fear of joint damage (185).

In our study of rehabilitation in postpolio patients, the participants rated which part of the programme they appreciated most. Individual physiotherapy was rated highest both in the Tenerife group and in the Norway group. In the Tenerife

group, the climate was rated second, followed by water-based exercises and social activities. In the Norway group, water-based exercises were rated second followed by social activities and self-training.

The patients with neuromuscular diseases included in our study report that it is not only the structured training programme or the warm climate that is important, but the combination of these components. Having time to recover after training/treatment was also reported to be important.

## SUMMARY OF EVIDENCE STATEMENTS FOR THE COMPONENTS OF PHYSIOTHERAPY INTERVENTIONS

The evidence for the efficacy of each component of a comprehensive rehabilitation programme are most thoroughly studied in RA patients (186). The efficacy may differ in other patient groups. However, the efficacy of a physiotherapy modality is, to some extent, supposed to be consistent.

### *EXERCISE THERAPY –HIGH EVIDENCE*

In general, exercise provokes a favourable response in terms of physical and psychological benefits in RA patients (31;37;46;145;187-189). Aerobic (dynamic) exercise programmes improve the components of health-related fitness, enhance psychological status, reduce pain and fatigue and have a positive effect on functional capacity without exacerbating disease activity or accelerating joint damage (31;37;42;145). Specific exercise aimed at enhancing joint range of motion (joint flexibility) or muscle strength (resistance training) results in some specific improvements (37;187). The majority of evidence comes from patients with chronic, stable RA in functional class I/III (31;37).

### *HYDROTHERAPY – ADDITIONAL FEELING OF WELL-BEING*

Exercise in water provides similar physical benefits to exercise on land but may have additional and important psychological effects (which positively impact on concordance) (187;189).

### *BALNEOTHERAPY*

Yurtkuran et al. conducted an RCT in 2005 comparing spa therapy to non-steroidal anti-inflammatory drug (NSAID) therapy and a combination of both in AS patients (37). It was found that spa therapy was more effective in relieving symptoms and improving spine mobility than NSAIDs alone, with the effect lasting up to six months (157)

In the 2008 update of Verhagen et al.'s Cocrane review about balneotherapy in RA patients, they conclude that an answer about the apparent effectiveness of balneotherapy cannot be provided at this moment. Seven trials were now included; however, the inconclusiveness was caused by methodological flaws (83).

In 2009, Falagas et al. did a systematic review of balneotherapy in various diseases. They found balneotherapy to improve pain in patients with rheumatological diseases and chronic low back pain in comparison to the control group in 17 (68%) of the 25 RCTs examined. This beneficial effect lasted for 10 days to one year in the studies reviewed. They concluded that there is a possibility that balneotherapy is associated with clinical improvement in rheumatological diseases mainly such as osteoarthritis, fibromyalgia, ankylosing spondylitis, rheumatoid arthritis and chronic low back pain. However, existing research is not sufficiently strong to draw firm conclusions (84).

*GROUP SUPERVISION*

Adoption of regular physical activity and exercise strategies is more successful if personalised contact with a health professional occurs in which the benefits and barriers to exercise are discussed and there is opportunity for group contact (145).

*PATIENT EDUCATION AND SELF-MANAGEMENT*

Educational interventions are provided to support patients to cope with the consequences of the disease. In RA, two systematic reviews on educational interventions consistently conclude that only interventions that involved behavioural change techniques provided a small but significant short-term effect on pain, functional disability and psychological status, while those that offered counselling or "information only" showed no additional benefit (190;191).

*THERMOTHERAPY*

Vivian Robinson et al. performed a Cochrane review in 2002, evaluating the effectiveness of different thermotherapy applications on objective and subjective measures of disease activity in patients with RA (192). Seven RCTs were included, showing no significant effect on objective measures of disease activity including joint swelling, pain, medication intake, range of motion (ROM), grip strength, hand function compared to a control (no treatment) or active therapy. However, no harmful effects of thermotherapy were reported. On this basis, they concluded that superficial moist heat and cryotherapy can be used as palliative therapy. Paraffin wax baths combined with exercises can be recommended for beneficial short-term effects for arthritic hands. However, these conclusions are limited by methodological considerations such as the poor quality of trials.

*ELECTROTHERAPY*

The data for clear benefits of the use of electrophysical agents in the management of RA is lacking. The present data set highlights conflicting results in mainly poor quality studies in which multiple interventions and outcomes confuse synthesis; therefore, little confidence can be attached to the findings. However, some agents, e.g. TENS suggest that short-term symptomatic relief may occur (193). Ultrasound applied in water to the dorsal and palmar aspects of the hand has shown increased grip strength as compared with placebo (194). There is 'silver' level evidence that low level laser therapy for up to four weeks in people with rheumatoid arthritis does decrease pain and morning stiffness. It does not appear, however, to have long-lasting effects (195).

*OCCUPATIONAL THERAPY*

Occupational therapy for rheumatoid arthritis is reviewed by Steultjens et al. in 2004 (196). Thirty-eight out of 58 identified occupational therapy studies fulfilled all inclusion criteria. The results of the best evidence synthesis shows that there is strong evidence for the efficacy of “instruction on joint protection” and that limited evidence exists for comprehensive occupational therapy in improving functional ability. Indicative findings for evidence that “provision of splints” decreases pain are found. Thus, there is evidence that occupational therapy has a positive effect on functional ability in patients with rheumatoid arthritis.

*MANUAL THERAPY*

Massage, a form of manual therapy, is the systematic manipulation of soft tissues of the body for pain reduction or other therapeutic purposes (197). To date, there is no controlled clinical trial on the effectiveness of massage in patients with RA or AS,

whereas a review on its safety concludes that adverse advents with the use of classic massage are rare (198).

Finally, although the use of complementary and alternative treatments is popular in patients with RA and AS, there are very few systematic reviews and RCTs in the complementary medicine area (199). In order to facilitate evidence-based practice in rheumatology, more research will be needed to guide clinicians' decisions in using complementary and alternative treatments for managing RA and AS.

The evidence of the different components of a comprehensive rehabilitation programme differs. Uhlig et al. have reviewed the effectiveness of comprehensive rehabilitation programmes, concluding that when effects on the various outcome measures are demonstrated, improvements can only with difficulty be attributed to a specific component of a comprehensive program. Thus, the overall performance of comprehensive rehabilitation programs, not the individual components, should be evaluated (52).

# CONCLUSIONS

To ease the burden of symptoms by improving self-performance and independence is the main objective of rehabilitation, according to Kesselring (200). Compensation of functional deficits, adaptation and reconditioning, together with management of symptoms, impairment, emotional coping and self-estimation, are all important long-term objectives. Although rehabilitation may not always have a direct influence on the progression of a disease, this form of intervention improves personal activities and participation in social activities, thereby improving quality of life.

Our study supports that a multidisiplinary in-patient rehabilitation programme of four weeks duration improves different aspects of health in both RA and AS patients. Physical exercise therapy increases physical capacity for at least three months, no matter the climatic setting. Disease activity in RA is marginally reduced in a cold climate, and moderately reduced in a warm climate rehabilitation setting for at least three months. Columnal mobility was still improved in 91% and 54% of the AS patients three months after intervention in warm and cold climate settings, respectively (LatFlex20). The improvements in patients' health assessments of pain, morning stiffness, physical function, disease activity and fatigue lasted six months in both RA and AS patients after rehabilitation in a warm climate, for three months in AS patients and only immediately after rehabilitation in a cold climate for RA patients. This demonstrates only a short-term ease of the burden of symptoms after a cold climate compared to a warm climate rehabilitation programme.

For the PPS patients, we revealed positive, sustained effects on physical function three months after a rehabilitation programme, no matter which climate setting. However, a persisting ease of the burden of symptoms appeared after rehabilitation in a warm climate only. An effect on depression was seen after the warm climate intervention as well as in the control patients during spring time.

The patients with neuromuscular diseases had sustained improvements on symptoms, tests of physical function and the Profile of Mood States (POMS) three months after a rehabilitation programme in a warm climate. These effects are compared to a control period without any intervention, thus we are not able to sort out which effect might be due to the warm climate, the programme, or the combination of these.

If I may be capable of generalizing on the basis of the different patients studied in this thesis, it seems that consistency in rehabilitation focusing on physical exercise improves physical capacity, no matter which diagnosis or climatic setting. Moreover, rehabilitation in a warm climate has shown to be superior when it comes to easing the burden of symptoms like pain and fatigue. This finding concurs with the studies indicating that symptoms like pain and stiffness are reduced in a stable climate with low humidity, and the demonstration that low temperature and low atmospheric pressure increase the risk of joint pain in rheumatic patients, and even in arthritic rats. The effects of weather conditions are supposed to be general, however, it is likely that climatic influence affects stiff and aching bodies more than the less weather sensitive symptoms. The persistent improved columnal mobility of almost all AS patients support that a warm, dry and stable climate might pose a better basis for the efficacy of mobility exercises. The improvements found in “moods state” and

depression among the NMD and PPS patients in the warm climate setting might be a consequence of improved personal activities and participation in social activities as stated by Kesselring as an effect of comprehensive rehabilitation.

The efficacy of phototherapy in psoriatic patients have been claimed to be mediated by an anti-inflammatory effect of UV-radiation for decades. The immunmodulatory changes in peripheral blood of psoriatic patients recently demonstrated in the study of Søyland and Heier et al. support this anti-inflammatory effect. The reduction of both T-cells and level of pro-inflammatory cytokines support the theory that being in a warm and sunny climate has a systemic effect. A systemic effect in psoriasis patients allows for similar immunological changes in other autoinflammatory diseases. This concurs to the moderate reduction of disease activity demonstrated in our RA patients treated in a warm climate. The differences in the clinical, radiologic, and serologic expression of rheumatoid arthritis (RA) in Greek and British patients demonstrated by Drosos et al. support that there might be both genetic and environmental factors influencing the disease expression, and the higher RA prevalence among Pakistanis living in England than in Pakistan supports the impact of environmental factors on the causation of RA.

However, the focus of this thesis was not why, but if there was a difference in efficacy when rehabilitation was performed in a warm climate or in a cold climate. We have no causational evidence of which factors are responsible for the demonstrated differences in effect in our studies. The combination of rehabilitation given in beneficial climatic surroundings has shown to be effective. Since rehabilitation implies a multifactorial approach to a problem, or more often a complexity of problems associated with a disease, each potential mechanism of

action is not supposed to give a thorough explanation of the improvements attained; however, they may still pose a rationale for the comprehension of an improvement above placebo level.

# FUTURE STUDIES

## RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

Recently, a systematic review collecting the evidence for the efficacy of comprehensive rehabilitation in a warm climate of patients with a wide variety of rheumatic diseases has been presented online (149). This review concludes that well-designed studies to validate and improve the low-to-moderate evidence found for the efficacy of comprehensive rehabilitation in a warm climate among patients with inflammatory rheumatic disease are greatly needed. In order to ascertain the effects of the comprehensive rehabilitation from the effects of the change of climate, one could design a RCT comparing a four week stay in warm climate with and without intervention.

## POSTPOLIO SYNDROME

Even though the efficacy of physiotherapy and regular, physical exercise in PPS patients has become clearer, the long-term effects (years) are not documented and deserve prospective studies. More studies of comprehensive, in-patient rehabilitation programmes are needed.

There is a need for randomised, controlled trials of strengthening and aerobic exercises versus no intervention, with a long-term follow-up. Studies of a comprehensive, in-patient rehabilitation programme for NMD patients have not been reported in scientific literature. To ascertain the climatic influence on the efficacy of an in-patient rehabilitation programme, there is a need for a randomised, controlled trial comparing in-patient rehabilitation in warm and cold climate, in addition to a control group with no intervention.

# ERRATA

The following changes have been made in the text after submission to the doctoral committee:

Title page (lines 12 and 13): “Department of Rheumatology “ is replaced by “Department of Rheumatology, Dermatology, and Infectious diseases, Division of Specialised Medicine and Surgery”

Title page (line 15): “Department of Research” is removed

Title page (line 17): “Institute of Clinical Medicine” is inserted

Title page (line 18): “Norway “ is inserted

Title page (line 25): The logos of the two involved hospitals are inserted

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# APPENDIX

## PAPERS INCLUDED I-IV

# I

II

**TITLE PAGE**

**Title**

The efficacy of rehabilitation for patients with ankylosing spondylitis: comparison between a 4-week rehabilitation programme in a warm and a cold climate

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**Running head**

Rehabilitation and climate for AS patients

**ABSTRACT**

**Objective:** To investigate the sustained effect of a rehabilitation programme for patients with ankylosing spondylitis (AS), and to compare the effect of this intervention given in a Mediterranean versus a Norwegian climate.

**Methods:** 107 AS patients applying for rehabilitation were randomised to a 4-week in-patient rehabilitation programme in Norway or in a Mediterranean country. The participants were evaluated clinically before and after the rehabilitation period (week 0 and 4) and in week 16. The ASsessments in Ankylosing Spondylitis working group's Improvement Criteria (ASAS-IC), and tests of spinal mobility and physical capacity were used to measure treatment response.

**Results:** At week 16, nearly all disease variables were still improved in both patient groups ($p \leq 0.027$). While the improvements in physical capacity were comparable, the improvements in patients' health assessments and spinal mobility were larger after rehabilitation in a Mediterranean country. Sustained improvement according to the ASAS20, Schober20% and lateral flexion20% was found in 50%, 43% and 91% of the patients in the Mediterranean group versus 23%, 25% and 54% of those in the Norwegian group ($p=0.006$, NS, $p \leq 0.001$, respectively).

**Conclusion:** This study shows that AS patients benefit from a 4-week rehabilitation programme in a Norwegian climate, but even more from a similar programme in a Mediterranean climate.

**Key Words**

ankylosing spondylitis climate rehabilitation physical therapy modalities treatment outcome randomized controlled trials

**Journal of Rehabilitation Medicine**

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## INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease that affects the axial skeleton, causing characteristic inflammatory back pain, stiffness, and often peripheral arthritis. The prevalence of AS is between 0.1% and 1.4% in Europe (1-3).

Physiotherapy and supervised exercise are widely accepted as part of the non-pharmacologic treatment of patients with AS. However, the awareness of published evidence on physiotherapy in AS is unsatisfactory (4;5). A recent updated Cochrane review summarising the available scientific evidence on the effectiveness of physiotherapy in the management of AS concludes that an individual home-based or supervised exercise program is better than no intervention; that supervised group physiotherapy is better than home exercises; and that combined inpatient spa-exercise therapy followed by group physiotherapy is better than group physiotherapy alone (6).

AS patients report variation in health status according to season and weather conditions (7). High doses of ultraviolet radiation may induce immunosuppression (8-10). Differences in daily light exposure influence the circadian rhythms of serum melatonin, cortisol, tumour necrosis factor {alpha} (TNF{alpha}), and interleukin 6 (IL6), and thus the disease activity, in patients with rheumatoid arthritis (11). Melatonin and TNF{alpha} (proinflammatory) were significantly higher in rheumatoid patients from a north European country with reduced daily light exposure than in matched controls or in rheumatoid patients from a south Europe country (12). Low temperature and low atmospheric pressure increase the risk of joint pain in rheumatic patients (13) and intensify pain in arthritic rats (14). An increase in pain and rigidity were associated both with decreased temperature and increased relative humidity in the arthritis sufferers of Aikman's study (15). According to Patberg and Rasker's review, RA variables are positively correlated with the humidity of the microclimate

at the patient's skin, and the classic opinion, "Cold and wet is bad, warm and dry is good for RA patients," seems to be true only as far as humidity is concerned (16).

However, climatic factors might have an additional effect for AS patients participating in a rehabilitation programme. No previous controlled study has evaluated the efficacy of physiotherapy in warm compared to cold climate for AS patients. However, climatic factors have been shown to influence RA patients participating in the same study (17). Some uncontrolled studies have reported sustained improvements in self-reported health status after 3 to 6 months (18-21). Hashkes found 60% responders to climatic therapy using the ASAS criteria for improvement (IC) (22), but this study did not include any follow up.

The current study was conducted to compare the sustained effect of a 4-week rehabilitation programme for AS patients in a Mediterranean and a Norwegian climate, using the ASAS international working group's core sets for physical therapy (PT) interventions (5), the ASAS-IC (23), and objective tests of physical capacity.

## MATERIALS AND METHODS

### Eligibility

The 107 AS patients were recruited from the applicants to a rehabilitation programme in a Mediterranean country, administered by the Section for Climate Therapy at Oslo University Hospital, Rikshospitalet or from the applicants to the North Norway Rehabilitation Centre (RNNK) in Tromsø. The main inclusion criteria were a diagnosis of ankylosing spondylitis (AS) (verified by a rheumatologist), a documented need for rehabilitation, age below 70 years, and reduced physical functioning, but ability to handle primary activities of daily living (P-ADL) without assistance. Eligible patients should not have attended a similar rehabilitation programme within the last 9-12 months before the intervention. Patients with concomitant

diseases that might influence the effect of the rehabilitation programme were excluded: unstable heart, lung or endocrinologic diseases, apoplexia cerebri, cancer, mental sufferings and any kind of abuse problem, in particular. The inclusion of patients was according to the doctor's application and enclosed medical records.

**Study design**

The study was a randomised, controlled, parallel group trial. All eligible patients were invited to participate. Those accepting the invitation were randomly assigned to a 4-week rehabilitation programme in Norway (North Norway Rehabilitation Centre (RNNK) in Tromsø or Skogli Rehabilitation Centre AS in Lillehammer), or a similar treatment in a Mediterranean country (Institute Igalo in Montenegro or Balcova Thermal Therapy Centre in Izmir, Turkey). Randomisation was done by a statistician with the Splus language for data analysis, and was stratified according to sex and type of articular involvement (axial/peripheral). The study period lasted from March 2003 until June 2004.

The participants were examined immediately before (week 0) and after (week 4) the intervention period. Three months later (week 16), all participants were re-examined at the Department of Rheumatology at Oslo University Hospital, Rikshospitalet or at the University Hospital of North Norway (UNN), Tromsø. They answered a questionnaire at week 0, 4, 16, and 28 as well.

**Intervention**

The participants followed the regular rehabilitation programmes at all centres. The main components of the therapy offered were individualised physiotherapy with exercises, group exercises, passive therapy, relaxation, and patient education.

***Active physiotherapy.*** Individualised physiotherapy was given once daily: on a couch, in the fitness department using specially constructed equipments, or in the pool. Group training (eight to 15 patients) was given twice daily: in the gym and in a temperature-controlled swimming pool. During a week the patients in the Mediterranean group had 15-17 obligatory sessions of active physiotherapy lasting 20-45 minutes, and the patients in the Norwegian group had 15-16 sessions of 30-60 minutes duration. The exercise therapy aimed at increasing endurance, mobility, and strength. While the Norwegian programme included more endurance training, the Mediterranean programme had more focus on mobility. At all treatment centres the patients were given the opportunity to attend additional, voluntary, physical activities.

***Passive therapy.*** This therapy comprised thermotherapy, massage, and electrotherapy. At the Mediterranean centres (thermo-) mineral water was used for balneotherapy in the swimming pools, bubble baths, and underwater massage. Two passive treatments of 10-15 min a day were usually given to each patient. At the Norwegian centres, patients received passive therapy merely when this was found indicated by the physiotherapist.

The programme included a 30-45 min supervised relaxation session two to four times a week at Lillehammer, Tromsø, and Balcova. At Institute Igalo activities such as yoga and tai chi were offered.

***Patient education.*** Disease-specific lectures about AS were given at all four centres focusing on diet, physical activity, self efficacy, coping techniques, and advice related to general health.

Treatment with disease modifying anti rheumatic drugs was kept constant during the intervention and follow up. However, disease related adjustments were allowed.

**Daylight and climate**

The study period in the warm climate was in May-June 2003 at Institute Igalo in Montenegro and September-October 2003 at Balcova Thermal Therapy Center in Izmir, Turkey, both located by the Mediterranean Sea. Mean daylight time was 14 h 59 min in Igalo and 11 h 51 min in Balcova, computed using National Mapping Division's sunrisenset program, version 2.2. The morning temperature in Igalo ranged from 15.6°C to 30.4°C, mean 24.4°C, and in Balcova from 15.0°C to 26.0°C, mean 20.1°C, measured at 8.00/ 7.30am at the Therapy Centre. The mean number of days with precipitation above 1.0mm during each 4-week rehabilitation period was 2 days in Igalo and 1 day in Balcova.

The study period in Norway lasted from March to May and September to December 2003. The patients living in the northern parts of Norway received their rehabilitation programme at RNNK in Tromsø, which is located on the Northern Norway coastline, while the patients living in the southern parts received their rehabilitation programme at Skogli in Lillehammer, which is located in the inland area. Mean daylight time was 12 h 46 min in Lillehammer and 15 h 41 min in Tromsø. The morning temperature in Lillehammer ranged from -9.3°C to11.8°C, mean 1.7°C and in Tromsø from -6.0°C to 14.9°C, mean 3.0°C measured at 7am at the Norwegian Meteorological Institutes. The mean number of days with precipitation above 1.0mm during each 4-week rehabilitation period was 7.5 days in Lillehammer and 12.0 days in Tromsø.

**Outcome Measures**

The patients were assessed for lumbar spinal mobility by the original Schober test: the increase with forward flexion of a 10 cm segment with the inferior mark at the level of the posterior superior iliac spines (24), and lateral lumbar flexion: the difference between the fingertips-to-floor distance in the upright position and at maximum lateral flexion (25). The

medical examinations included chest expansion: the difference in the chest circumference between full expiration and full inspiration at the 4th intercostal space (26) and erythrocyte sedimentation rate (ESR, mm). Exercise capacity was measured by the 6-Minute Walk Test (6MWT) (27), and physical capacity was measured by the Timed Up and Go (TUG) (28). The total TUG distance was 20 metres, this walking distance and time were measured to calculate walking pace. The same assessor performed the medical examinations on the same patient throughout the whole study period.

The patients assessed their own health status by: patient's global assessment of disease activity (VAS 0-10 cm), fatigue (VAS 0-10 cm), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (29;30), and Bath Ankylosing Spondylitis Functional Index (BASFI) (31;32).

The ASsessments in Ankylosing Spondylitis working group's Improvement Criteria (ASAS-IC) were used to measure treatment response. An ASAS20 improvement is $\geq$20% relative improvement and absolute improvement of $\geq$1 unit (on a scale of 0-10) in 3 or more of the following 4 domains: patient's global assessment, patient's perception of pain (question 2 of the BASDAI), inflammation (mean of question 5 and 6 of the BASDAI), and function (BASFI), with no worsening by $\geq$20% and $\geq$1 unit in the remaining domain (23). ASAS40 improvement was defined as attaining a $\geq$40% relative improvement and an absolute improvement of $\geq$2 units in 3 or more of the 4 domains, with no deterioration from baseline in the remaining domain (33).

The response at week 16 was chosen as a main outcome to evaluate sustained effect.

**Ethics**

The Regional Ethics Committee and The Norwegian Social Science Services/ Data Inspectorate approved the study, and written, informed consent was obtained from all participating patients.

**Statistics**

Sample size was calculated with the Sample power programme. For patient's assessment of pain (VAS; 0-10 cm), 80% power, a minimum clinically significant difference (MCSD) at 0.9 and a SD at 2.2, we needed 100 participants in each climate group to detect a difference between the two treatment groups. Statistical analyses were undertaken with the SPSS version 13.0.

Continual data is presented as mean and SD or median and $25^{th}$, $75^{th}$ centiles according to whether the observations show normal distribution. To compare two groups we used the Pearson Chi-Square Test, or Fisher's Exact Test when appropriate, for categorical variables, independent Samples T-Test for continuous variables with normal distribution, and Mann Whitney U-Test for continuous variables without normal distribution.

The clinical response is given as the mean difference from baseline with corresponding standard deviation (SD). Paired Samples T-Test and Independent Samples T-Test were used for within group and between groups analysis, respectively. The chosen level of significance is probability (p) values $\leq 0.05$.

Since Bonferroni correction for multiple comparisons presumes independency between the variables tested and the tests in this study were on the same subjects using highly correlated variables, Bonferroni correction was judged to be too conservative (34).

## RESULTS

### Patient disposition

Totally 325 eligible AS patients were invited to participate (figure 1). From these, 154 patients were randomised for treatment in a Mediterranean country, n=77 or in Norway, n=77, and 107 patients were analysed as completers, n=65 in a Mediterranean country (40 in Turkey and 25 in Montenegro) and n=42 in Norway (13 in Tromsø and 29 in Lillehammer).
As many as 171 persons declined to participate in the study, additionally 10 patients randomised to the Mediterranean group and 28 patients randomised to the Norwegian group withdrew their consent after randomisation. Only 3 (1+2) patients were lost to follow up, and 6 (1+5) patients did not meet the Modified New York Criteria for Ankylosing Spondylitis (1984) at the first medical examination and were thus excluded from the analysis (35).

The known reasons for withdrawal after randomisation before treatment were practical considerations, n=9, dissatisfaction with the randomisation result, n=4, acute trauma/ hospitalisation, n=3, responsibility at home, n=2, or no need for rehabilitation (improved health status), n=2. The reasons for withdrawal were comparable whether randomised to rehabilitation in Mediterranean climate or in Norway. Eighteen patients withdrew without giving us any reason.

There was no significant difference between the participants, n=107 (65+42) and the non-participants, n= 218 (171+10+1+1+28+2+5) of this study with regard to age (data not shown), but the proportion of men was higher among the non-participants (69% versus 57%, p=0.029).

The patients who discontinued after randomisation, n=47 (10+1+1+28+2+5), were comparable to the completers, n=107 (65+42) regarding age, sex, and type of articular involvement (axial/peripheral) (data not shown). A higher number of patients completed the study among those randomised to the Mediterranean group, n=65, than those randomised to

the Norwegian group, n=42, ($p \leq 0.001$), but the completers of the two groups did not differ in regard to age, sex, and type of articular involvement (axial/peripheral) (data not shown).

**Patient baseline characteristics**

The demographic and disease characteristics were comparable in the 65 patients treated in the Mediterranean climate [42% women, mean age 48 (range 28-70) years] and the 42 patients treated in the Norwegian climate [45% women, mean age 51 (range 30-62) years] (table I). The number of patients using DMARDs or prednisolone at baseline was lower in the Mediterranean than in the Norwegian group ($p=0.007$ and $p=0.011$ respectively). Still, the baseline values of all outcome measures were comparable (table II and III).

**Efficacy**

Clinical response was expressed as mean difference from baseline at 4, 16, and 28 weeks after initiation of the 4-week rehabilitation programme. Changes in the patient's assessments of health status are presented in table II, and the spinal mobility, ESR, and tests of physical capacity in table III.

At week 16 all examined variables, except chest expansion and ESR, improved significantly among patients in both study groups ($p \leq 0.027$). The improvements at week 16 were larger for patients treated in Mediterranean countries than for those treated in Norway for all examined variables except for the patient's global assessment, chest expansion, and the tests of physical capacity ($p \leq 0.049$).

After 28 weeks all patient's assessments of health status (patient's global, spinal pain, morning stiffness, BASFI, BASDAI, and fatigue) were still significantly improved in the Mediterranean group ($p \leq 0.001$), but not in the Norwegian group.

At week 16, the proportion of patients who met the ASAS20 and ASAS40 improvement criteria was 50% and 29% in the Mediterranean group and 23% and 10% in the Norwegian group ($p=0.006$ and $p=0.022$, respectively), (figure 2). The proportion of patients who achieved a 20% and 40% improvement in Schober's test was 43% and 29% in the Mediterranean group and 25% and 10% in the Norwegian group (NS and $p=0.025$, respectively) (figure 3A). The proportion of patients with 20% and 40% improvement in lateral flexion was 91% and 75% in the Mediterranean and 54% and 39% in the Norwegian group ($p \leq 0.001$) (figure 3B).

**Medication**

Thirty-one (48%) of the 65 Mediterranean group patients and four (10%) of the 42 Norwegian group patients had ceased or reduced their use of analgesics during the 4-week rehabilitation period ($p \leq 0.001$). Seven patients (11%) had initiated or increased their use of analgesics 16 weeks after initiation of intervention in the Mediterranean group, compared with no patients in the Norwegian group ($p=0.041$). It was no statistical difference in the number of patients that initiated/increased or ceased/reduced NSAIDs, DMARDs, biological drugs and prednisolone between the two groups within the study period (data not shown).

**DISCUSSION**

This study ascertains the effect of a 4-week rehabilitation programme for AS patients performed either in a Mediterranean or in a Norwegian climate. Close to all patient's assessments of health status, spinal mobility measures, and tests of physical capacity improved significantly 3 months after completion of the programme (week 16) in both climate settings. The improvements in the patient's assessments of health status and spinal mobility

measures were larger when the rehabilitation was performed in a Mediterranean country rather than in Norway, while the tests of physical capacity showed comparable improvements in both climate settings.

The proportion of ASAS20/ASAS40 responders at 16 weeks after the rehabilitation programme was 50%/29% in the Mediterranean group and 23%/10% in the Norwegian group. The immediate (week 4) efficacy in the Mediterranean group (79% ASAS20 responders) was similar to that of anti-TNFα therapy previously found for AS patients (36).

The obtained effects of the rehabilitation programme decline with time in contrast to the continuous anti-TNFα therapy. This concurs with the uncontrolled study of Lubrano et al., being the first to evaluate the effectiveness of a 3-week intensive rehabilitation programme by the ASAS response criteria (37). It is not known whether repeated rehabilitation periods could give an additive efficacy in AS patients.

Brandt et al. have suggested to include spinal mobility and acute phase reactants to the original four domains ASAS-IC, which are a composition of patients' health assessments (33). Schober's test and thoracolumbar lateral flexion have proved to be among the most valid measures of spinal mobility, shown as significant correlations with radiological sum scores (38).

The participants of our study had both restricted anterior (Schober's test) and lateral lumbar flexion as well as chest expansion at baseline when compared to normal values (24-26). The mean improvements in the Schober's test of this study span from 0.1 to 0.7 cm, which are comparable to other studies of different exercise programmes for AS patients (39;40). Pile et al. have calculated the mean inter-observer variation to be 0.7 cm and the mean intra-observer variation to be 0.6 cm for the modified Schober's test (41). The high degree of variation between each measure in individual patients makes it difficult to define the observed improvement to be of any clinical significance. According to Viitanen et al., the

Schober's test is both a valid and reliable measurement, but not very sensitive to change (38;42). When using measures insensitive to change, Felson et al. recommend to define change on an individual basis, focusing on enumerating which patients improve in a trial, rather than on the mean level of improvement (43). Thus, the fact that the number of patients achieving 20%/40% improvement in Schober was 43/29 in the Mediterranean group and 25/10 in the Norway group might be more illustrative than the mean change for the efficacy 16 weeks after initiation of intervention in this study.

Lateral lumbar flexion is a responsive measure judged by a high standardised response mean (SRM) (0.84), and has been recommended among the spinal mobility measures (33). The number of patients having 20%/ 40% improvement in lateral flexion remained high at week 16: 91/75 in the Mediterranean group and 54/39 in the Norway group.

The obtained improvements in spinal mobility seem to be more stable than the ASAS improvements in this study. This might indicate that an intensive rehabilitation programme could postpone the stiffening process in the columna of AS patients. According to Lubrano et al., rehabilitation was superior to anti- TNFα therapy for improvements in anthropometric measures (44). Thus, physiotherapy and physical exercise may be a substantial supplement to medical treatment in order to improve mobility AS patients. Warm and stable climatic conditions may enhance rheumatic patients' capacity to perform physical exercise (20), and this might explain why the improvements were larger when the rehabilitation was performed in a Mediterranean climate.

The tests of physical capacity showed sustained, comparable improvements after 16 weeks for both patient groups. The mean change in the 6-Minute Walk Test is judged to be of clinical significance when compared to studies of patients with respiratory diseases (45;46). The improvements in Timed Up and Go confirmed that the patients had improved their walking pace.

This study has some methodological limitations that have to be taken into consideration. More patients dropped out before the study started in the Norwegian group than in the Mediterranean group. This may have influenced the comparability of the two groups. We found some differences in baseline drugs, but the baseline values of all outcome measures were comparable.

The climatic conditions were a main difference between the Mediterranean therapy and the Norwegian therapy given in this study, but we cannot ignore that the rehabilitation programmes had some differences even though the main components were similar. The Norwegian programme tended to focus more on endurance training and the Mediterranean programme more on mobility. Passive therapy including balneotherapy was given on a larger scale in the Mediterranean than in the Norwegian centres. Spa therapy has been shown to provide additional beneficial effect over standard treatment consisting of physical exercise and drug treatment alone for patients with ankylosing spondylitis (39;47;48). Thus, our conclusion about the differences in efficacy of rehabilitation in warm and cold climates must take into account more than the relationship between climatic conditions and AS. Further studies are needed to ascertain which are the most important contributing factors to these differences.

In conclusion, this study shows that AS patients had a sustained positive effect of a 4-week rehabilitation programme both in a Mediterranean and in a Norwegian climate. The improvements in the patient's assessments of health status and spinal mobility measures were larger and better maintained at least 3 months after rehabilitation in a Mediterranean climate, while the improvements in physical capacity were comparable between the two groups. These results support the ASAS/EULAR recommendations of non pharmacological therapy (including education, exercise and physiotherapy) as an important part of the management of AS (5).

**ACKNOWLEDGEMENTS**

The authors are grateful to all persons participating in the study. We thank Karin Øien Forseth, MD, PhD and Gunnstein Bakland, MD for assistance with the data collection, Marianne Strand Svendsen for coordinating the participants, consultant Johan Kofstad at the Department of Medical Biochemistry for help with the blood tests analysis, and Biostatistic unit at Oslo University Hospital, Rikshospitalet for help with the statistics.

**Funding**

This study was financed by the Section for Climate Therapy, Department of Rheumatology at Oslo University Hospital, Rikshospitalet, and supported by a grant from the Norwegian Foundation for Health and Rehabilitation via the Norwegian Rheumatism Association.

**Competing interests**

None declared.

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**Table I** Baseline characteristics for AS patients receiving rehabilitation in a Mediterranean country or in Norway

| | **Mediterranean group n=65** | **Norwegian group n=42** |
|---|---|---|
| Demographic data | | |
| Female sex, n (%) | 27 (42) | 19 (45) |
| Age, years, mean (SD; range) | 48 (10; 28 – 70) | 51 (8; 30 - 62) |
| Married or living with a partner, n (%) | 51 (79) | 30 (71) |
| Years of education, mean (SD) | 13 (3) | 12 (3) |
| Employed full time/part time, n (%) | 30 (46)/9 (14) | 20 (48)/6 (14) |
| Once on sick leave during last 6 months, n (%) | 17 (47) | 14 (58) |
| Disease characteristics | | |
| Disease duration, years, mean (SD) | 17 (10) | 18 (9) |
| HLA-B27 positive, n (%) | 57 (88) | 38 (93) |
| *Co-morbidity* | | |
| Hypertension, n (%) | 12 (19) | 13 (31) |
| Metabolic disorders, n (%) | 8 (12) | 2 (5) |
| Other diseases, n (%)* | 7 (11) | 6 (14) |
| Baseline drugs (%) | | |
| NSAIDs or coxibs daily/when needed, n (%) | 37 (58)/20 (31) | 26 (62)/10 (24) |
| Analgesics daily/when needed, n (%) | 6 (9)/42 (65) | 4 (10)/19 (46) |
| DMARDs, n (%) | 7 (11) | 13 (33) § |
| Prednisolone, n (%) | 4 (6) | 9 (24) § |
| Daily prednisolone dose, mg, mean (SD) | 5 (4) | 5 |
| Biological treatment, n (%) | 1 (2) | 3 (9) |

*Coronary artery disease n=3, renal diseases n=3, migraine n=3, asthma bronchiale n=2 and cancer n=2.
§p<=0.01 versus patients treated in the Mediterranean group.
NSAID, Non-steroid anti inflammatory drug; DMARD, disease-modifying antirheumatic drug.

| **Table II** Responses in patient's assessments of health status at 4, 16 and 28 weeks after initiation of rehabilitation (VAS; 0-10 cm). | **Baseline values** | **Changes from baseline** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **week 4** | **p value** | **week 16** | **p value** | **week 28** | **p value** |
| ASAS IC component | | | | | | | |
| Patient's global | | | | | | | |
| Mediterranean group | 5.4 (2.0) | -3.7 (2.2) | 0.001 | -2.1 (2.6) | 0.001 | -1.5 (2.6) | 0.001 |
| Norwegian group | 5.0 (1.9) | -1.7 (1.9) | 0.001 | -1.2 (2.2) | 0.001 | -0.5 (2.5) | 0.210 |
| Difference between the groups | | | 0.001 | | 0.073 | | 0.069 |
| Spinal pain (BASDAI 2) | | | | | | | |
| Mediterranean group | 6.2 (2.0) | -4.2 (2.5) | 0.001 | -2.3 (3.2) | 0.001 | -1.4 (2.3) | 0.001 |
| Norwegian group | 5.8 (1.8) | -1.9 (1.9) | 0.001 | -0.8 (2.3) | 0.027 | -0.3 (2.3) | 0.374 |
| Difference between the groups | | | 0.001 | | 0.007 | | 0.035 |
| Morning stiffness (BASDAI 5 and 6) | | | | | | | |
| Mediterranean group | 4.9 (2.3) | -3.1 (2.1) | 0.001 | -2.2 (2.2) | 0.001 | -1.7 (2.2) | 0.001 |
| Norwegian group | 5.0 (2.0) | -1.8 (1.6) | 0.001 | -1.2 (2.2) | 0.001 | -0.6 (2.0) | 0.060 |
| Difference between the groups | | | 0.002 | | 0.028 | | 0.026 |
| BASFI | | | | | | | |
| Mediterranean group | 4.3 (2.0) | -2.6 (1.7) | 0.001 | -1.3 (1.9) | 0.001 | -0.95 (1.8) | 0.001 |
| Norwegian group | 4.3 (1.5) | -1.2 (1.2) | 0.001 | -0.52 (1.2) | 0.010 | -0.38 (1.2) | 0.056 |
| Difference between the groups | | | 0.001 | | 0.016 | | 0.085 |
| BASDAI | | | | | | | |
| Mediterranean group | 5.0 (1.7) | -3.3 (1.9) | 0.001 | -2.0 (2.3) | 0.001 | -1.3 (1.8) | 0.001 |
| Norwegian group | 4.8 (1.3) | -1.6 (1.3) | 0.001 | -0.7 (1.7) | 0.013 | -0.3 (1.6) | 0.347 |
| Difference between the groups | | | 0.001 | | 0.001 | | 0.004 |
| Fatigue* | | | | | | | |
| Mediterranean group | 7.0 (3.6,8.5) | -4.2 (2.7) | 0.001 | -2.7 (3.3) | 0.001 | -2.3 (2.8) | 0.001 |
| Norwegian group | 6.1 (3.5,7.4) | -1.4 (2.6) | 0.001 | -1.5 (2.7) | 0.001 | -0.6 (2.9) | 0.172 |
| Difference between the groups | | | 0.001 | | 0.049 | | 0.007 |

Baseline values are shown as mean (SD), unless stated otherwise, and changes from baseline are shown as mean difference from baseline (SD).
*median ($25^{th}$, $75^{th}$ centile). Number of patients treated (n) was 65 in the Mediterranean group and 42 in the Norwegian group.
ASAS-IC, Assessments in Ankylosing Spondylitis working groups Improvement Criteria; VAS, visual analogue scale; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index.

| **Table III** Responses in spinal mobility, ESR and tests of physical capacity at 4 and 16 weeks after initiation of rehabilitation | **Baseline values** | **Changes from baseline** | | | |
|---|---|---|---|---|---|
| | | **week 4** | **p value** | **week 16** | **p value** |
| Spinal mobility | | | | | |
| Anterior lumbar flexion (Schober), cm | | | | | |
| Mediterranean group | 3.3 (1.6) | 0.7 (1.0) | 0.001 | 0.5 (0.9) | 0.001 |
| Norwegian group | 3.2 (1.5) | 0.1 (0.5) | 0.137 | 0.2 (0.5) | 0.003 |
| Difference between the groups | | | 0.001 | | 0.038 |
| Lateral lumbar flexion, right, cm | | | | | |
| Mediterranean group | 8.6 (4.4) | 4.9 (3.9) | 0.001 | 4.5 (3.8) | 0.001 |
| Norwegian group | 9.9 (5.7) | 2.3 (3.5) | 0.001 | 1.5 (2.8) | 0.002 |
| Difference between the groups | | | 0.001 | | 0.001 |
| Lateral lumbar flexion, left, cm | | | | | |
| Mediterranean group | 8.3 (4.5) | 5.1 (3.7) | 0.001 | 4.7 (3.7) | 0.001 |
| Norwegian group | 9.6 (5.4) | 2.4 (3.3) | 0.001 | 1.8 (3.1) | 0.001 |
| Difference between the groups | | | 0.001 | | 0.001 |
| Chest expansion, cm | | | | | |
| Mediterranean group | 3.7 (1.6) | 0.7 (1.4) | 0.001 | 0.3 (1.5) | 0.081 |
| Norwegian group | 3.9 (1.9) | 0.2 (0.8) | 0.174 | 0.3 (1.1) | 0.142 |
| Difference between the groups | | | 0.023 | | 0.792 |
| ESR, mm* | | | | | |
| Mediterranean group | 17.0 (10.0,36.5) | 1.0 (11.0) | 0.489 | -8.3 (10.9) | 0.001 |
| Norwegian group | 12.0 (6.0,30.5) | -3.5 (10.6) | 0.039 | -2.5 (10.6) | 0.116 |
| Difference between the groups | | | 0.041 | | 0.014 |
| Tests of physical capacity | | | | | |
| 6-Minute Walk Test (6MWT), m | | | | | |
| Mediterranean group | 559 (84) | 84 (64) | 0.001 | 68 (65) | 0.001 |
| Norwegian group | 566 (99) | 61 (53) | 0.001 | 59 (54) | 0.001 |
| Difference between the groups | | | 0.071 | | 0.470 |
| Timed Up and Go (TUG),speed (20m/second) | | | | | |
| Mediterranean group | 1.5 (0.3) | 0.2 (0.2) | 0.001 | 0.2 (0.2) | 0.001 |
| Norwegian group | 1.5 (0.3) | 0.2 (0.2) | 0.001 | 0.1 (0.2) | 0.027 |
| Difference between the groups | | | 0.069 | | 0.116 |

Baseline values are shown as mean (SD), and changes from baseline are shown as mean difference from baseline (SD), unless stated otherwise. *median ($25^{th}$, $75^{th}$ centile). Number of patients treated (n) was 65 in the Mediterranean group and 42 in the Norwegian group.
ESR, erythrocyte sedimentation rate.

**Figure Legends**

**Figure 1.** Summary of patient disposition, *non-participants in italics, n=218 (171+10+1+1+28+2+5).* ***** The patients excluded from the analysis did not meet the Modified New York Criteria for Ankylosing Spondylitis (1984) at the first medical examination (35).

**Figure 2.** Values above the bars are the percentages of the patients who met the Assessments in Ankylosing Spondylitis working group's improvement criteria (ASAS-IC), ASAS20= 20% improvement and ASAS40= 40% improvement. The responses are measured at week 4, week16, and week 28 after initiation of treatment in the Mediterranean, n=65, or in the Norwegian climate, n=42. The differences between the groups are marked on the figure.

**Figure 3.** Values above the bars are the percentages of the patients who had 20% and 40% improvement in **A)** anterior lumbar flexion (Schober) and **B)** lateral lumbar flexion on either the right or the left side. The responses are measured immediately after treatment (week 4) and 16 weeks after initiation of treatment in the Mediterranean, n=65, or in the Norwegian climate, n=42. The differences between the groups are marked on the figure.

## Figure 1 Patient flow

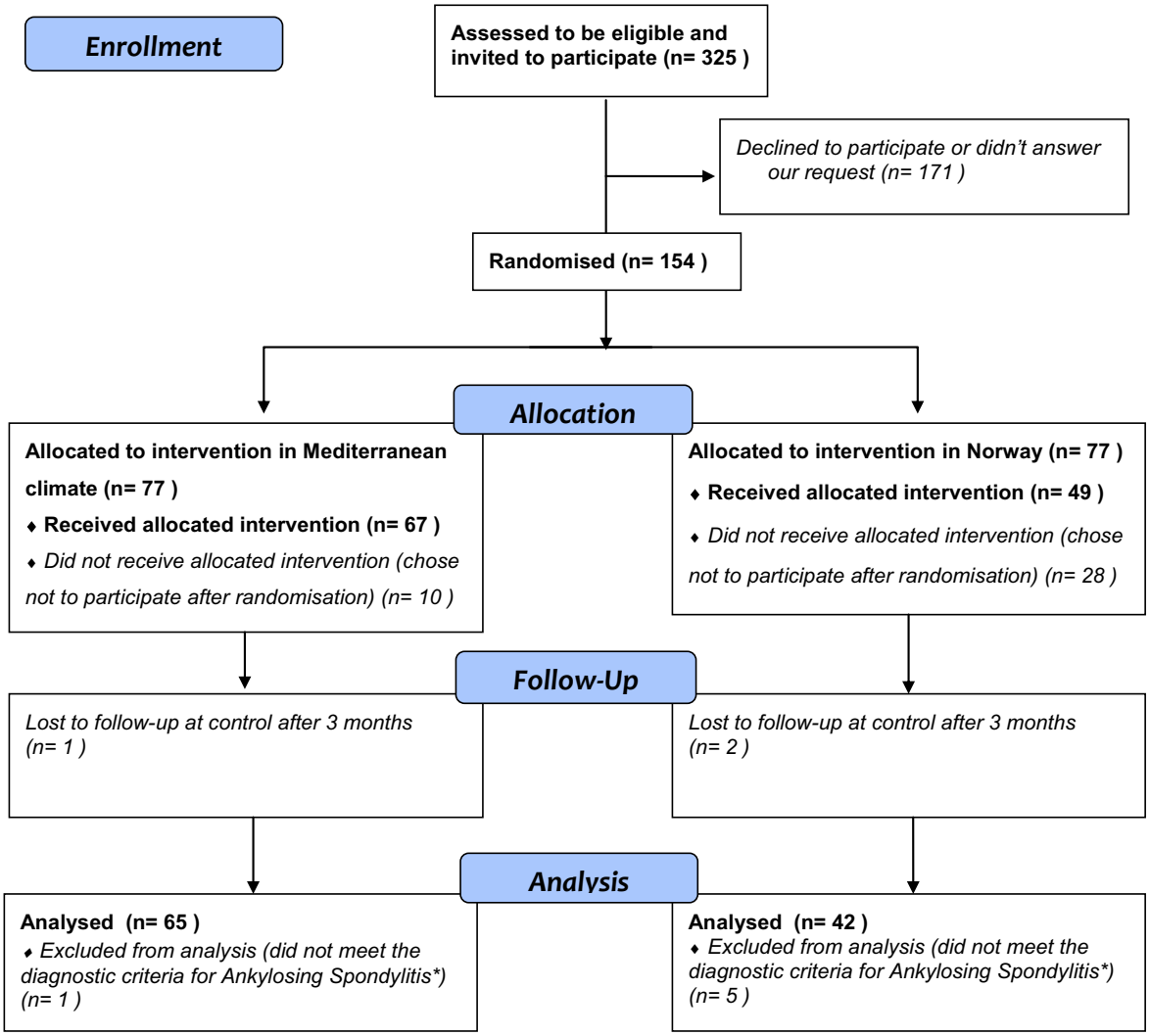


Figure 2 ASAS improvement

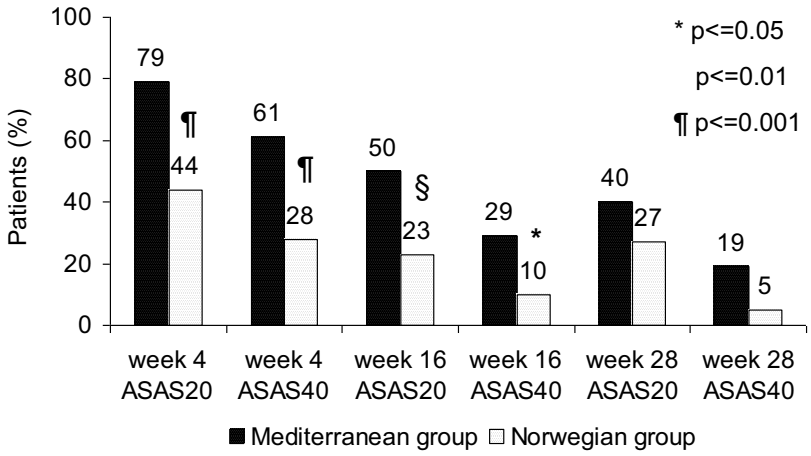


Figure 3A Schober 20 and 40% improvement

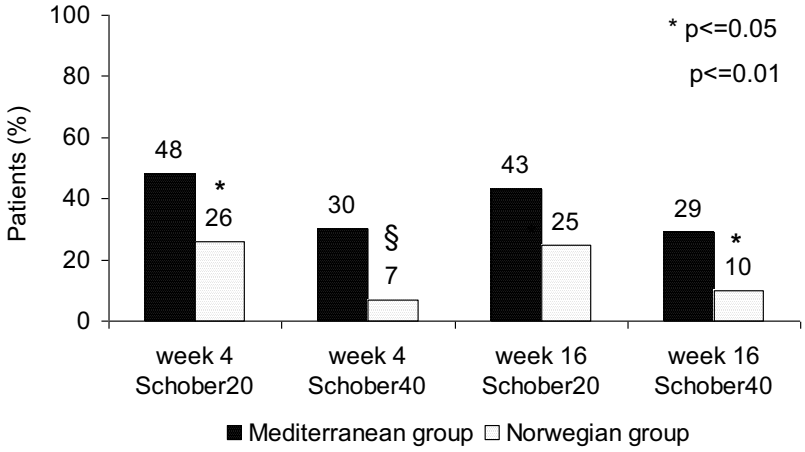
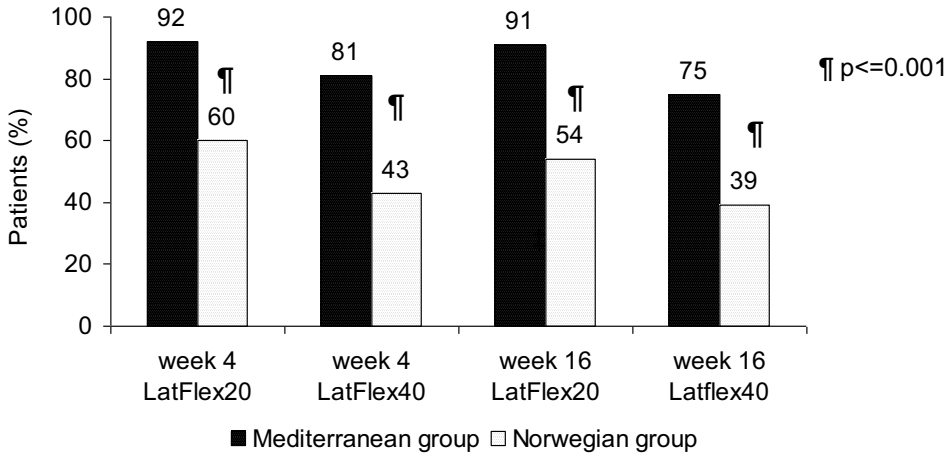


Figure 3B Lateral flexion 20 and 40% improvement



III

IV

J Rehabil Med 2007; 39: 554–559

**ORIGINAL REPORT**

# PATIENTS WITH NEUROMUSCULAR DISEASES BENEFIT FROM TREATMENT IN A WARM CLIMATE

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***Objective:*** **Several studies have shown positive effects of treatment of chronic diseases in a warm climate. The aim of this study was to evaluate the long-term effect of a 4-week rehabilitation programme in a warm climate for patients with neuromuscular diseases.**

***Design:*** **A randomized controlled trial with a cross-over design. One period of intervention and one period of "life as usual".**

***Patients:*** **A total of 60 persons with a neuromuscular diagnosis.**

***Methods:*** **Long-term effects were defined as changes in physical and psychological functions persisting after 3 months. Several scales were used according to the World Health Organization's classification of functioning.**

***Results:*** **A comparison of the changes in the 2 periods showed significantly better results for all primary outcome scales in favour of the intervention. Mean difference in changes in pain (VAS scale), 6-min walking test and "timed up and go" were 9.0 (SD 28.8) units, 52 (75) m and 1.0 (2.3) sec, $p = 0$, 03, $< 0.01$ and 0.01, respectively. Median difference in changes in "Fatigue Severity Scale" and "Life Satisfaction Scale" were 0.4 (–0.5, 1.7) and 0.0 (0.0, 1.0), $p = < 0.01$ and 0.01, respectively.**

***Conclusion:*** **This study shows positive long-term effects on different dimensions of health after a 4-week rehabilitation programme in a warm climate for patients with neuromuscular diseases. This effect might be due to the programme, the warm climate, or a combination of both.**

*Key words:* neuromuscular disease, climate, rehabilitation, comparative study, treatment outcome.

J Rehabil Med 2007; 39: 554–559

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Submitted May 19, 2006; accepted March 9, 2007

## INTRODUCTION

The number of persons suffering from a neuromuscular disease in Norway is approximately 5000 (1–6). The heterogeneous group of neuromuscular diagnoses can be divided into 3 main groups; myopathies, where the disease is located in the muscle fibre or its energy metabolism, neuropathies (disease in the peripheral nerves), and neuromyopathies, where both the muscle fibres and the nerves are affected (1–6). There are hereditary, congenital neuromuscular diseases in all of these 3 main groups. The diagnoses are relatively slowly progressive (2, 3, 6). Even though neuromuscular disorders are a heterogenic group, both in terms of pathophysiology and clinical manifestations, it is possible to identify common impairments that influence quality of life and ability to cope with everyday living. Some of the common problems and complaints are muscle weakness of various severity, exercise intolerance, reduced endurance, fatigue, pain and problems with ambulation (1, 7, 8).

Many individuals with neuromuscular diseases have reported that staying in countries with a warm climate for a period, or following a rehabilitation programme in countries with a warm climate, has positive effects on their health. The reported effects have been on both a physical and a psychosocial level, including health-related quality of life and general well-being. In Norway there is a long tradition of sending patients to warmer climates for intensive physiotherapy. This health service was originally offered to patients with rheumatic diseases. A public report about this concept concludes that patients with other chronic, somatic diseases might also benefit from treatment in a warm climate (9).

Recommending treatment in a warm climate for various patient groups, especially persons with neuromuscular diseases, is controversial. Requests for such treatment from these patients themselves are increasing. This study was set up as a result of the claim that the effect of treatment in a warm climate should be evaluated thoroughly. The aim of this study was to evaluate whether treatment in a warmer climate had long-term effects on physical, psychological and social dimensions of health in persons with neuromuscular diseases. Long-term effects were defined as changes in physical and psychological functions persisting 3 months after intervention.

## METHODS

This study was announced in 6 of Norway's largest daily newspapers and in the Norwegian neuromuscular organization's newsletter. Information about the study was also sent to the local groups of



 ISSN 1650-1977
doi: 10.2340/16501977-0088

the Norwegian neuromuscular organization and to the 2 university hospitals in Norway with special units for neuromuscular diseases (Rikshospitalet-Radiumhospitalet Medical Centre and University Hospital of North Norway).

The main inclusion criterion was a neuromuscular disease of hereditary, slowly progressive type, diagnosed by a neurologist. In addition, participants should be able to handle primary activities of daily living without assistance (10). Participants were recruited from persons who answered the announcement and met the inclusion criteria.

Exclusion criteria were other medical conditions that could influence safe participation in the rehabilitation programme in a warm climate, such as serious cardiovascular disease, serious psychiatric conditions, and alcohol or drug addictions.

Use of a manual or powered wheelchair did not exclude persons from the study, but due to airline company restrictions the inclusion of persons with an absolute need for a powered wheelchair was limited.

A total of 99 persons applied to participate in the study. Of these, 67 met the inclusion criteria, and after a random draw 60 were invited to participate.

The study followed a cross-over design with 2 intervention periods (Fig. 1). The first period started (first baseline) in May 2003, with a 4-week intervention in June for half of the participants, and a re-test in October (3 months after intervention) for all participants. The second period started in May 2004 with a baseline test (second baseline), and intervention was offered to the other half of the patients. Again, all participants were re-tested in October. Participants selected for intervention in the first or second period were determined by randomization, after stratification on diagnosis and use of powered wheelchair. Randomization was performed after the first baseline examinations.

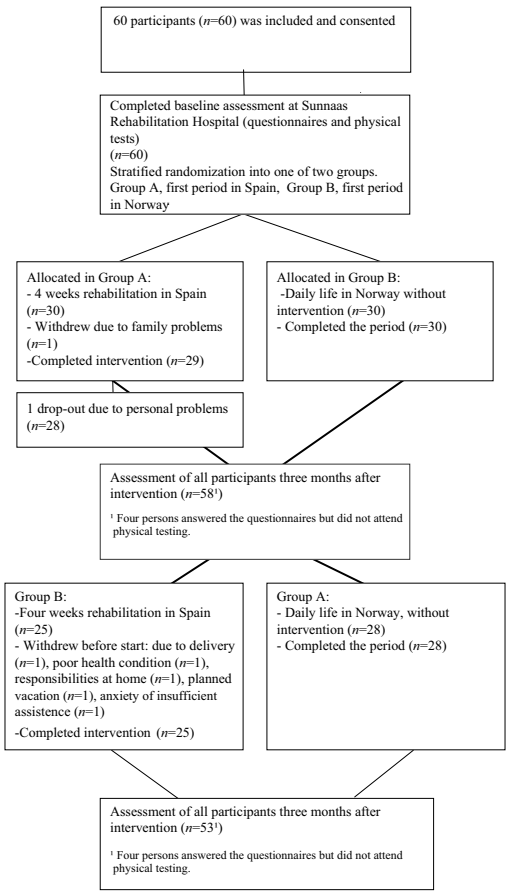


*Fig. 1.* Study design and flow of participants through each stage of the trial.

The intervention was performed at Reuma-Sol centre, a modern rehabilitation centre situated on the coast of Spain (Costa Blanca), with facilities such as gym and swimming pools. The climate in Spain during the intervention periods was mostly dry and sunny, with mean temperatures of 25°C. The rehabilitation programme at Reuma-Sol was specially organized for the intervention periods (2003 and 2004) of this study. The participants received a combination of individual and group therapy with low to moderate intensities regarding both strength and endurance training. Depending on the weather and temperature, the indoor or outdoor pools were used for daily training, both in groups and for individual self-training activities. Furthermore, the programme included classes in relaxation, group training in the gym and instruction in self-training. The participants were a heterogeneous group and, in order to be able to provide an adapted level of training, the group was divided into 3 training groups based on clinical evaluation of physical function by the physiotherapists. In addition, each person was prescribed an individually adapted training programme based on his or her functional level.

The participants attended daily training/treatment in the swimming pool (60 min) and daily group training in the gym (60 min). Individual physiotherapy was received on average 4 times a week. The organization of the daily programme gave the participants opportunity to recover, do exercise or take a walk on their own, according to their individual need. A physician and a physical therapist from Sunnaas Rehabilitation Hospital were responsible for a patient education programme.

The study period May to October includes the Norwegian summer. Norwegian climate during summer varies throughout the country. In northern Norway, the summer period is shorter and the temperature is lower than in the south, where the weather is more stable and dry. During this period in Norway the participants were told to "live as usual", besides participating in the test procedures. Some of them had regular physiotherapy and/or pool training sessions or other physical activities, while others had no physical therapy or training.

The outcome measures were chosen due to the complexity of a clinical evaluation of patients with neuromuscular diseases, which requires that a large variety of physical and psychological symptoms and complaints are taken into consideration. They also aimed to cover the 3 levels of the World Health Organization (WHO)'s defined consequences of disease; body functions and structures, activities and participation (11). Based on the most common problems and previous findings during treatment in a warm climate for other patient groups, the following five primary outcome measures were chosen: for body functions and structures, pain registered on a visual analogue scale (VAS) (12) and Fatigue Severity Scale (13, 14); for activities, endurance (measured by a 6-minute walking test) (15, 16) and mobility/balance (measured by "timed up and go") (17); and, for participation, Life Satisfaction Scale (18, 19). Secondary outcome measures were: Profile of Mood States (POMS) (20), Health-related problems (measured by Holger Ursin Inventorium) (21), Rivermead Mobility Index (15), and fast walking (measured by a 20-m walking test) (15, 16).

The participants were examined immediately before (week 0) and 3 months after ending the 4-week rehabilitation period (week 16). Long-term effects of intervention were defined as changes in physical and psychological function persisting 3 months after intervention.

Several of the outcome measure scales used in this study are based on numerical scales, and some are based on ordinal scales. Descriptive statistics for the ordinal scales are presented as median and quartiles, and the corresponding tests are non-parametric; Mann-Whitney *U*-test for unpaired data and Wilcoxon signed-rank test for paired data. Descriptive

statistics for the numerical scales are presented as mean and standard deviation (SD), and the corresponding tests are parametric tests; 2-sample and paired *t*-tests for unpaired data and paired data, respectively.

The data from the cross-over study were analysed as described elsewhere (22: p. 467–471). No significant period or carry-over effects were found for the changes, and the analyses were therefore performed on the material as a whole, not regarding the order in which intervention was given. Paired *t*-tests and Wilcoxon test for paired samples were used to analyse the changes from baseline (May) to re-test (October), both for the intervention period and for the control period.

Paired *t*-tests and Wilcoxon test for paired samples were also used to compare the changes in the intervention period with the changes in the control period. The numbers reported in the results (*p*-values and confidence intervals (CI)) were not adjusted for multiple testing, as all tests represent comparisons of only 2 different settings (intervention and "life as usual"). However, the choice of 5 different primary measures still raises the question of adjustment due to multiple testing, and a Bonferroni-type approach was considered, with a correction factor of 5. Two-sample *t*-tests and Mann-Whitney *U*-tests were used to analyse gender differences. No other stratified analyses were performed. The computer program SPSS 12.0 was used for all analyses. A *p*-value less than 0.05 was considered statistically significant.

### *Ethics*

The study was approved by the internal ethics committee at the Sunnaas Rehabilitation Hospital, University of Oslo, based on the fact that an almost identical study on patients with post-polio syndrome was approved by the Regional Ethics Committee of Eastern Norway the year before (23). All participants gave their written consent, and could withdraw from the study at any time without giving a specific reason.

## RESULTS

The study design, number of participants and drop-outs are shown in Fig. 1. There were some missing values because some participants only answered postal questionnaires and did not meet for physical testing. Due to drop-out and missing physical tests, the total numbers of measurements used in the analyses varied between 42 and 53. All participants followed the prescribed programme with only minor deviations, based on therapists' statements.

Demographic factors and disease related factors, including diagnoses, are summarized in Table I. More women than men (38 vs 22) participated in the study. This does not reflect the gender distribution in the patient population. Although the participants were able to handle primary activities of daily living (ADL) without assistance, the median score on Sunnaas ADL Index (0–36) was 32.5. This indicates that the group had a considerable reduction in functional ability. Most of the participants were in need of orthopaedic devices and technical aids, and 20 persons had other diseases not related to their primary diagnosis. These were diseases that did not interfere substantially with the training, such as mild hypertension, allergy, asthma, diabetes mellitus and hyper/hypo-thyroidism. Hereditary motor and sensory neuropathy (HMSN) was the most frequent diagnosis among the participants ($n = 23$), twice as often as limb-girdle muscular dystrophy ($n = 10$) and myotonic dystrophy ($n = 11$). A small group of the participants were diagnosed with spinal muscular atrophy ($n = 3$).

Baseline data from the first test, before randomization, are shown in Table II. This table also gives descriptive statistics for changes in all outcome measures related to both intervention in Spain, and to a stay in Norway during summer. The effects of intervention, expressed as changes from baseline (week 0) to re-test 3 months after 1 month of intervention (week 16), showed improvement in all outcome measures, except for the

Table I. *Patient characteristics. Mean and standard deviation (SD) are given for age, age at diagnosis and body mass index (BMI). Median and quartiles are given for activities of daily living (ADL) score*

| Patient characteristics | Persons randomized to participate in a rehabilitation programme in Spain during the first period and to "life as usual" in Norway during the second period | Persons randomized to "life as usual" in Norway during the first period and to participate in a rehabilitation programme in Spain during the second period | All |
|---|---|---|---|
| Participants (*n*) | 30 | 30 | 60 |
| Gender, female/male (*n*) | 15/15 | 23/7 | 38/22 |
| Age, years | 42.5 (10.9) | 46.0 (12.4) | 44.3 (11.7) |
| Age at diagnosis, years | 26.0 (16.6) | 28.0 (14.5) | 27.0 (15.4) |
| Married/ cohabitant (*n*) | 16 | 22 | 38 |
| Above basic education (*n*) | 26 | 27 | 53 |
| Full or part-time employment (*n*) | 11 | 9 | 20 |
| ADL-score, Sunnaas ADL index | 33.5 (29.7, 36.0) | 32 (27.7, 36.0) | 32.5 (29.0, 36.0) |
| Wheelchair, manual (*n*) | 5 | 7 | 12 |
| Wheelchair, powered (*n*) | 7 | 11 | 18 |
| BMI* | 24.0 (3.6) | 26.0 (5,5) | 25.0 (4.8) |
| Other diseases (*n*) | 6 | 14 | 20 |
| On prescribed medication (*n*) | 8 | 16 | 24 |
| Diagnoses | | | |
| Hereditary motor and sensory neuropathy, HMSN (*n*) | 11 | 12 | 23 |
| Limb-girdle muscular dystrophy (*n*) | 5 | 5 | 10 |
| Myotonic dystrophy (*n*) | 6 | 5 | 11 |
| Spinal muscular atrophy (*n*) | 2 | 1 | 3 |
| Other (*n*) | 6 | 7 | 13 |

*BMI: weight / height$^2$.

Table II. *Outcome measures from the first baseline, before randomization. Summary of changes in outcome measures related to intervention in Spain (I) and to "life as usual" Norway (N). Differences between intervention in warm climate vs "life as usual" in Norway*

| | | First baseline, before randomization | | Changes from baseline (week 0) to re-test (week 16) | | Difference in changes from week 0 to week 16 between I and N | | |
|---|---|---|---|---|---|---|---|---|
| Outcome measures | *n* | Mean (SD) *Median (Q1, Q3) | Min–Max | Mean (SD) *Median (Q1,Q3) | *p* | Mean (SD) *Median (Q1, Q3) | 95% CI | *p* |
| *Primary outcome measures* | | | | | | | | |
| Pain (VAS) (0–100 mm) | 51 | 24.5 (25.1) | 0–92 | I: 9.2 (21.9)<br>N: 0.2 (15.1) | < 0.01<br>0.90 | 9.0 (28.8) | [0.9, 17.1] | 0.03 |
| Fatigue (Fatigue Severity Scale) (1–7)* | 53 | 4.7 (4.0– 5.5) | 1.8–6.8 | I: 0.5 (–0.2, 1.6)<br>N: –0.1 (–0.7, 0.4) | < 0.001<br>0.14 | 0.4 (–0.5, 1.7) | | < 0.01 |
| Life Satisfaction (Life Sat. Scale) (1–6)* | 53 | 5.0 (4.0, 5.0) | 3.0–6.0 | I: 0.0 (0.0, 1.0)<br>N: 0.0 (–1.0, 0.0) | 0.23<br>< 0.01 | 0.0 (0.0, 1.0) | | 0.01 |
| Walking endurance (6-min walking test) (m) | 44 | 387 (85) | 175–556 | I: 54 (65)<br>N: 2 (38) | < 0.001<br>0.62 | 52 (75) | [29, 75] | < 0.01 |
| Mobility/balance (timed "up and go") (sec) | 42 | 8.8 (5.1) | 4.0–38.0 | I: 1.0 (1.4)<br>N: 0.0 (1.5) | < 0.001<br>1.0 | 1.0 (2.3) | [0.3, 1.8] | 0.01 |
| *Secondary outcome measures* | | | | | | | | |
| Feeling, affect and mood (POMS totalscore)* | 47 | 126 (105, 141) | 81–189 | I: 13 (1, 24)<br>N: –3 (–22, 11) | < 0.001<br>0.23 | 13 (–7, 39) | | < 0.01 |
| Health-related problems (Ursin Invent.) (0–90)* | 52 | 9.0 (6.3, 18.0) | 0.0–29.0 | I: 2.0 (–1.0, 6.0)<br>N: –1.0 (–7.0, 2.0) | 0.01<br>0.07 | 4.0 (–1.8, 10.0) | | < 0.01 |
| Mobility (Rivermead Mobility Index) (0–15)* | 53 | 14.0 (11.0, 15.0) | 5.0–15.0 | I: 0.0 (0.0, 0.0)<br>N: 0.0 (–0.5, 0.0) | 0.93<br>0.11 | 0.0 (–0.5, 1.0) | | 0.40 |
| Walking speed (20 m walking) (sec) | 43 | 17.3 (10.7) | 9.0–78.0 | I: 1.8 (3.9)<br>N: –0.7 (3.3) | < 0.01<br>0.13 | 2.6 (6.7) | [0.5, 4.7] | 0.02 |

*Indicating outcome measures based on ordinal scales, analysed with non-parametric statistics. Descriptive statistics are presented as medians and quartiles.
SD: Standard Deviation; VAS: Visual Analogue Scale; POMS: Profile of Mood States.

*status quo* found in the Rivermead Mobility Index and life satisfaction. In contrast, long-term effects of being in Norway during the summer, expressed as changes in outcome measures from week 0 to week 16, showed mostly non-significant, but slightly negative, results. Life satisfaction represented the only significant outcome measure, with a negative change from week 0 to week 16.

Table II also shows differences between intervention and "life as usual" in Norway, expressed as changes from week 0 to week 16 in the 2 periods. The changes, summarized in means and medians are in favour of the intervention in warm climate for all outcome measures, except for the Rivermead Mobility Index, which did not show any significant change. No gender differences were found (data not shown).

All *p*-values and confidence intervals given in Table II are reported without adjustment for multiple testing. However, all significant *p*-values found in the primary measures in Table II, except for the overall difference in pain, would still have been significant if adjusted by a factor of 5.

## DISCUSSION

This study shows positive long-term effects on physical function, health-related quality of life and general well-being following a 4-week rehabilitation programme in a warm climate for persons with neuromuscular diseases. Statistically significant improvements were found in the primary outcome measure for pain (VAS), endurance (6-min walking test (6MWT)), fatigue (Fatigue Severity Scale) and mobility (timed "up and go") after a 4-week rehabilitation programme in a warm climate. Whether these improvements are clinically significant is debatable. In a study on acute pain in emergency medicine (24), the minimal clinically significant difference (MCSD) in VAS pain score is determined to be 12 mm (95% CI: 9–15 mm). This study concludes that the MCSD in VAS pain score does not differ with the severity of pain experienced. Another study of patients with both traumatic and non-traumatic pain found the MCSD in VAS pain score to be 9 mm (95% CI 6–13 mm), and that the MCSD did not differ significant according to age, sex and cause of pain (25). Hence, our finding of a 9.0 mm (95% CI 0.9–17.1) mean difference between intervention (Spain) and Norway in change from baseline might be considered borderline clinically significant.

In the present study the mean baseline of the 6MWT was 387 m, and the mean difference for the intervention group was 54 m, which represents a 14% improvement. Other studies with 6MWT as the primary outcome measure differ in their definition of MCSD, from 30 and 56 m (26, 27). Enright (28) reports that a 12–40% mean improvement from baseline values has been published for various interventions.

In fact, some improvements attained in this study are on the border of clinical significance. Bearing in mind that these patients have neuromuscular diseases of a slowly progressive nature, this could be an interesting finding. If the improvements were artificially better results due only to the positive attention of being included in a study; the so-called Hawthorne effect (29), one should expect the same effect for both the Norway and Spain period.

Why should patients with neuromuscular diseases profit from treatment in a warm climate? It has been shown previously that persons with neuromuscular disorders may profit from regular physical training and treatment (30–33). However, when the physical training is carried out in a warm climate, a number of other factors are introduced that might also influence the result. Not only the higher temperature, but the contact with other people with the same problems, the change of environment, being far away from home and daily duties such as work and housework, and less limitations of physical activity might be of importance. This study did not control for these factors, thus one has to look upon the intervention as multifactorial. Two similar studies of training in a warm climate have shown a better effect of physiotherapy in a warm climate than in a cold climate for patients with neuromuscular diseases (34) and post-polio syndrome (23), respectively; although neither study was controlled for the additional factors related to a warm climate.

When isolating the different aspects of treatment in a warm climate is difficult, the interpretation of the mechanism of effect becomes complicated. The patients report that it is not only the structured training programme or the warm climate that is important, but the combination of these. Having time to recover after training/treatment was also thought to be important. Finally, the patients found it beneficial that the rehabilitation was provided for a group of patients with similar diagnosis. Many of the participants experience social isolation at home due to their physical limitations. To meet other people with the same types of diagnoses can be valuable in terms of handling the stress that may derive from loss of abilities regarded as valuable (35).

The questionnaire Life Satisfaction Scale did not show significantly improved quality of life 3 months after a 4-week rehabilitation period in Spain. This is in contrast to the impression based on the participants' statements. A possible explanation may be that this questionnaire focuses on satisfaction with life in general and everyday life, and might not be sensitive to possible changes in aspects such as coping and self-esteem.

Many of the participants in the present study regularly followed physical training and treatment at home 1–2 times a week. Weekly training and treatment with a frequency of 1–2 times per week might have more effect on preserving functional level/maintaining function, while a continuous, co-ordinated training programme at an adapted level appears to be more useful for improving physical function.

In this study, long-term effect was defined as 3 months; after this no further follow-up was performed. Eleven months after intervention (second baseline) the gained effect was returned to the first baseline level. The fact that no carry-over effect was found is methodologically important when using cross-over design, and this indicates that the effect of the intervention vanishes before 11 months. Dahl et al. (34) reported an effect on the 6-min walking test 6 months after intervention for patients with neuromuscular disease. Strumse et al. (23) showed that effect on most outcomes persists 6 months after intervention in patients with post-polio syndrome.

When it comes to methodological considerations, there are some potential biases in our study: the fact that the participants self-selected into this study implicates a selected part of the total patient population. More women than men (38 vs 22) participated in the study, and since this does not reflect the gender distribution in this patient population, it might be a bias. Differences in the composition of the 2 groups comprise fewer problems in cross-over designs: all participants undergo the same intervention and it is the comparison between Norway and Spain that is interesting.

This study includes persons with different neuromuscular diseases. Ideally, one should study each diagnosis in isolation, but since each neuromuscular disease has a low prevalence, it is difficult to find enough patients for this purpose. However, as this study focuses on changes at the functional level, which is a common subject for these patients, it might be acceptable to merge different conditions.

A co-ordinated rehabilitation programme in a warm climate is considered a valuable complement to the existing programme for these patients. It is important that the basic medical and training services in national rehabilitation centres are available for all, and especially for those with contraindications to travelling abroad. Treatment in a warmer climate could be included in an individual rehabilitation plan, based on a recommendation from a specialist.

In conclusion, this study shows positive effects on different dimensions of health of at least 3 months' duration following a 4-week rehabilitation programme in a warm climate for patients with neuromuscular diseases. However, the study does not show what part of the programme is the most effective. Treatment in a warm climate comprised 2 main aspects; intensive physical training/treatment and warm climate, but there were also a variety of confounding variables, such as being away from home, social contact, and being free from everyday duties, allowing the possibility of recovery after training. There is a need for future studies with a complementary design, such as a control group following an organized training/treatment programme in Norway and a group in a warm climate without intervention.

## ACKNOWLEDGEMENTS

This study is financed by Department of Treatment abroad at Rikshospitalet-Radiumhospitalet Medical Centre, Oslo. The authors are grateful to all persons participating in the study.

*Conflict of interest:* None declared.

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