Pulmonary Function in Patients with Ankylosing Spondylitis

A cross sectional controlled study

Gunnhild Berdal

Master Thesis

Department of Health Sciences
Institute of Health and Society
Faculty of Medicine

UNIVERSITY OF OSLO

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Abbreviations

AS – Ankylosing Spondylitis

ASAS – Assessment of SpondyloArthritis international Society

ASDAS - Ankylosing Spondylitis Disease Activity Score

ATS – American Thoracic Society

BASDAI – Bath Ankylosing Spondylitis Disease Activity Index

BASFI - Bath Ankylosing Spondylitis Functional Index

BAS-G - Bath Ankylosing Spondylitis Patient Global Assessment

BASMI - The Bath Ankylosing Spondylitis Metrologi Index

BMI – Body Mass Index

CRP - C-Reactive Protein

CT – Computed Tomography

DMARD - Disease ModifyingAantirheumatic Drugs

ECCS – European Community for Coal and Steel

ESR – Eryhtrocyte Sedimentation Rate

EULAR – European League Against Rheumatism

FEV_1 - Forced Expiratory Volume in 1 second

FEV_1/FVC % – Absolute FEV_1/FVC-ratio

FRC – Functional Residual Capacity

FVC – Forced Vital Capacity

HLA-B27 – Human Leukocyte Antigen- B27

IBD - Inflammatory Bowel Disease

IBP – Inflammatory Back Pain

ILD – Interstitial Lung Disease

MET - Metabolic Equivalent of Task

MRI – Magnetic Resonance Imaging

NPV – Negative Predictive Value

NSAID – Non-Steroid Anti Inflammatory Drugs

NRS – Numeric Rating Scales

OSAS – Obstructive sleep apnoea syndrome

PEF – Peak Expiratory Flow

PFT – Pulmonary Function Test

PPV – Positive Predictive Value

QOL – Quality Of Life

RV – Residual Volume

RA – Rheumatoid Atrhritis

SES – Socio Economic Status

SpA - SpondyloArthrides

TLC - Total Lung Capacity

TNF - Tumor necrosis factor

VO_{2peak} – Peak Oxygen Uptake

Abstract

Background: Pulmonary involvement is a known manifestation in patients with ankylosing spondylitis (AS), emerging either as interstitial lung disease or in the form of restrictive pulmonary function. The reported prevalence of pulmonary involvement varies depending on the diagnostic methods applied. In some AS patients, inflammation in the thoracic vertebrae and costovertebral joints result in fusion, ossification and rigidity of the thorax. Hence, the associations between the typical clinical features and pulmonary function should be explored.

Objectives: To compare pulmonary function in patients with AS and population controls, and to study associations between pulmonary function and disease related variables, cardio-respiratory fitness and demographic variables in patients with AS.

Methods: In a cross-sectional controlled study, 147 patients with AS and 121 randomly selected population controls underwent comprehensive examinations including demographic variables, laboratory (C-reactive protein (mg/l), ESR) and clinical measures (disease activity (ASDAS, BASDAI), anthropometric (BASMI), cardio-respiratory fitness (VO_{2peak}), patient-reported physical function (BASFI) and pulmonary function test (PFT) (spirometry). Univariate ANCOVAs were performed to explore group differences in pulmonary function adjusting for relevant variables, and a multiple model was used to estimate the explanatory power of independent variables (demographic, disease related, VO_{2peak}) on restrictive ventilatory impairment (FVC%).

Results: AS patients showed significantly lower PFT values compared with the controls; forced vital capacity (FVC%) (97% vs 105%, $p<0.001$), forced expiratory volume in 1 sec (FEV_1%) (90% vs 99%, $p<0.001$) and peak expiratory flow (PEF%) (95% vs 99%, $p=0.05$). Significantly more patients than controls were categorized with a restrictive respiratory pattern (18% vs 0%, $p<0.001$). BASMI, chest expansion and male gender contributed significantly and independently in a multiple regression model predicting the variation in FVC% in AS patients, and the final model explained 46 % of the variance ($p<0.001$).

Conclusion: This study showed significantly reduced pulmonary function in AS patients compared with population controls and with reference data. Restrictive ventilatory impairment was found in 18% of the patients. Furthermore, male gender and impaired spinal

mobility and chest expansion were significantly associated with reduced pulmonary function, whereas measures of disease activity, physical function and cardio-respiratory fitness did not contribute significantly in explaining pulmonary function.

Sammendrag

Bakgrunn: Lungeaffeksjon er kjent hos pasienter med Bekhterevs sykdom (ankyloserende spondylitt), og forekommer enten som insterstitiell lungesykdom (ILD) eller restriktiv lungesykdom. Den rapporterte forekomsten av lungesykdom hos pasienter med Bektherevs sykdom varierer med hvilken diagnostisk metode som er anvendt. Hos noen pasienter kan inflammasjon i thorakale vertebrae og costovertebrale ledd resultere i sammenvoksninger, forbeninger og redusert mobilitet i thorax. Følgelig bør assosiasjoner mellom typiske kliniske trekk og lungefunksjon studeres.

Hensikt: Sammenlikne lungefunksjon hos pasienter med Bektherevs sykdom og kontrollpersoner. Studere assosiasjoner mellom lungefunksjonsvariabler og sykdomsrelaterte variabler, aerob kapasitet og demografiske variabler hos pasienter med Bektherevs sykdom.

Metode: I en tverrsnittsstudie ble 147 pasienter med Bektherevs sykdom og 121 tilfeldig valgte kontrollpersoner uten artritt undersøkt med henblikk på demografiske variabler, laboratoriemessige (CRP, ERS) og kliniske tester (sykdomsaktivitet (ASDAS, BASDAI), antropometriske mål (BASMI), aerob kapasitet (VO_{2peak}), selvrapportert fysisk funksjon (BASFI) og lungefunksjonstester (spirometri). Univariate ANCOVA justert for relevante variabler ble benyttet for å utforske forskjeller mellom gruppene med hensyn til lungefunksjon, og en multivariat regresjonsanalyse ble brukt for å beregne forklaringskraften til de uavhengige variablene (demografiske, sykdomsrelaterte, VO_{2peak}) i forhold til restriktiv ventilasjonsinnskrenkning (FVC%).

Resultater: Bekhterevpasientene viste signifikant lavere lungefunksjonsmål sammenliknet med kontrollgruppen; forsert vital kapasitet (FVC%) (97% vs 105%, $p<0.001$), forsert expiratorisk volum på 1 sekund (FEV_1%) (90% vs 99%, $p<0.001$) og maksimal ekspiratorisk luftstrømshastighet (PEF%) (95% vs 99%, $p=0.05$). Signifikant flere pasienter enn kontrollpersoner ble kategorisert med et restriktivt respiratorisk mønster (18 % vs 0 %, $p<0.001$). BASMI, thoraxekspansjon and hankjønn bidro signifikant og uavhengig til å predikere variasjonen i FVC% i den multiple regresjonsmodellen, og den endelige modellen forklarte 46% av variansen i FVC% ($p<0.001$).

Konklusjon: Studien viste en signifikant nedsatt lungefunksjon hos pasienter med Bekhterevs sykdom sammenliknet med kontrollpersoner og referanseverdier. Restriktiv ventilasjonsinnskrenkning ble funnet hos 18 % av pasientene. Hankjønn og redusert mobilitet i columna og redusert thoraxekspansjon var signifikant assosiert med svekket lungefunksjon, mens mål på sykdomsaktivitet, fysisk funksjon og aerob kapasitet ikke bidro signifikant til å forklare lungefunksjon.

Introduction

During the past 14 years I have worked as a clinical physiotheraphist at several hostpitals in Oslo, mainly at surgical divisions providing postoperative physiotherapy to a variety of different patient groups. Clinical practice has been a constant inspiration for me to seek new knowledge, and a major motivating factor when I joined the Master's Degree Programme at Department of Health Sciences, Faculty of Medicine, University of Oslo.

As a student at Department of Health Science, I was in January 2010 introduced to the research team at Diakonhjemmet Hospital and to the research field of rheumatology. I entered this project with rather limited knowledge of both the disease Ankylosing Spondylitis (AS) and of pulmonary function tests, but my academic interest was quickly aroused.

AS is a chronic lifelong disease that strikes young employable individuals in a phase of life when people usually are preoccupied with establishing families and making careers. The consequences of the disease are complex, multiple and various, involving both the patient and his or her environment. Several pulmonary disorders have been described in patients with AS, and these can be associated with significant morbidity and mortality. In general, the ability to work and function in daily life is related to pulmonary function, and patients with reduced pulmonary function have more respiratory complaints. Previous studies have shown that pulmonary involvement is common in AS. However, only a few studies, based on small numbers of participants, have examined the characteristics of pulmonary function in these patients. Our knowledge of pulmonary impairment in patients with AS is therefore limited.

The purpose of descriptive research is to document the nature of a phenomenon through systematic collection of data. This cross sectional study was launched to study a broad spectre of disease aspects, including pulmonary function, in a group of AS patients. Additionally, a group of population controls was examined to make comparisons. The study includes the largest number of subjects in the literature, and may contribute to increase the knowledge of pulmonary manifestations in patients with AS. The project was carried out as a multidiciplinary study, however with a firm foundation in biomedical theory, which is reflected in the instruments applied to characterize the participants. Therefore this thesis is written from a biomedical perspective.

The objectives of this study were to characterize pulmonary function variables measured by spirometry in patients with AS, and to examine whether these variables differ from those observed in population controls. Further, to identify possible demographic, disease specific and physical fitness factors related to impaired pulmonary function in patients with AS, and finally, to explore gender differences in pulmonary function and clinical measures in AS patients and population controls.

The knowledge, skills and decisions of health professionals, as well as the patient's own actions are important factors in managing chronic diseases. Increasing the knowledge of pulmonary function abnormalities in AS may elucidate the clinical importance of such manifestations, and may also influence clinical decisions about adequate examinations and follow-up treatment in this patient group.

1 Background

Breathing is the basic rhythm of life

Hippocrates (1)

1.1 Ankylosing Spondylitis

1.1.1 History

The diagnostic term *ankylosing spondylitis* (AS) derives from the Greek root *ankylos*, meaning 'bent', and *spondylos*, which is the Greek word for spinal vertebra. Nowadays, *ankylosis* means joint stiffening or fusion, and refers to the process that leaves the spinal column stiff and immobile. The suffix *–itis* means inflammation. The name therefore suggest that AS is an inflammatory disease of the spine that may lead to curving and stiffening of the back (2).

Studies of prehistoric skeletons and Egyptian mummies have revealed that the disease now called AS has afflicted mankind since ancient times (3-5). Among the probable sufferers was the well known Egyptian Pharaoh Ramses II (2).

The first historically description of AS appeared in the literature in 1559 with Realdo Colombo's book De Re Anatomica, in which he described the anatomy of two skeletons with abnormalities typical of AS. Still, the very first clinically description of AS is generally credited to an Irish physician; Bernhard Connor (1693). Connor described a disinterred human skeleton that had a marked spinal curvature. Additionally, the ilium, sacrum, lumbar- and thoracic vertebrae and some of the ribs were fused at "the joinings", resulting in one continous bone (Figure 1). Connor also discussed the possible consequences of such increased curvature on movement and respiration in the living patient (4;5).

The medical interest in AS was stimulated by a series of publications in the late nineteenth century by the Russian neurologist Vladimir von Bechterew in St. Petersburg. His classic descriptions of AS gave rise to the term Bechterew's disease, currently used in Norway.

The early anatomical and clinical descriptions established AS as a discrete disease entity, but the concept of AS evolved with the emergency of advances in science and medicine. Among the many landmarks in the history of AS, the probably most important emerged in the fields of roentgenology, epidemiology and genetics (4).

Figure 1 First representation of a skeleton with AS in its final state by Bernhard Conner, London, 1695. From Kahn, M.A. (2003) Ankylosing Spondylitis: The facts, s. 8 (2).

The first radiographic examination of an AS patient was published in 1899 by Valentini, only a few years after W.C. Roentgen's famous discovery of the X-rays (1895). Roentgenology has provided diagnostic tools of great value, still applied today in the work up and staging of the AS disease (2;6;7). By the 1950s, scientific reports disclosed relationships between AS and several other forms of arthritis, conceptualized as spondyloarthropathies (SpAs), sharing similar clinical and genetic characteristics. Finally, the most recent and significant chapter in the history of AS involves the revelations of an infectious etiology and a genetic predisposition to the disease (4). The strong association between AS and human leukocyte antigen (HLA-B27) was reported for the first time in 1973 (8), and it has later been proposed that infectious agents in the bowel flora may interact with HLA-B27 and trigger the disease, although the evidence is marginal (6;8;9).

1.1.2 Etiology

Despite recent advances in research, the cause of AS is not yet fully understood. There is a strong genetic component, and about a third of this effect is explained by the HLA-B27 (6). Approximately 90-95% of Caucasian AS patients in Central Europe and North America are positive for the HLA-B27 antigen; in contrast, the antigen is present in only 6%-10% of healthy individuals. The risk of developing AS is as high as 5% in HLA-B27-positive individuals, and substantially higher in HLA-B27-positive relatives of patients. HLA-B27-positive individuals with first-degree relative with AS have a 6 to 16 times greater risk of developing the disease themselves than do B27-positive individuals with no family history of AS. However, most of HLA-B27-positive individuals remains healthy (6).

Bacterial infections are suggested to trigger events in the pathogenesis of some SpAs, as documented in reactive arthritis (ReA), but no specific microbe has yet been identified as the causative agent in AS (9).

1.1.3 Epidemiology

Prevalence

AS is found worldwide, but there is a wide geographic variation in the reported estimates, and the prevalence also appears to vary among ethnic groups. These discrepancies may be caused by variations in population frequencies of HLA-B27 and by differences in study designs and diagnostic criteria applied (10;11). There also seems to be a decreasing north to south gradient in the susceptibility to AS, so that HLA-B27-positive people in northern Norway may be at higher risk of developing the disease than HLA-B-27-postive people in southern Europe, suggesting that environmental factors may play a part (8).

The highest prevalence of AS has been found among male Haida Indians in northern Canada (4-6%) and among Eskimo populations in Alaska (2.5%) (4;11), whereas the disease is nearly absent in African and Japanese people (8). The overall prevalence of ankylosing spondylitis is between 0.1-1.4%, with most of these data coming from Europe (6). The reported adult prevalence in northern Norway is between 1.1-1.4 % (males: 1.9-2-2% and females: 0.3-0.6%) (12). A British survey showed that approximately 5 % of patients presenting low back

pain to their primary care physician have this disease (13;14). The presence of inflammatory back pain features increases the probability of axial SpA (i.e.AS and undifferentiated SpA with predominantly axial involvement) from the background 5 % prevalence to 14 % (15).

Age and sex distributions

AS initially affects young people and it is a chronic, progressive disease. The disease onset is most commonly between 20 and 30 years of age, with an average first appearance at 26 years. About 80 % of the patients develop their first symptoms at an age younger than 30 years, and less than 5 % of the patients present at older than 45 years (6). The clinical picture of juvenile onset differs from that of adult onset by a more frequent involvement of peripheral joints, especially hip involvement (4). Early onset of symptoms is associated with worse functional outcomes (16), and functional limitations generally increase with duration of disease (8).

AS occurs more frequently in men, with a ratio of approximately 2:1, and the disease pattern varies by sex. Some suggest that the disease tends to be more severe in men (17). Male patients have more structural (radiographic) changes than female patients (6;18;19), but women report poorer health than men (3;19). The spine and pelvis are most commonly affected in men, along with some involvement of the chest wall and peripheral joints. In contrast, women seem to have less severe involvement of the spine, more asymptomatic sacroiliitis (17;20;21) and more peripheral arthritis (3;4;17;19;22;23). A recent Norwegian study showed that women with AS report more participation problems in everyday activities than do men with AS. The sex differences in levels of reported function and perceived problems were only partly explained by biological or anatomical changes; the underlying mechanisms for this may possibly be ascribed to psychological or social factors, but still remain unknown (24).

Socioeconomic impact and employment perspectives

Because AS usually starts at an early age, the lifetime socioeconomic consequences can be important for the patient as well as for society. The (in-)ability to continue in paid or unpaid work can be valued in monetary terms as productivity costs, and the disease related health

resource use can be valued as direct costs. Of the total costs of the disease, the productivity costs are estimated to represents the major proportion (73.6%), with functional disability as the most important predictor of total costs (4).

In Norway, Gran and Skomsvoll conducted a long-term study of 100 patients with AS (25). Most of the functional losses appeared during the first 10 years of the disease, and correlated significantly with occurrence of peripheral arthritis, radiographic spinal changes and development of a bamboo spine. Cessation of work occurred at approximately 16 years of disease duration and was significantly associated with female sex, low education levels, bamboo-spine, uveitis and comorbidity. A recent report (26) states that functional restrictions in patients with a disease duration of 20 years are greater in those with a history of physical demanding jobs, more comorbid conditions and in smokers, than in those with higher levels of education and a family history of ankylosing spondylitis (6).

Socioeconomic status (SES) may influence both disease severity and prognosis. A study in United Kingdom analyzed the employment rate of 1044 male patients with AS. They found that higher socioeconomic status may be related to less severe disease and a better prognosis than lower socioeconomic status. Altogether 85% of the patient cohort was in full employment at the time of assessment, and 15% were unemployed. The unemployed patients had increased disease activity and lower psychosocial well-being (27).

A systematic literature review found that employment rates among patients with AS ranged from 55% to 89%, and in half of these studies, employment was below 70%. Work disability ranged from 3% to 41% and higher than 20% in half of the studies. Several studies identified older age, longer disease duration, lower level of education, reduced physical functioning, pain and more physical demanding jobs to be significant risk factors for work disability (28).

1.1.4 Clinical features

Symptoms

AS is a chronic systemic inflammatory rheumatic disease that primarily affects the axial skeleton (spine and sacroiliac joints). The hallmark symptom is sacroiliitis, i.e. inflammation of the sacroiliacal joints (29). Peripheral joint involvement is present in about 30 % of patients

with AS, most often including hip, knee and shoulder joints (3;21;30). A striking feature of the disease is the high frequency of inflammation at entheses, called enthesitis; clinically presented as pain, tenderness or swelling at the bony insertions of joint capsules, ligaments and tendons (3;29). There are several extra-skeletal manifestations of AS, the most common being acute anterior uveitis. Cardiovascular, enteric, renal and neurologic complications have been described. Additionally, different types of pulmonary involvement have been reported (4;30).

The most common characteristic initial symptom is inflammatory back pain of insidious onset, often dull in character and difficult to localize. The pain is generally felt deep in the gluteal area and/or in the lumbar region, often with a distinct sharp pain in the sacroiliac region. Nocturnal pain may wake the patient from sleep, and some find it necessary to move about for a few minutes before returning to bed. The pain may be accentuated on coughing, sneezing or sudden twists of the back. Involvement of the thoracic spine (including costovertebral joints) and enthesitis at costosternal areas and manubriosternal joints may cause chest pain and inability to expand the chest fully on inspiration. The pain is accompanied by a second major early symptom; back stiffness that is usually worse in the morning. Morning stiffness typically improves with activity and the stiffness returns with prolonged periods of inactivity (29).

Back pain is an extremely common symptom in the general population. However, the inflammatory back pain due to AS has special features, and is regarded to differ from back pain owing to other causes, by five factors: (1) age at onset < 40 years, (2) insidious onset, (3) persistence > 3 months, (4) association with morning stiffness and (5) improvement with exercise. If four or five of these criteria are met, the presence of inflammatory back pain is strongly suggested (8;29;31).

Loss of spinal mobility is the main characteristic symptom of AS, and it is explained by inflammation or structural damage, or both. Spinal inflammation may arise as spondylitis, spondylodiscitis or spondylarthritis. Inflammation of the spinal ligaments, inter-vertebrae structures and facet joints causes pain and stiffness, and gradually results in fibrosis and calcification of the elastic structures. The junctions between the inter-vertebral discs and the margin of the vertebral bones are replaced by bone and the vertebrae become “squared”, and ultimately fused through evolution of bony bridges (syndesmopythes). In advanced stages of the disease, the fusion typically ascends the spine, forming a long bony column referred to as

"bamboo spine", observed radiographically. The structural changes in AS are mainly caused by osteoproliferation, rather than osteodestruction, although low bone density, osteoporosis and increased rate of vertebral fractures may add to both the hyperkyphosis, predominantly seen in men with AS, and to the burden of the disease. The pathological processes in the spinal column may lead to loss of necessary dynamic functions, resulting in problems with daily activities, such as car driving, housekeeping, social interaction and work in those who are most affected (3;4;6;21;29). However, the association between loss of spinal and thoracic mobility and pulmonary function is unclear.

Physical findings

Principal physical findings are reduced mobility of the lumbar spine with restrictions of forward flexion, lateral flexion and extension, and limited expansion of the thoracic cage. The initial loss of mobility is usually due to pain and muscle spasms, rather than ankylosis. SI joint involvement may be evident from palpation, but presence of pain elicited by direct pressure is not a reliable indicator of sacroiliitis. There may be detectable inflammation of peripheral joints, most often girdle joints (hip and shoulders), with reduced range of motion. Acute anterior uveitis occurs in 25-30% of patients and is almost always unilateral. Inflammation of enthesial sites may take place at many locations, such as the costosternal junctions, spinous processes, iliac crests, greater trochanter, ischial tuberosities and heels, causing tenderness. As the disease progresses, the untreated patient may lose normal posture; characteristically the lumbar lordosis become flattened, the thoracic kyphosis exaggerated, the rib cage more rigid and the neck may stoop forward (4;29).

Laboratory and radiographic findings

Although no laboratory test is diagnostic of AS, the HLA-B27 is an important factor for early diagnosis (6) because most patients possess the HLA-B27 antigen. Among patients with active disease, 50-70% will have an increased level of C-reactive protein (CRP) and a raised erythrocyte sedimentation rate (ESR). However, measurement of these acute face reactants appears to have restricted value in determining disease activity. Previous studies have shown

poor correlation between clinical signs of disease activity (pain, stiffness, sleep disturbance) and CRP and ESR (4).

Imaging is crucial for the diagnosis and classification of AS. In established disease, conventional radiography reveals structural changes in the sacroiliac joints in more than 95% of patients (6). However, radiographic changes may only reflect the consequences of inflammation (structural damage) rather than inflammation itself, which may be detectable by magnetic resonance imaging (MRI), often years before the appearance of radiographic sacroiliitis (7). MRI has therefore proved especially useful for identification of early sacroiliitis. Further, radiographic changes reflect the disease process and are characteristically seen in the axial skeleton, especially the disco-vertebral, apophyseal, costovertebral and costotransverse joints (29).

1.1.5 Diagnosis and classification

In most cases, ankylosing spondylitis is suspected on clinical grounds, and the best pointers are offered by the patient's symptoms, the family history and the articular and extra-articular findings (8). However, several years may pass between onset of symptoms and definite diagnosis, and the reported average diagnosis delay is about 6 to 11 years (3;13;15;32-34). This is unfortunate, because very effective new treatments have now become available and an early diagnosis may potentially slow down disease progression and reduce the damaging effects that can occur over time (15;34).

Diagnostic criteria serve as a useful aid in establishing a correct diagnosis, and thereby increasing the opportunity to offer the individual patient appropriate intervention (3;10;11). Further, the concept of disease definition and the use of appropriate diagnostic and classification criteria are basic to clinical research, as well as clinical practice. It enables scientists (and health workers) to speak the same language, and to construct groups of patients with similar characteristics so that they may be compared with a reasonable chance of detecting real differences and similarities.

Van der Linden (8) points out the distinction between diagnostic and classification criteria: Effective diagnostic criteria should be highly sensitive at an early stage of the disease, which usually implies loss of specificity. In contrast, classification criteria deals with groups of

diseased persons and are primarily intended for epidemiologic purposes. At present, there are no validated diagnostic criteria for AS, but classification criteria may still be used as a kind of diagnostic check list, although many patients at early disease stages may not fulfil the requirements. The current most commonly used classification criteria for AS are the Modified New York criteria (Table 1) (35).

Table 1

THE MODIFIED NEW YORK CRITERIA FOR ANKYLOSING SPONDYLITIS, 1984

A.	**Diagnosis**
	1. Clinical criteria
a.	Low back pain > 3 months duration, improved by exercise and not relieved by rest
b.	Limitation of motion of the lumbar **s**pine in both the sagittal and frontal planes
c.	Limitation of chest expansion relative to normal values for age and sex
	2. Radiological criteria
	Bilateral sacroiliitis, grade 2 ≥ or Unilateral sacroiliitis, grade 3-4
B.	**Grading**
	Definite AS is present if:
	The radiological criterion is associated with at least one clinical criterion.
	Probable AS is present if:
a.	Three clinical criteria are present
b.	The radiological criterion is present without any signs or symptoms satisfying the clinical criteria (other causes of sacroiliitis should be considered)

From Dagfinrud, H. (2005) Ankylosing Spondylitis: Disease impact and research evidence of physiotherapy interventions, s 24 (3). Note: These are classification criteria primarily designed for research purposes

According to these criteria, classification is based on the presence of radiographic changes which may not be detectable in early stages of the disease, thus contributing to the delay of diagnosis. Rudwaleit et.al. (15) has demonstrated a new approach to help clinicians diagnose axial SpA at an early stage in patients with IBP but without radiographic sacroiliitis, and the Assessment of SpondyloArthritis international Society (ASAS) has recently improved the classification criteria for axial SpA (7). The new ASAS classification criteria are defined as: presence of sacroiliitis by radiography or by MRI plus at least 1 SpA feature (“imaging arm”), or presence of HLA-B27 plus at least 2 SpA features (“clinical arm”) (Figure 2).

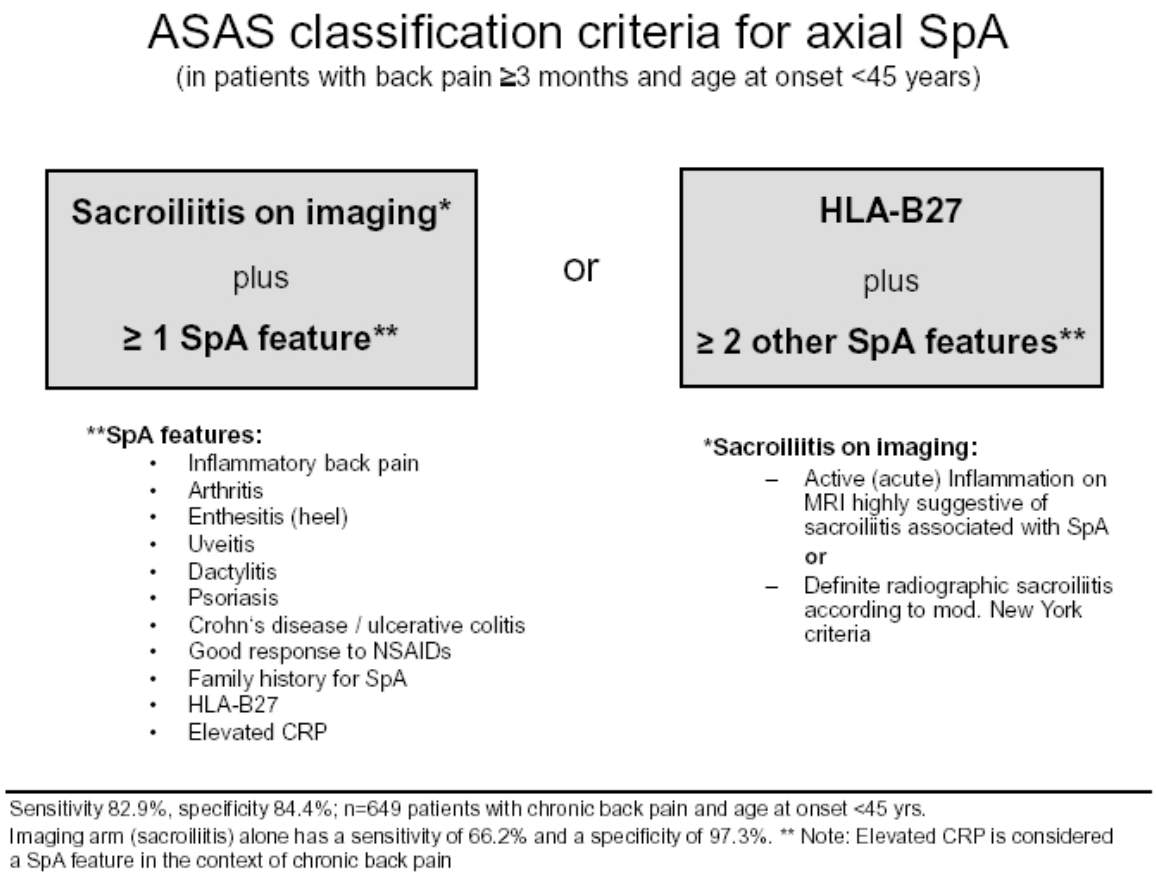

Figure 2 The new ASAS classification criteria for axial SpA can reliably classify patients for clinical studies, and will perform quite well as diagnostic criteria if applied by rheumatologists. From: Rudwaleit et.al. The Development of Assessment of SpondyloArthritis international Society (ASAS) Classification criteria for Axial Spondyloarthritis (Part II): Validation and Final Selection, Ann Rheum Dis, published online 2009 (7).

1.1.6 Disease course and prognosis

The disease course of AS is highly variable and characterised by spontaneous remissions and exacerbations, especially in early stages (3;29). A progressive loss of functional capacity is typical, with most of the impairment occurring in the first decade of the disease (25;36). The majority of the patients remain fully employed (29), but self-reported general health in AS patients are significantly worse compared to the general population, especially concerning physical health, i.e. physical function, vitality and bodily pain (21). Data from the German rheumatological database show that patients with AS have functional impairment, pain and reduction in well-being similar to that among patients with RA (37). However, the disorder is

most often compatible with long survival despite disability, and few patients are entirely immobilized.

Although it is difficult to predict the ultimate prognosis for an individual patient, the overall prognosis is influenced by several factors, including severity in early disease, development of extra-articular complications, stage of disease at time of diagnosis and beginning of therapy, quality of management, and degree of patient compliance with suggested treatment (29). Patients with hip joint involvement or completely ankylosed cervical spine are more likely to become disabled (36), and spinal fracture, especially at a cervical site, is regarded the most serious complication as fractures in this area can result in quadriplegia (4), or in half of such cases, death (38). Amor et. al. (39) identified several predictive factors of poor or benign longterm outcome early after onset of SpA in a study of 328 patients with spondylo-arthropathy; hip arthritis, ESR>30 mm/h, poor efficiency of NSAIDs, limitation of lumbar spine mobility, sausage-like finger or toe, oligoarhtritis and disease onset $\leq$16 years. If none of these factors were present at entry a mild outcome could be predicted (sensitivity: 93%, specificity: 78%). Hip-arthritis was associated with a 23-fold increase in the risk of severe disease. If a hip was involved or if three factors were present, a severe outcome was predictable (sensitivity: 50%) and a mild disease practically excluded (specificity: 98%).

There appears to be some gender differences in the course of AS. Several reports show that women have a later age of onset (40), milder disease (41;42) and more extra spinal involvement (22), but others report no differences in clinical presentation between the sexes (17). The results of several studies differ, and no consistent picture has yet emerged. Pregnancy does not improve the symptoms of AS, but may temporarily aggravate the disease. Hormonal status, fertility, course of pregnancy and child birth have been reported to be normal (43)

Recent evidence suggest that the metabolic syndrome might be more common in patients with AS. The metabolic syndrome is defined as at least 3 out of five symptoms: dyslipidemia (reduced HDL), elevated triglyceride levels, elevated blood pressure, adipositas and elevated fasting glucose. Metabolic syndrome promotes mortality from cardiovascular disease and some studies report an association with systemic inflammation. Additional risk factors for cardiovascular disease in patients with AS are chronic steroid use, decreased physical activity, and, related to decreased physical activity and steroids, the development of obesity and hypercholesterolemia (21). Further, there is a higher risk of cardiomyopathy, pericarditis and

aortitis in AS patients (44-46), and symptomatic aortic valve insufficiency or dilatation of the ascending aorta occurs in up to 10% of cases. Symptomatic aortitis or abnormalities of the aortic root may occur between 20 and 30% of affected patients (47).

Smoking is reported to have a negative effect on several measures of disease severity, including spinal mobility, functional index, stiffness and spine radiographic scores, and might be associated with poor long-term outcome in patients with AS (48-50). However, there has not been any interventional study to support this observation, and the impact of smoking on AS is still unclear.

Premature mortality is increased in AS, independent of treatment modalities (51). A Finnish study observed a mortality rate 1.5 times higher in patients with AS than in the general population (52). Excess deaths were mainly caused by AS itself, but circulatory, gastrointestinal, respiratory and renal diseases, and violence, also caused more deaths than expected. The excess mortality of cardiovascular disease in AS has been estimated to be 20% to 40% compared to the general population (21), and recent studies suggest connections to abnormality of lipid regulation and microvascular changes. Moreover, in a previous study of 836 AS patients who had not been treated with radiation, death from respiratory disease was 1.5. higher than expected (53).

1.1.7 Recommendations for the management of AS

Current treatment guidelines for AS recommend appropriate medication and mobility exercise as the two cornerstones of treatment (54-56). Pharmacological and non-pharmacological treatments are complementary, and both are of value in the initial and continuing treatment of patients with AS.

Figure 3 shows the ASAS/EULAR[1] recommended management strategies for AS based on clinical expertise and research evidence. The importance of non-pharmacological treatments throughout the disease course, early introduction of NSAIDs, alternatives for peripheral disease and options for refractory disease are emphasised.

[1] The ASessment in AS (ASAS) International Working Group/European League Against Rheumatism

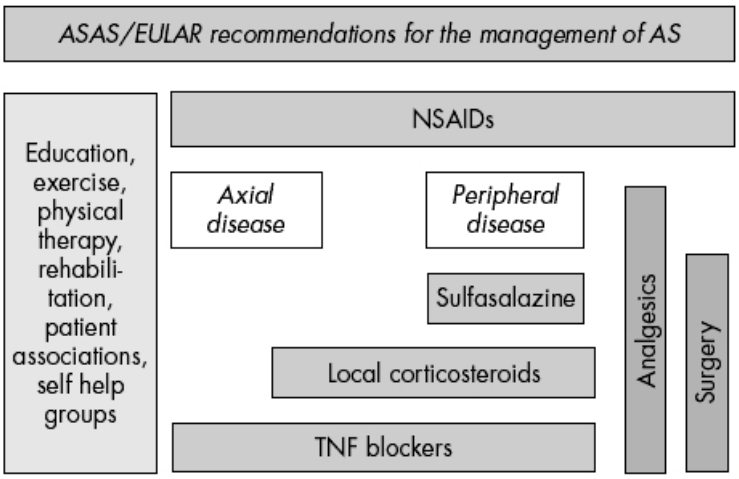

Figure 3 Flow chart summary of the recommended management of AS, based on clinical expertise and research evidence. The disease progression with time moves vertically from top to bottom. From: Zochling et.al. ASAS /EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2006, 65, s 446 (55)

Physiotherapy is widely recognized as one of the most important aspects of disease management. Patient education and daily exercises are considered of great importance to maintain or improve spinal mobility and fitness and to reduce pain in AS (57;58). Controlled studies of physiotherapy are rare, but significant gains from exercise has been demonstrated over relatively short periods of time (59). The most recent systematic review of physiotherapy for AS, reviewing 11 RCTs, summarised the available scientific evidence on the effectiveness of physiotherapy interventions (60), and concluded 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.

The main focus in exercise programmes for AS patients has traditionally been on flexibility exercises to improve spinal mobility, but the awareness of a higher risk for cardiovascular disease in AS (61;62) has put forward a stronger emphasis on cardiorespiratory endurance training to reduce the risk factors. The importance of aerobic exercise as part of the treatment plan is supported in a recent study of experts' opinion, concluding that health professionals experienced in the management of patients with AS hold a favourable opinion on the efficacy of exercising for disease control and health benefits (58). Thus, it seems to be general

agreement on the importance of exercise as a part of the disease management for AS, but the effects of exercise on pulmonary function is not thoroughly examined.

1.2 Pulmonary manifestations of AS

A wide spectrum of pulmonary manifestations has been reported in AS, including apical fibrosis and fibrocystic changes, bronchiectasis, interstitial lung disease (ILD), pleural thickening and pleural effusion, brochiolitis obliterans and chest wall restriction (30;63). Spontaneous pneumothorax is a rare manifestation, but not uncommon in patients with an underlying fibrocystic lung disease (64;65), and pulmonary superinfections has been reported to occur in up to one-third of the patients with apical cavitation (66).

The most typical respiratory abnormality seen in AS is a restrictive ventilatory defect (67-75). A restrictive defect is manifested in a reduction of total lung capacity (TLC), as well as vital capacity (VC), and the pulmonary function test (PFT) is characterized by low forced vital capacity (FVC) and low forced expiratory flow in one second (FEV1) with normal or high FEV1/FVC ratio (76). Usually, the abnormality in pulmonary function is mild (45).

There are different opinions in the literature concerning the possible reasons for restrictive lung function in AS. Some favour mechanical causes due to bony ankylosis of the costovertebral and costotransverse joints resulting in chest wall rigidity (69;77-80) as restrictive pulmonary impairment in AS frequently is associated with a low thoracic expansibility (67;73-75;81). Others claim that ongoing inflammatory processes in the thoracic joints explain limitations of chest excursions, by causing pain and stiffness, and thus contributing to reduced pulmonary function (68;69;73). Anterior chest wall involvement is reported to occur in 50 % of AS patients, with enthesitis located to the manubriosternal symphysis and sternocostoclavicular joints as the most affected sites (82). The thoracic rigidity may also lead to ventilatory disturbances with hyperinflation of the lung bases and severe hypoventilation of the apicies (69;73) which in turn may lead to poor airway clearance, chronic inflammation and fibrosis. Others suggest that pleuropulmonary tissue is an independent primary target in AS (70;83), and that inflammatory processes in the lung parenchyma with tendency to fibrosis might be as significant as mechanical factors in the development of reduced pulmonary function in AS (73;84;85). A likely explanation to the

lung abnormalities in AS may be a disease specific inflammatory process parallel to the development of joint manifestations (69).

Rosenow el al. observed pleuropulmonary involvement in 28 (1.3%) of 2080 patients with AS (86). Recent studies using high resolution computer tomography (HRCT) have confirmed that AS directly involves the lungs with a variety of pulmonary parenchyma changes. The most common manifestations are non-specific interstitial disease and apical fibrosis (68;70;77). HRCT abnormalities have been found in patients with mild symptoms and minimal structural damage (69), and apical fibrosis has even been reported to precede the first joint symptoms, well before loss of chest wall flexibility (87;88). Interstitial lung disease (ILD) influences both the arterial blood gases and the lung mechanics, and is, like chest wall restriction, typically manifested in PFT as a restrictive pattern (89). It is not possible to differentiate chest wall from pulmonary interstitial involvement using routine dynamic PFT (90). The pulmonary changes in AS begin in early stages of the disease, and some of them increase with disease duration (69;70;77;78;83;84;91;92).

With progression of AS, the thoracic kyphosis is often increased, the chest becoming immobilized in an inspiratory position throughout the respiratory cycle (68). Earlier studies have confirmed that increased contribution of the diaphragm and abdominal muscles compensate for reduced chest wall mobility in AS, especially during hyperventilation. (93-98). The compensatory effect of the diaphragm is a probable explanation of the fact that patients with AS have only mild respiratory symptoms, or none at all (81). However, the mechanical conditions can lead to reduced strength or atrophy of intercostal or accessory muscles, making the diaphragmic breathing work abnormally high, resulting in fatigue and lack of extra resources when needed. Thus, AS patients may be respiratory vulnerable if abdominal muscles cannot function properly, as might occur after abdominal surgery (80).

Pulmonary parenchymal disease in AS is typically clinically silent, unless extensive or secondarily infected by bacteria or fungi (30;90). Patients with pulmonary infection may complain of cough, sputum production or dyspnea, and hemoptysis may occur in the presence of cyst formation, brochiectasies or intracavitary mycetoma. The most common pathogen isolated is *Aspergillus fumigatus*, followed by various species of mycobacteria (45;46).

Symptoms from the thorax include dyspnea, difficulties in moving the chest wall, tightness in the ribs and muscles of the thoracic cage, more particularly anteriorly, but also in the flanks,

chest aches, stiffness, inability to fill the chest satisfactorily on deep inspiration and chest wall pain during forced inspiration (99;100). Although most AS patients are respiratory asymptomatic, previous reports have exposed negative influences of pulmonary involvement on both functionality and quality of life (70-72;101) which may affect the daily life of these patients and be clinically important.

Smoking is believed to promote apical fibrosis and interstitial inflammation (69), besides being a major risk factor for chronic obstructive pulmonary disease (COPD) (102), and may deteriorate existing lung disease in AS patients.

According to recent reports, the prevalence of obstructive sleep apnea syndrome (OSAS) is higher in AS patients (23 %) than reported in the general population (3-7 %), and may be one of the causes of fatigue in AS (103). It has been suggested that AS may predispose to sleep apnea by different mechanisms, including restriction of the oropharyngeal airway from cervical spine disease or temporomandibular joint involvement causing pharyngeal or tracheal compression, cervical spine disease causing compression of the medulla respiratory center resulting in central depression of respiration, or by restrictive lung disease (104). OSAS is associated with traffic accidents involving drivers who fall asleep (105), systemic hypertension (106), cardiovascular disease (107) and disorders of glucose metabolism (108).

1.2.1 Prevalence of pulmonary involvement

The prevalence of pulmonary involvement in AS vary depending on the diagnostic methods applied. Recent reports show a frequency of restrictive ventilatory impairment between 20 and 57% using spirometry (Table 2) (71;75;77;78;83-85;103;104;109;110). Studies conducting radiographic evaluation report an occurence of pulmonary involvement between 1 and 15% in patients with AS, while studies using high resolution computed tomography (HRCT) report a higher prevalence; between 40 and 85% (69-71;73;75;78;84-86;91;92;110;111), even in patients with early disease, normal chest radiograph and without respiratory symptoms. The most commonly observed HRCT changes are apical fibrosis, ILD, bronchiectasis, mosaic pattern, subpleural nodules, pleural thickening, septal thickening, emphysema, small airway involvement and mild non-specific interstitial changes (70;75;77;78;84;85;92;109;110). These abnormalities are usually subtle and does not correlate

with pulmonary function test variables (75;77;83;109;110;112), or functional or disease structural severity data (77;78;110) according to most studies. Long-term prospective studies are needed to grasp the clinical significance of the HRCT abnormalities; i.e. whether the findings progress and become associated with clinical symptoms (63). Further, most of the present studies are limited by lack of appropriate control subjects, and it is difficult to determine whether the HRCT abnormalities are due to AS or related to other causes, such as tobacco use, previous tuberculosis or the effect of medications.

Table 2 Prevalence of abnormal spirometry in patients with AS according to earlier reports

	Number of patients	Normal pulmonary function, n (%)	Restrictive pattern, n (%)	FVC% cut-off	Obstructive pattern, n (%)
Solak (103)	31	15 (48)	16 (53)	<80	0 (0)
Dincer (71)	36	21 (58)	12 (33)	<80	1 (3)
Baser (83)	26	18 (69)	8 (31)	-	0 (0)
Sampaio-Barros (75)	46	10 (22)[a]	24 (52)	<80	6 (13)
Ayan-Ardic (109)	20	11 (55)[b]	4 (20)	-	1 (5)
El Maghrahoui (110)	55	37 (67)	16 (29)	<75	2 (4)
El Maghrahoui (77)	55	34 (62)	19 (35)	<75	2 (4)
Erb (104)	17	9 (53)	8 (47)	-	0 (0)
Turetchek (78)	21	9 (48)	12 (57)	-	0 (0)
Senocak (84)	20	12 (60)	6 (30)	-	2 (10)
Casserly (85)	26	16 (62)	7 (27)	<75	3 (12)

[a] 6 patients were unable to perform PFT. [b] Additionally 4 AS patients (20%) were categorized with small airway disease defined by a low FEF25-75 ratio in the absence of reduced FEV1/FVC ratio

Table 2 shows reported rates of PFT abnormalities in patients with AS. The prevalence of a restrictive pattern varies between 20 and 57 % in the different studies. The study samples are, however, quite small; the numbers of included patients vary between 20 and 55. Further; the samples differ with regard to patient charachteristics like age, disease duration, sex-ratios and smoking habits. Additionally, the applied FVC% cut-off points vary, or are not stated in the different reports, making comparisons difficult.

1.2.2 Evaluation of pulmonary disease

A physical examination should include observation of the breathing rate and breathing pattern, general appearance, posture and chest shape (1). Finger clubbing or other signs denoting hypoventilation should be sought. Measurement and evaluation of chest expansion should be done. Auscultation may reveal crackling sounds suggesting secretions, parenchymal disorder or fibrosis, indicating a need for further investigations (1;69). Sputum cultures for mycobacteria and fungi should be considered whenever pulmonary superinfection is suspected (30). PFT should be performed to look for a restrictive pattern, especially in patients with severe or long-standing disease. Measurement of TLC may be considered to ascertain a restrictive defect if its presence is not already evident from extrathoracic causes. If lung parenchyma pathology is suspected it may be useful to assess the transfer factor for carbon monoxide (TLCO), as it is often diminished in ILD (113). A chest radiograph should be obtained routinely, but HRCT may be considered in selected patients, including those with a restrictive pattern that cannot be explained only by mechanical factors, those with symptoms or abnormal chest radiographic findings. HRCT may also be used as a screening tool to rule out tuberculosis before treatment initiation with TNF inhibitors (69;78). The severety of lung function abnormality is related to the degree of acute inflammation as measured by the ESR, the thoracic expansibility and the duration of the disease (45;73;114).

1.2.3 Management of respiratory impairments

Management of respiratory impairments in AS is mainly aimed at treating pulmonary superinfections using antifungal or antibacterial agents (30;45;46). Surgical intervention with thoracotomy and lobectomy can be complicated by bronchopleural fistel and chronic empyema in as many as 50% of cases, and is therefore rarely indicated (45). If pulmonary abnormalities are present, a careful follow-up for any signs or symptoms of brochiectasis or secondary infections of cavitary lesions is recommended (46).

Prophylactic measures including smoking cessation and physiotherapy to improve overall and respiratory function may be useful, along with DMARDs and NSAIDs (69). Treatment with anti-inflammatory agents for arthritic symptoms does not alter the course of pulmonary disorder in these patients (30;79). There is little evidence of the effect of physiotherapy on

pulmonary impairment in AS. However, experience shows that the patients usually benefit from exercise with focus on increasing thoracic mobility and counteracting the tendency toward an exaggerated dorsal kyphosis (46). Fisher demonstrated an association between vital capacity and chest expansion, and between vital capacity and exercise tolerance, suggesting that efforts should be directed not only towards improving chest wall mobility but also towards cardiorespiratory fitness in patients with AS (74). Aerobic exercise may improve pulmonary function in patients with AS, as well as indirectly contribute to increase the spinal and chest wall flexibility (115).

2 Aims of the study

The specific aims of this study were to characterize pulmonary function variables measured by spirometry in patients with AS, and to examine whether these variables differ from those observed in population controls. Further, to identify possible demographic, disease specific and physical fitness factors related to impaired pulmonary function in patients with AS, and finally, to explore gender differences in pulmonary function and clinical measures in AS patients and population controls.

2.1 Reasearch questions

The research questions were:

1. What is the prevalence of reduced pulmonary function in AS patients?
2. Is pulmonary function in AS patients reduced compared to a control group?
3. Are background factors, disease-specific factors, physical activity and exercise capacity associated with restrictive pulmonary impairment in patients with AS?
4. Do male and female AS patients differ in pulmonary function and clinical measures?
5. Do male AS patient and male controls differ in pulmonary function and clinical measures? Do female AS patient and female controls differ in pulmonary function and clinical measures?

The questions 1, 2 and 3 will be discussed in the paper “Pulmonary Function in Ankylosing Spondylitis”. The questions 3, 4 and 5 will be explored in the chapters Extended results and General discussion.

3 Materials and Methods

3.1 Study design

This thesis is based on a cross sectional, controlled study, where pulmonary function in AS patients were compared to that of population controls. Examinations were accomplished during a period from May 2008 to March 2010.

3.2 Inclusion of patients and population controls

Patients were recruited from a hospital based register of patients with AS (Diakonhjemmet, Oslo). Comprehensive examinations of patients recorded in this register were performed during 2002 and 2003, focusing on physical function, health related quality of life, disease activity and activity limitations (3;24;116). This cross sectional follow-up study included respondents from the two previous data collections. In addition to the previously considered variables, this examination also included cardiovascular examinations, measures of physical capacity, physical activity and measures of pulmonary function.

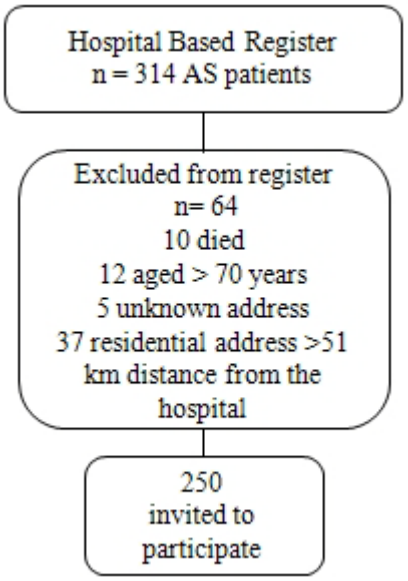

Figure 5 Flow chart of the patients recruited from the Diakonhjemmet Hospital register

A total number of 250 patients aged 18-70 years, diagnosed with AS according to the New York Criteria (117), and living within a 50 km distance of Diakonhjemmet Hospital were invited to participate. 162 patients accepted invitation, 12 withdrew from the study and 3 were later excluded because they had not carried out the pulmonary function test.

Population controls were recruited from a list of randomly selected people generated from the national register by Statistics Norway to match stratification of the patients for age, sex and place of residence. A history of arthritis was considered as exclusion criterion. The Central Office for Norwegian Residents Register approved the selection procedure. 329 letters were sent to invite potential controls, and 140 subjects accepted participation. They were examined simultaneously and according to the same protocol as the AS patients. 10 controls were later excluded from this study because they had not carried out the pulmonary function tests, 6 withdrew from participation, 1 was excluded due to language difficulties and 2 were excluded because of age younger than 30.

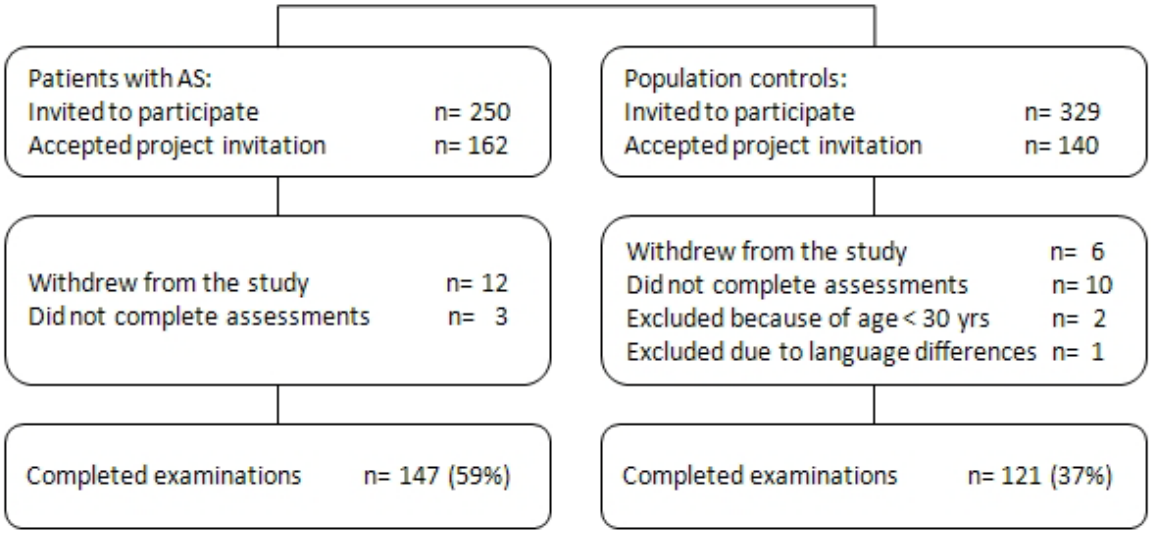

Figure 6 Flow chart of the inclusion process

The non-responding AS patients (p=0.04) and controls (p=0.003) were significantly younger, predominantly male (n.s.) and typically living in the eastern part of Oslo (p=0.01 and p=0.06) compared to the AS patients and controls that positively responded to project invitation.

3.3 Participants

147 AS patients and 121 population controls completed the self reported instruments, the clinical examinations and the laboratory and physical tests. Data from these examinations will be included in the forthcoming analyses with focus on pulmonary function.

3.4 Measurements in the survey

3.4.1 Socio-demographic and disease related variables

Socio-demographic and disease related information was recorded for all participants, and include the variables age, gender, disease duration, pulmonary co-morbidity, smoking history, education level, current occupational status and marital status.

3.4.2 Assessment of pulmonary function

The primary function of the lung is gas exchange (118), and this task is solved by the four mechanisms; ventilation, distribution of ventilation, perfusion and diffusion (89). Pulmonary function tests (PFTs) are performed in order to diagnose and classify disease processes that impair lung function. A series of PFTs have been developed, but none mirrors all the mechanisms involved during respiration, and no single PFT is diagnostic of a specific disease (89). In this project, our sole focus has been on measuring ventilatory function, by using spirometry. Ventilation is the movement of air between the outside of the body and the alveoli, i.e. the dynamic process of inspiration and expiration (1). The ventilation is produced by the action of skeletal muscles on the chest wall, which is coupled to the lungs by pleural pressure. The chest wall consists of the spine, the rib cage, and caudally, the diaphragm and the abdominal compartment (119). The respiratory muscles extend from the mastoid process to the pubic symphysis, and are active during inspiration, while normal expiration is largely passive, lung elastic recoil providing the driving pressure (1).

The normal chest is ideal for the neuromuscular bellows mechanism, and any anatomical or functional abnormality of the bony thorax, increases dead space ventilation and the work of breathing. Most diseases affecting the lungs or the thorax, also influence their mechanical (elastic) properties, and consequently impede the movement of air (68;89). Lung diseases are broadly classified as those leading to airflow obstruction, volume restriction, or a combination

of these (120). Assessment of the mechanical properties of the respiratory system can be done either by measuring static lung volumes using body plethysmography, which is expensive and time consuming, or by measuring the dynamics of inspiration and expiration using spirometry, which allows an effective, accurate and reproducable assessment of the functional state of the respiratory system (89;121).

Pulmonary Function Test - Spirometry

Pulmonary function was measured by using a spirometer (Spida 5, USB Spirometry from Micro Medical Ltd, United Kingdom, 2006). Spirometry is a physiological test that requires recordings of how an individual inhales or exhales volumes of air as a function of time. The primary signals measured are dynamic lung volumes and flow (122). Spirometry is valuable as a screening test of general respiratory health, but does not lead directly to an aetiological diagnosis. The indications are multiple, for instance screening individuals at risk of having pulmonary disease, measuring effect of the disease on pulmonary function, assessing prognosis and therapeutic intervention and describing the course of diseases that affect lung function. Further, it is recommended and commonly used in epidemiological surveys and clinical research (113;121-123).

Test procedure

Spirometry requires cooperation between the subject and the examiner, and the results are dependent upon technical as well as personal factors. During the data collection, the equipment was calibrated daily and quality control procedures were followed (122). Spirometric testing was carried out in a quiet environment, and performed by a trained physiotherapist in accordance with guidelines set by the American Thoracic Society and the European Respiratory Society (ATS/ERS) (122). The physiotherapist explained and demonstrated the appropriate posture and technique prior to the subject's performance. The subject's background characteristics (i.e. age, sex, ethnicity, smoking habits, weight and heigth measured at time of testing) were plotted into the computer software attached to the Spida 5. The subject was instructed to sit with head slightly elevated, nose-clip attached and lips closed around the mouthpiece, to breathe calmly for a few respiratory cycles, then inhale rapidly and completely with a pause of < 1second at TLC, and exhale forcefully and maximally until no more air could be expelled while maintaining an upright posture (closed

circuit method). The test was accompanied by vigorous coaching by the instructor, and repeated for a minimum of three acceptable manoeuvres, but no more than eigth. Manoeuvres were considered acceptable if the difference between the largest and the next largest FVC and FEV1 was ≤ 150 ml, if they had good starts and were free from artefacts, such as cough, early termination, sub-maximal effort, leak or obstructed mouthpiece. The quality of the spirometric test was entered, and the largest FVC and FEV1 recorded for further analysis.

Variables, curves and interpretations

The results of the dynamic spirometry were expressed in terms of the relationships of forced expired volume to time as described by the volume-time curve (Spirogram, Figure 6). They were also expressed as the relationship of maximal flow to lung volume described by the flow-volume curve (Figure 7 (b)). The pulmonary function test generated the following variables:

FVC – Forced Vital Capacity; the maximal volume of air delivered during an expiration made as forcefully and completely as possible starting from full inspiration; i.e. vital capacity performed with a maximally forced expiratory effort, expressed in litres.
FEV_1 – Forced Expiratory Volume in one second; the volume, expressed in litres, delivered in the first second of the FVC manoeuvre.
PEF – Peak Expiratory Flow; the maximum expiratory flow achieved from a maximum forced expiration, starting without hesitation from the point of maximal lung inflation, expressed in liter/minute.
FEV_1/FVC% - FEV_1 /FVC x 100. The absolute ratio; derived from observed values (not percent predicted).

The observed measures of FVC, FEV_1 and PEF will be presented along with percentages of predicted values (FVC%, FEV_1% and PEF%) to control for the influence of age, gender and height (124). The absolute ratio (FEV_1/FVC%) will be applied in the interpretations, not percent predicted. The published equations of the European Community for Coal and Steel (ECCS) was used as reference data in our spirometry equipment (125). Additionally, data from the population controls served as reference and basis for comparisons.

Two major types of pulmonary dysfunctions can be defined by spirometry; obstructive patterns and restrictive patterns. The primary diagnostic criterion for airflow obstruction is a

reduced FEV1/FVC%< 70%. Other measurements can be used to stage obstructive disease, and to support or assist in making conclusions based on this variable when FEV1/FVC% is borderline (102;123). Spirometry is less accurate at predicting pulmonary restriction (120). The gold-standard diagnosis of restrictive pulmonary impairment requires measurement of the total lung capacity (TLC), but a low spirometric FVC% together with a normal or high FEV1/FVC% ratio has traditionally been classified as a restrictive abnormality (120;126). However, a low FVC can be a consequence of true restrictive pulmonary disease, or of airflow obstruction with excessive air trapping, and mixed abnormalities characterized by the coexistence of obstruction (low FEV1/FVC%) and restriction (low FVC/TLC) do occur, although seldom (89;120;124).

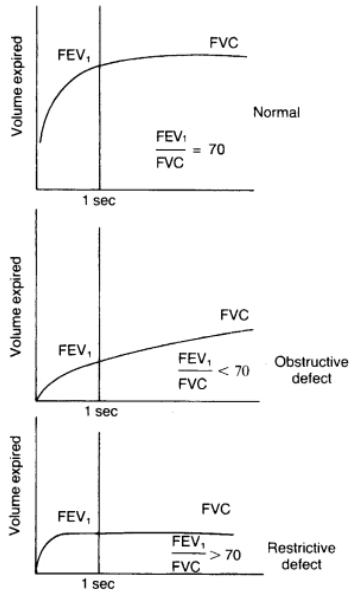

Figure 6 Spirograms; volume-time curves: Normal trace shows most of the FVC expelled within 1 second. Obstructive pattern shows prolonged expiration. Restrictive pattern shows reduced FVC, all of which is expelled within 1 second due to augmented recoil. From Hough, A. (2001) Physiotherapy in Respiratory Care. An evidence based approach to respiratory and cardiac management, 3.ed.,United Kingdom, s 59 (1).

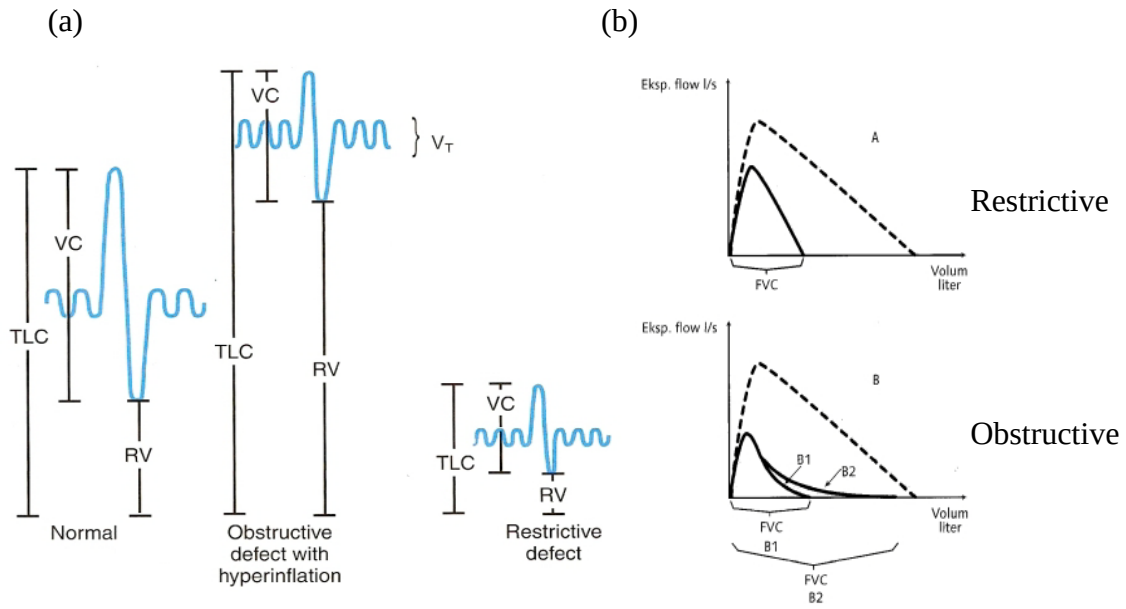

Figure 7 (a) Static volumes and capacities; variations for different disorders. Hyperinflated lungs show increased TLC and RV. VC is reduced in both obstructive and restrictive defects. Restrictive defects show a decrease in all volumes. From Hough, A. (2001), s 56 (1). (b) Flow-volume curves: Restrictive defect with low FVC and comparatively high expiratory flow with a steep fall from PEF gives the curve a pointed cap appearance. Obstructive defect (B1) with low FVC and low expiratory flow gives the descending curve a concave character, (B2; typical presentation of emphysema). From Giæver, P. Lungesykdommer (2008), 2. Utg, Universitetsforlaget, Oslo, Norway, s. 33 (89).

Figure 7 exemplifies that obstructive and restrictive defects can demonstrate a similar reduction in VC/FVC although huge differences in TLC (a), but they present characteristically different flow/volume-curves (b). In absence of access to TLC, spirometry can be used to distinguish between restrictive and obstructive impairments by evaluating the shape of the flow-volume curve. Restrictive defects will characteristically produce a curve that falls steeply, while obstructive defects will give the descending curve a concave character (89).

The cut-off point for FVC%, the marker parameter of restrictivity, was set at 80%. Aaron et. al. have shown that the probability of a restrictive defect is linearly related to the degree of reduction in FVC for all values <80% of predicted (Figure 8). Combining the FVC and the FEV1/FVC improves the predictive ability of spirometry; for all values of FVC < 80% of predicted, the likelihood of restrictive disease increases as the FEV1/FVC ratio increases (120). Thus, we evaluated both the FVC% and FEV1/FVC% results in our cohort.

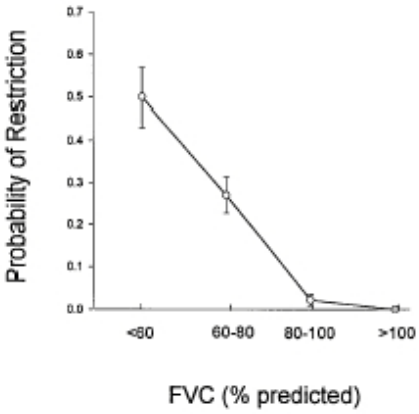

Figure 8 Ability of FVC percent predicted to independently predict pulmonary restriction. From Aaron SD, Dales RE, Cardinal P, How Accurate is Spirometry at Predicting Restrictive Pulmonary Impairment? Chest 1999, 115,s. 872 (120).

Based on interpretation of the individual test results compared to the ECCS reference values, the patients and population controls were categorized as having either restrictive ventilatory pattern (FVC≤80%, FEV_1/FVC≥70%, decreased or normal FEV_1), obstructive ventilatory pattern (FEV_1/FVC<70%, decreased FEV_1, normal or decreased FVC) or normal pulmonary function (FVC>80%, FEV_1>80%, FEV_1/FVC>80%) (76;102;120;125) (Figure 9).

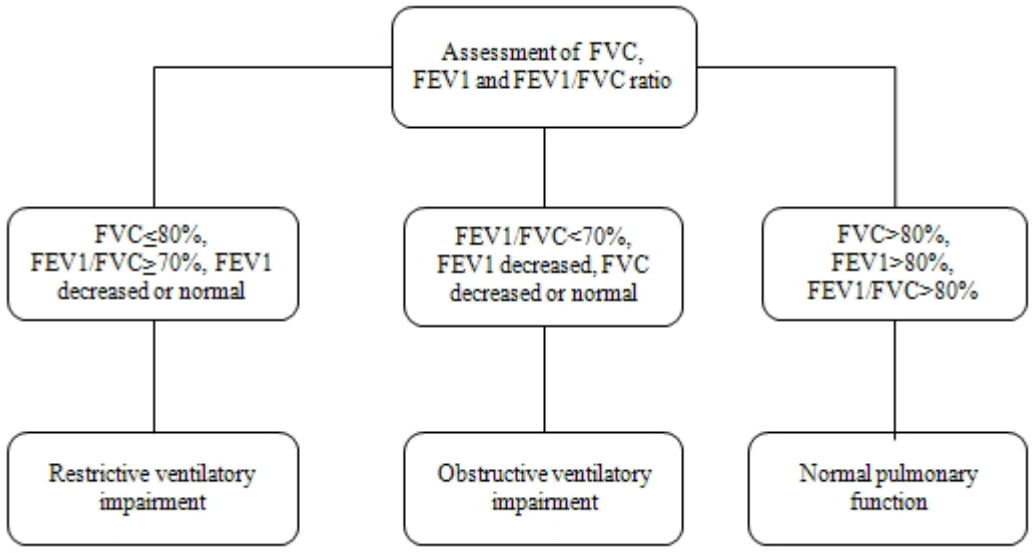

Figure 9 Flow chart of interpretation of spirometry results

Sources of variability

Interpretation of PFTs depends on establishing the variation of interest (the signal) and its relation to all other sources of variation (the noise). When PFT is used as an aid in diagnostic classification, the signal is the patient's results compared to the expected results of subjects without the disease, but similar in the characteristics that determine lung function (126). The largest single source of within subject variability is wrong performance of the test. In our project, test quality was recorded and taken into account during the interpretations of the results. Variations may refer to technical factors, such as instrument problems, body and head position during test, effort dependence of maximal flows and circadian rhythms. The most important host factors causing between-individual variability are sex, size and aging, which accounts for approximately 30, 22 and 8%, respectively, of the variation in adults (126).

In healthy populations there is great variation in spirometric values even after taking into account age, height, gender and ethnic group. Environmental factors such as exposure to tobacco smoke, exposure to environmental and occupational pollution, socioeconomic status, and genetic factors, as well as past and present health, influence the test results. About 27 % of the inter-individual variation remains unexplained (126). There are substantial differences between the equations used to predict normal pulmonary function, because of differences among the populations studied as well as technical and procedural differences. Reference equations provide a context for evaluating the PFT results. It is therefore important to select equations for reference use that are well matched with the patients. In our case, the study being situated in Europe, we chose reference values based on European populations, rather than e.g. American equations, as we considered these more appropriate for our study population. Additionally, the PFT results of the population controls served as reference data.

The classification of pulmonary abnormality based on PFT values has been a controversial subject in the literature (113;124-128). The GOLD guidelines originally recommended a FEV_1/FVC ratio below 0.70 as indicative of obstructive lung disease, and the practice of classifying values of FVC and FEV_1 below 80 % of predicted as abnormal is widespread in clinical laboratories. However, the use of fixed ratios, as well as the use of fixed percent of predicted values for FEV_1 and FVC as methods of defining levels of pulmonary function abnormality is not supported by the ATS or the ERS (113;124;126). This is because lower limits of normal are variable, and because the process of aging and age-confounded factors such as smoking and occupational exposures affects lung volumes. The use of a fixed ratio

may lead to an over diagnosis of obstructive pulmonary impairment in the elderly, especially of mild disease (126). Some claim that it also introduces a sex bias (113). A statistically acceptable approach for establishing lower limits of any spirometric measure is to define the lowest 5% of the reference population as below the lower limit of normal. This implies a 5% false positive misclassification, a rate generally considered acceptable (126). In contrast with a fixed value, the use of the 5^{th} percentile does not result in an overestimation of ventilatory defects in older people with no history of toxic exposures (124). However, most of the published studies on pulmonary function in AS use percent of predicted values and fixed cut-off points for spirometric measures. For purposes of simplicity and comparability we chose the same strategy in this present study, although being aware of the risks involved.

Reproducability

FEV_1 is the most repeatable lung function parameter. Measurement of FVC requires good effort from the test subject, and is therefore less reproducable. The pattern of reduced FVC and increased FEV_1/FVC is often caused by sub-maximal inspiratory or expiratory efforts (124). All lung function measurements tend to be more variable when made weeks to months apart, than when repeated at the same test session, or even daily, as the reproducibility is affected by within day variations. The highest FEV_1, FVC and PEF values occur at about noon. The within day variability is greater in smokers and in patients with respiratory symptoms, and is additionally age dependent (113). The average standard deviation of repeated measurements of FVC and FEV_1 is 150 ml (122).

Validity

Validity is the degree to which an instrument measures what it is supposed to measure (129). The standardized procedures for lung function testing (122;124;126;127;130) have been developed to ensure maximum validity and minimal variability of recordings. However, an instrument may be valid for a wide range of uses with different types of samples, but each use requires new supporting evidence. To our knowledge, there is no published validation study of spirometry applied to patients with AS.

Ability to predict restrictivity

The ability of spirometry to predict a true restrictive disorder has been determined to a positive predictive value (PPV) of 58%, with a sensitivity of 63% for a classic restrictive ventilatory pattern (120). Glady et al found that FVC correlates strongly with TLC (r= 0.66) and inversely with FEV_1/FVC ratio (r= -0.41). According to their calculations, a combination of FVC < 85% of predicted and $FEV_1/FVC \geq 55\%$ performed the best in predicting restriction, with a combined sensitivity of 96% (specificity 61 %, PPV 40%, negative predictive value (NPV) 98%) (131). This implies that only patients with an FVC < 85% who also have an FEV_1/FVC ratio $\geq 55\%$ require further lung volume measures to confirm a restrictive defect, and that spirometric data can be used to exclude a restrictive ventilatory disorder.

3.4.3 Assessment of AS

Disease activity; BASDAI, ASDAS, ERS, CRP

Disease activity was measured by the patient-reported questionnaire Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Appendix 7) (132). BASDAI consists of six numeric rating scales (NRS) relating to major symptoms relevant to AS: fatigue, spinal pain, joint pain, localised tenderness and morning stiffness (measured in 2 items: degree and duration of stiffness). The BASDAI items range from none (0) to very severe (10) symptoms. The mean score of five items (mean of the two morning stiffness items plus the four remaining items) generates at total score applied as an estimate of disease activity (3). The test is shown to be user friendly, reliable and reflects the whole spectrum of the disease (132).

Laboratory tests for the inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) was done to add further information on disease activity.

Additionally, due to well known limitations of the BASDAI (133), we adopted the newly developed instrument ASDAS (Ankylosing Spondylitis Disease Activity Score). ASDAS is the first validated disease activity index in AS which combines patients-reported assessments and acute face reactants. It includes CRP levels in addition to patient-reported assessments of total back pain, duration of morning stiffness, the BASDAI question on peripheral joints and

patient global assessment of disease activity. The responses are given on Numeric Rating Scales (NRS). The scores were categorized according to published cut-offs (134) with low ASDAS defined as <1.3, moderate ASDAS <2.1, high ASDAS < 3.5 and very high ASDAS >3.5. The ASDAS is a continous measure and, as such, comparable to the BASDAI. It can be used to discriminate between groups of patients, or over time after an intervention, and it provides information about the actual disease activity state that has been reached (133).

Self-reported physical function; BASFI

Self-reported physical function was measured with the questionnaire Bath Ankylosing Spondylitis Functional Index (BASFI) (Appendix 8). BASFI includes 8 questions relating to disease specific function on activity level (e.g put on socks or stockings, pick up pen from floor, rise from a supine lying position on the floor) and 2 questions relating to the person's ability to cope with everyday life (e.g. ability to perform physical loaded work and fulfil working obligations at home or at work). The responses are given on NRS. The mean score of 10 items gives the final BASFI score ranging from 0 (easy) to 10 (impossible) (3). BASFI has been demonstrated to have good reliability and construct validity (135-137), and is recommended for use in research and clinical practice (138).

Disease severity and anthropometric measures

The Bath Ankylosing Spondylitis Metrologi Index (BASMI) (Appendix 9) was used to assess disease severity in terms of anthropometrics. BASMI is a combined index comprising five clinical examinations of the spinal column and the hip joints; i.e. the distance from tragus to wall (TWD), lumbar flexion (lumbar Schober), lateral lumbar flexion, cervical rotation and intermalleolar distance.

TWD was measured in standing position with heels and buttocks touching the wall, knees straight, shoulders back, hands by the side. The distance between tragus of the ear and wall during maximal effort to draw the head back without raising the chin above its usually carrying level was measured on both sides to the nearest 0.1 cm, using a rigid ruler, and the mean of the left and right distance calculated.

Lateral lumbar flexion was measured in the same starting position as above. The patient was asked to bend to the right side as far as possible without lifting the left foot/heel or flexing the

right knee, and maintaining a straight posture with heels, buttocks and shoulders against the wall. The distance (cm) from the third fingertip to the floor with subject bent to the side was measured with tape measure, and subtracted from the distance from fingertip to floor when the subject stood upright. The maneouvre was repeated on the left side, and the better of two tries was recorded for left and right. The mean of left and right gave the final result for lateral spinal flexion (to the nearest 0.1 cm).

Lumbar flexion was measured by setting marks in upright position at the level of the spina iliaca posterior superior (SIPS) and 10 cm above the first mark. The distraction of the marks when the subject bent forward as far as possible, keeping the knees straight, was measured in cm. Normally the initial 10 cm increases to 16 cm or more.

Cervical rotation was measured with subject sitting upright on a chair, head in neutral position, gonyometer placed on top of the head. Subject rotated head as far as possible, keeping the shoulders still and without flexing or side flexing the neck. Rotational angle to the right and to the left was measured, and the mean of the two measures recorded.

Intermalleolar distance was measured with patient supine with knees straight and the feet pointing straight up. Patient was asked to separate legs along the resting surface as far as possible, and the distance between medial malleoli was measured (cm).

Each of the five measurements was classified into 11 equal sections, and the mean of the five scores produced a BASMI score ranging from 0.0 to 10.0, low score indicating normal function (3;139). The test is quick, reproducible and sensitive to change across the disease spectrum (140). The BASMI is useful for characterising the outcome of AS; including the effect of radiological structural changes and soft tissue involvement (141-143). The tests are shown to be valid, reliable and responsive in multiple studies of AS measurements (128;141;144;145), and the score is comparable to that of the BASDAI and the BASFI (139;142;146).

Chest expansion was measured with measuring tape as the difference in centimeter to the nearest 0.1 cm, between maximum inspiration and maximum expiration, measured at the level of the xiphoid process. The better of two attempts was recorded.

Body Mass Index (BMI) was calculated from the formula weight/height^2 (kg/ cm^2).

3.4.4 Assessment of aerobic capacity (VO_{2peak})

Aerobic capacity or cardio-respiratory fitness was evaluated by a maximal walking test for estimation of peak oxygen uptake (VO_{2peak}), according to the Balke modified protocol (Appendix 10) (147;148). The test is a multistage treadmill test of graded exercise. It was chosen because it could be adapted individually to each participant regardless of cardio respiratory fitness level. The participants started with warm up walking on the treadmill for five minutes, with an individual adapted speed and 2.5 % inclination. Based on heart rate (HR) during warm up it was decided at what speed they should walk during the test. The speed was kept constant in the beginning of the test, while the inclination increased 1.5 % every minute. When 15 % inclination was reached, the speed was increased with 0.3 km/h every minute. The HR was recorded at the end of each work load (Polar sport tester, Finland). In addition, the participants were asked to rate their perceived exertion (RPE) on Borg's Rating scale (6-20) (149). The test was stopped when the participants could not further increase either the inclination or the speed, and reported RPE between 17 and 20 on the Borg Scale. The estimated maximal oxygen uptake was calculated based on the The American College of Sports Medicine (ACSM) formulas for graded walking or running (150) (Table 3).

Table 3 The American College of Sports Medicine formulas was used for estimation of peak oxygen capacity (150)

Graded walking (speeds ≤8.0 km/h):
$VO_2 ml \cdot kg^{-1} \cdot min^{-1} = (0.1 \cdot ms^{-1} + 1.8 \cdot ms^{-1} \cdot percent\ grade + 3.5)$

Graded running (speeds >8.0 km/h):
$VO_2 ml \cdot kg^{-1} \cdot min^{-1} = (0.2 \cdot ms^{-1} + 0.9 \cdot ms^{-1} \cdot percent\ grade + 3.5)$

ms= speed in meters $\cdot min^{-1}$

3.4.5 Assessment of physical activity

Physical activity was measured by the International Physical Activity Questionnaire long form (IPAQ-L) (Appendix 11), which provided a MET-score (metabolic equivalent task) for each respondent (151). MET describes the intenstity of the work; 1 MET is the energy

consumtion during rest. The IPAQ was developed as an instrument for cross-national monitoring of physical activity and inactivity. It assesses physical activity across a comprehensive set of domains including leisure time physical activity, domestic and gardening (yard) activities, work-related physical activity and transport-related physical activity. The questionnaire has been developed and tested for use in 18 to 69- year- old adults in diverse settings (152). The questions address the time spent being moderately or vigorously physical active during a typical week in the summer and a typical week in the winter. Computation of the total scores requires summation of the duration (in minutes) and frequencies (days) for all the types of activities in all domains. METs are multiples of the resting metabolic rate and a MET-minute is computed by multiplying the MET score of an activity by the minutes performed. MET-minute scores are equivalent to kilocalories for a 60 kilogram person. Kilocalories were computed from MET-minutes using the following equation: *MET-min x (weight in kg/60 kg).* Data collected with IPAQ will be reported as a continuous measure; i.e. a median value of an overall total physical activity MET-minutes/week-score computed as sum of the activity in all domains, according to the IPAQ Research Committee proposals (153).

3.5 Statistical analysis

Statistical analyses were performed using the SPSS software (Statistical Packages for the Social Sciences) for Windows, version 17.0. The Independent Sample T test was used for intergroup comparisons of continuous, normally distributed data, and the Mann Whitney U test for comparisons of skewed distributions (55;56). Results are presented as mean (SD) or median (min-max) values. Categorical data emerged when individuals were categorized into one or two, or more, mutually exclusive groups (57). Intergroup comparisons of categorical data were analyzed using the Chi Square test and the Fisher's exact test (55;57).

Bivariate and multivariate statistical models were applied to examine associations between pulmonary function measures, demographic and clinical variables. The Pearson product-moment correlation coefficient (r) was calculated to determine the bivariate associations between normally distributed variables, and the Spearman's rho (r_s) was used to evaluate correlations between skewed, non-linear distributions (55-57). A multiple backward stepwise

regression analysis (154) was performed to identify how much of the variance of the dependent variable FVC% (the marker parameter of restrictive ventilatory impairment (58)), could be explained by the independent variables (56). A p-value of 0.05 or less was accepted as statistically significant.

3.6 Ethics

All potential research subjects received written information about the objectives, methods, sources of funding, anticipated benefits and potential risks of the study, as well as the expected duration of examination and the potential discomfort it might entail. They were informed of the right to refuse to participate in the study without specifying a reason, and the right to withdraw consent to participate at any time without reprisal. Patients are often vulnerable and in a dependent relationship with health workers. It is therefore important to be cautious when seeking informed consent. All participants in this study gave their written consent before inclusion, and the procedures followed the World Medical Association Declaration of Helsinki (155) (Appendix 1-2).

The examinations were performed at the hospital, providing an immediate proximity to emergency medical treatment if needed. Most of the clinical examinations done by the physiotherapist were not considered to be risky. However, the cardio respiratory fitness test required maximal effort, a situation which might constitute a potential risk. A physician (cardiologist) was informed in advance of each test situation, and relevant information from the medical journal was obtained. Patients with severe heart failure were excluded. The physiotherapist conducting the test had a portable telephone, and an automatic electronic defibrillator was accessible. Assessment of the risks involved and the safety of the individual patient was based on anamnetic information and feedback from the patient during the test, and done by an experienced physiotherapist.

The protocol was reviewed and approved by The National Committee for Medical Research Ethics, Southern Norway, (S-02059 and S-03066) (Appendix 3-5). The Data Inspectorate, Norway, provided licence to store and register individual health information (08/00165-2/sve) (Appendix 6). Every precaution was taken to protect the privacy of the research subjects and the confidentiality of their personal information.

4 Paper

The present article is currently in the process of submission and does not represent the final version.

Restrictive pulmonary impairment is associated with reduced spinal mobility in patients with ankylosing spondylitis

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INTRODUCTION

Ankylosing Spondylitis is a chronic, systemic, inflammatory, rheumatic disease affecting mainly the axial skeleton and sacroiliac joints, causing characteristic inflammatory back pain and resulting in varying degree of structural and functional impairments (1). AS may also be associated with extra-spinal manifestations, involving peripheral joints, eye, bowel and an increased risk of cardiovascular morbidity (2;3). Additionally, pulmonary involvement is a known manifestation, emerging either as interstitial lung disease or in the form of restrictive pulmonary function. In previous studies, the frequency of pulmonary involvement vary depending on the diagnostic method applied, and is reported to be between 20 to 53 % using spirometry (4-7), between 1 and 15% with radiographic evaluation and between 40 and 80 % in studies where high resolution computed tomography were applied (7-13).

AS is characterized by inflammation in the thoracic vertebrae and in the costovertebral joints, causing pain, gradually fusion and ossification of the joints, ultimately resulting in increased dorsal kyphosis, rigidity of the thorax and permanent chest wall immobility (14;15). Reduced lung volumes have been suggested to be a consequence of chest wall limitation, due to reduced mobility of the thoracic cage (7;16). However, reports have differed regarding whether pulmonary function worsens with disease progression (14), and whether restriction, if present, correlates with limitation of chest wall movements (8;14;15;17;18). The associations between anthropometric, musculoskeletal and disease related factors and pulmonary function abnormalities are unclear and need to be explored.

The objectives of this study were to characterize pulmonary variables in patients with AS, and to examine whether, and in what respect, these variables differ from those observed in population controls. Further, to investigate possible associations between pulmonary function and demographic, disease specific and laboratory measures, as well as measures of cardio-respiratory fitness and physical activity level.

MATERIALS AND METHODS

Study design and selection of patients and population controls

In a cross sectional study, patients were recruited from a hospital based register, diagnosed with AS according to the New York Criteria (19). Population controls were randomly

selected by Statistics Norway to match stratification of the AS patients for age, gender and residential area. The only exclusion criterion was a history of inflammatory arthritis. The controls were examined according to the same protocol as the AS patients.

Ethics

All participants gave their written consent before inclusion, and the procedures followed The World Medical Association Declaration of Helsinki. The protocol was reviewed and approved by The National Committee for Medical Research Ethics, Southern Norway (S-02059 and S-03066), and the Norwegian Data Inspectorate provided licence to store and register individual health information (08/00165-2/sve).

Clinical assessments and self reported data

Demographic variables (age, disease duration, education level, smoking history, work and marital status) were recorded for all participants using a questionnaire. Disease activity was measured by inflammatory markers (C-reactive protein (mg/l), Sedimentation Rate (mm/time) SR), by the self-administered instrument Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (21) and by the AS Disease Activity Score (ASDAS) (22). BASDAI consists of six numeric rating scales (NRS) relating to major symptoms relevant to AS: fatigue, spinal pain, joint pain, localised tenderness and morning stiffness. The BASDAI items range from none (0) to very severe (10) symptoms. The mean score of five items (mean of the two morning stiffness items plus the four remaining items) generates a total score applied as an estimate of disease activity (21;23). The ASDAS includes CRP-levels in addition to patient assessment of peripheral joint pain/swelling, total back pain, duration of morning stiffness (BASDAI Q1, Q2 and Q6) and patient global assessment of disease activity. The responses were given on NRS. The scores were categorized according to published cut-offs with low ASDAS defined as <1.3, moderate ASDAS < 2.1, high ASDAS < 3.5 and very high ASDAS > 3.5 (24). The ASDAS can be used to discriminate between groups of patients, and it provides information about the actual disease activity state that has been reached (22).

Patient-reported physical function was measured with the Bath Ankylosing Spondylitis Functional Index (BASFI). BASFI consists of eight questions relating to specific functions on activity level and two questions reflecting the person's ability to cope with everyday life. The

responses were given on NRS. The mean score of 10 items gave the final BASFI score ranging from 0 (easy) to 10 (impossible) (23;25).

Anthropometric measures were examined by the Bath Ankylosing Spondylitis Metrology Index (BASMI) (26), by chest expansion and by body mass index (BMI). BASMI includes five clinical examinations of spinal column and hip joints; that is the distance from tragus to wall (TWD), lumbar flexion (l-Schober), lateral lumbar flexion, cervical rotation and inter-malleolar distance. Each of the five measurements was classified into 11 equal sections, and the mean of the five scores produced a BASMI score from 0 to 10; low score indicating normal function. The end values of 0 and 10 were kept open to ensure that BASMI was suitable for assessing spinal mobility across the whole range of disease severity (27).
The test is comprehensive, quick, reproducible and sensitive to change across the disease spectrum (26), and is shown to be valid, reliable and responsive (28-31). Chest expansion was measured with tape measure circumferentially around the chest on level with the xiphoid process. The difference (cm) in circumference of the chest between maximum inspiration and maximum expiration was recorded (best of two attempts, rounded at 0.1 cm) (30).
Measurements of the weight and height were recorded and the BMI was estimated by the formula weight (kg)/height^2(cm) (32) .

Cardio-respiratory fitness was evaluated by a maximal walking test for estimation of maximum oxygen uptake (VO_{2peak}), according to the Balke modified protocol (33;34), using a multistage treadmill test of graded exercise. The estimated peak oxygen uptake (VO_{2peak}) was computed from The American College of Sports Medicine (ACSM) formulas for graded walking (speeds$\leq$ 8km/h, $VO_2 ml \cdot kg^{-1} \cdot min^{-1} = (0.1 \cdot ms^{-1} + 1.8 \cdot ms^{-1} \cdot inclination\ (\%) + 3.5)$ or running (speeds>8 km/h, $VO_2 ml \cdot kg^{-1} \cdot min^{-1} = (0.2 \cdot ms^{-1} + 0.9 \cdot ms^{-1} \cdot inclination\ (\%) + 3.5)$ (35).

Pulmonary function test

All participants underwent a pulmonary function test (PFT), evaluated by means of a spirometer (Spida 5, USB Spirometry from Micro Medical Ltd, United Kingdom, 2006). The spirometric measurements were performed with the subject sitting upright with a nose clip attached. Spirometric testing was done by a trained physiotherapist in accordance to guidelines set by the American Thoracic Society and the European Respiratory Society (ATS/ERS) (36) and included measurements of:

FVC – Forced Vital Capacity; the maximal volume of air delivered during an expiration made as forcefully and completely as possible starting from full inspiration; i.e. vital capacity performed with a maximally forced expiratory effort, expressed in litres.
FEV_1 – Forced Expiratory Volume in one second; the volume, expressed in litres, delivered in the first second of the FVC manoeuvre.
PEF – Peak Expiratory Flow; the maximum expiratory flow achieved from a maximum forced expiration, starting without hesitation from the point of maximal lung inflation, expressed in liter/min.
FEV_1/FVC% - the absolute ratio; derived from observed values (not percent predicted) (litres/litres x100). Primarely used in the diagnostics of obstructive ventilatory disease (36-38).

Additionally, observed values were expressed as percentage of predicted values to control for the influence of age, sex, weight and height. The published equations of the European Community for Coal and Steel (ECCS) (39) was internalized in the spirometry equipment and used as reference data. Additionally, data from the population controls served as reference and basis for comparisons. Repeated measurements were performed until three acceptable manoeuvres were obtained, and the largest FVC and FEV_1 values were recorded for further analysis. Based on these results, the patients were categorized as having restrictive ventilatory pattern (FVC≤80%, FEV_1/FVC≥70%, decreased or normal FEV_1), obstructive ventilatory pattern (FEV_1/FVC<70%, decreased FEV_1, normal or decreased FVC) or normal pulmonary function (FVC>80%, FEV_1>80%, FEV_1/FVC>80%) (37;39-43).

Statistical analysis

Statistical analyses were performed using the SPSS software (Statistical packages for the social sciences) for Windows, version 17.0. A priori power calculation was done to establish the number of population controls, based on the distribution and difference in a self-reported general health score (SF-36) between patients and the general population (20). According to this calculation, we aimed at reqruiting 120 population controls. The Independent Sample t test was used for intergroup comparisons of continuous, normally distributed data, and the Mann Whitney U test for comparisons of skewed distributions (44;45). Results are presented as mean (SD) or median (min-max) values. Intergroup comparisons of categorical data were analyzed using the Chi Square test and the Fisher's exact test (44;46). Results are presented as

summaries of observed frequencies (counts) together with rounded percentages. Univariate ANCOVAs were performed to explore differences in pulmonary function between patients and controls adjusting for age, gender, height and smoking status. Bivariate and multivariate linear models were applied to examine associations between pulmonary function measures, demographic and clinical variables. A multiple linear model was used to estimate the explanatory power of independent variables (demographic, disease related, VO_{2peak}) on restrictive ventilatory impairment (FVC%). A p-value of 0.05 was accepted as statistically significant.

RESULTS

Demographic variables

Two hundred and fifty patients with AS were invited, and 162 gave their informed consent to participate. Fifteen did not complete the pulmonary assessments, thus, a total of 147 of 250 (59%) patients, are included in the analyses. Three hundred and twenty nine letters were sent to invite potential controls and 139 accepted participation. Of these, a total of 121 of 329 (37%) population controls completed the pulmonary function test and are included in the analyses.

For both the AS patients and the population controls, the participating subjects were older ($p=0.04$ and $p=0.03$, respectively) and a higher proportion were living in the western part of Oslo ($p=0.01$, $p=0.06$, respectively) compared with the non-participating subjects. There were no significant differences in gender between participating and non-participating subjects among AS patients and population controls.

Demographic variables of the AS patients and the population controls are shown in Table 1. Patients were younger ($p=0.01$), more educated ($p=0.03$) and a higher proportion reported to receive social security benefits ($p<0.001$) compared with controls. The other parameters showed no significant differences between the groups.

Table 1: Characteristics of patients and population controls			
Demographic characteristics	AS Patients (n=147)	Controls (n=121)	p -value
Age (yr) median (range)	48.5 (30-70)	56.0 (30-70)	0.01[a]
Male n (%)	93 (63.3)	68 (56.2)	0.24[c]
Height (cm), mean (SD)	174.1 (9.7)	173,4 (8.9)	0.54[b]
Weight (kg) mean (SD)	77.4 (13.7)	77.5 (13.7)	0.98[b]
BMI (kg/cm^2) mean (SD)	25.5 (3.5)	25.7 (3.7)	0.59 [b]
BASDAI	4.1 (2.0)	1.8 (1.6)	<0.001[b]
BASFI	2.1 (0-10)	0.3 (0-6.3)	<0.001[a]
BASMI	3.3 (1.8)	1.7 (0.9)	<0.001[b]
CRP	3.0 (1,57)	1.0 (1,103)	<0.001[a]
ESR	16.5 (1,90)	8.0 (1,70)	<0.001[a]
VO_{2peak} (ml/kg/min)	39.4 (8.0)	40.4 (7.5)	0.002[b]
Smoking			
Lifelong non-smoker, n (%)	74 (50,0)	59 (48.8)	
Ex-smoker, n (%)	48 (32.4)	38.2 (30.6)	0.81[c]
Current smoker, n (%)	26 (17.6)	22.9 (20.7)	
>12 yr education, n (%)	103 (71)	68 (57)	0.03[c]
Currently employed, n (%)	111 (76.6)	99 (83.2)	0.18[c]
Social security benefit, n (%)	57 (39.4)	15 (12.6)	<0.001[c]
Married/cohabitant, n (%)	99 (67)	71 (60)	0.20[c]
Anti-TNF-alpha medication	32 (22)	-	

[a] Mann Whitney U test, [b]Independent Sample T test, [c] Chi Square test for independence

Pulmonary function in patients and controls

PFT exposed significantly lower values for the AS patients compared to the controls with regard to FVC% (97 vs105, p<0.001), FEV_1% (90 vs 99, p<0.001), and PEF% (95 vs 99, p=0.05). Most of the AS patients were categorized with normal pulmonary function, but 18 % (n=27) were categorized with restrictive pattern. As none of the population controls showed a restrictive pattern, the proportion of pulmonary impairment in the two groups was significantly different (p<0.001) (Table 2). Among the 27 AS patients with a restrictive pattern, 21 (78%) were males, median age was 57 years (range 33, 68), median disease duration was 27 years (range 18, 46), 9 (33%) were using biological anti-tumor necrosis factor therapy and 15 (56%) were lifelong non-smokers. The AS patients with a restrictive pattern had a mean (SD) BASMI score on 5.4 (1.8) and mean (SD) chest expansion 2.9 cm (1.8) (data not shown). Approximately 10% of the AS patients and 9% of the controls were categorized with obstructive pattern; a non-significant difference which will not be paid any further attention in this paper.

Table 2 Pulmonary function in AS and controls

PFT	AS patients (n=147)	Controls (n=121)	ß (95%CI)	p-value
FVC (litres) mean (SD)	4.0 (1.2)	4.1 (1.0)	0.3 (0.14,0.45)	<0.001
FVC%	97.2 (18.1)	104.9 (15.2)		<0.001
FEV_1 (litres) mean (SD)	3.1 (0.9)	3.2 (0.9)	0.3 (0.18,0.43)	<0.001
FEV_1%	89.8 (16.0)	98.5 (14.5)		<0.001
PEF (litres/min) mean (SD	464.7 (121.4)	469.1 (120.1)	20.5 (1,41.1)	0.05
PEF%	95.2 (17.6)	99.4 (16.6)		0.05
FEV_1/FVC%	76.5 (7.5)	77 (6.4)		0.38
Respiratory pattern				
Normal n (%)	105 (71.4)	110 (90.9)		<0.001
Restrictive pattern n (%)	27 (18.4)	0		< 0.001
Obstructive pattern n (%)	15 (10.2)	11 (9.1)		0.76

FVC: Forced Vital Capacity, FEV_1: Forced Expiratory Volume in one second, PEF: Peak Expiratory Flow, FVC%, FEV_1%, PEF%: predicted percentages adjusted for age, sex, smoking and height measured at time of testing (adjustments made in the device), FEV_1/ FVC%: absolute ratio derived from observed values. Independent Sample t-test was used for comparison of continuous variables, Chi-Square-Test for counts. Linear regression (ß (95% CI)) was used to control for age, sex and height in the observed measures FVC (l), FEV_1 (l), PEF (l/min).

Associations between pulmonary function and relevant variables

A multiple regression model was build to assess how demographic and clinical variables and aerobic capacity could predict the variation in FVC% in the patient group. Sex, BASMI and chest expansion contributed significantly, and the final model explained 46% of the variance in FVC% ($p<0.001$) (Table 3).

Table 3 Multiple linear regression analyses showing associations to predict forced vital capacity (%)

	Crude estimates ß[1] (95 % CI[2])	p-value	Adjusted estimates[3] ß (95% CI)	p-value	Final model R2
Age					
Continuous	-0.3 (-0.6, -0.05)	0.02	—		
Gender					
Female	Reference		Reference		
Male	-8.3 (-14.2,-2.3)	<0.01	-8.2 (-12.9, -3.5)	0.001	0.45
Smoking[a]					p<0.001
Lifelong non-smokers,	Reference		—		
Ex-smokers and smokers	2.9 (-3.0,8.8)	0.33			
Education[b]					
≤12 years	Reference		—		
>12 years	0.3 (-6.3,6.8)	0.94			
ASDAS					
Continuous	-1.4 (-4.5, 1.7)	0.36	—		
BASFI					
Continuous (0-10)	-1.9 (-3.3,-0.5)	<0.01	—		
BASMI					
Continuous (0-10)	-5.6 (-6.9, -4.3)	<0.001	-4.1 (-5.4, -2.7)	<0.001	
Chest expansion					
Continuous	4.0 (2.8, 5.1)	<0.001	2.7 (1.6, 3.9)	<0.001	
VO_2peak					
Continuous	0.6 (0.2,0.9)	<0.001	—		

[1] Estimated regression coefficients. [2] CI, confidence interval. [3] Adjusted for the other variables in the table
[a] Smoking (lifelong non-smokers vs ex-smokers and smokers). [b] Education (≤12 years or >12 years). — = not significant in the adjusted model

DISCUSSION

This study showed significantly impaired pulmonary function in the AS patients compared to reference data and to the population controls. Furthermore, strong negative associations were found between pulmonary function and the typical clinical features of AS; reduced spinal – and chest wall mobility.

The results of this study are in agreement with previous studies, but a lower prevalence of restrictive abnormalities was observed. We found a prevalence of 18% of restrictive disorders, compared to the reported prevalence between 27 and 57% in other studies (4-7;9;10;13;43;47-50). However, these studies included small sample sizes, ranging from 17 to 55 subjects, potentially influencing the representativeness. Another possible explanation of the lower

prevalence of restrictive impairment in this study may be attributed to the assessment of pulmonary function. Calculations of lung volumes are related to body size, and standing height is the most important correlating variable (43). However, patients with AS often loose height due to increasing dorsal kyphosis as the disease progresses, and in some of the previous studies patient's original height or height from arm span measurement were therefore used to calculate predicted normal values (15;51;52). In our study, the tragus-to-wall-distance (as an expression of increased kyphosis) was associated with loss of height (cm) (r_s=0.52, p<0.001) (data not shown). However, since the reliability of recalled height may be questionable, we used height measured at time of testing in accordance with the ATS/ERS guidelines (43), and we may therefore have failed to discover some cases of restrictive pulmonary impairment.

Further, the population in this study was well educated, married or cohabitant, primarily of Norwegian ethnicity and recruited from an non-industrial (sub-) urban district area with high socio-economic status (SES). Within the city of Oslo, differences in health, exercise habits and mortality rates between districts are significant, and strongly related to SES (53-56). Adverse effects of low SES on pulmonary function are well documented, as low SES often is associated with unfavorable environmental conditions, such as increased exposures to indoor and outdoor pollution, increased occupational exposures and decreased access to health care. Moreover, genetic factors influencing lung function may be attributable to differences in SES (42). The high SES values in this sample may be associated with the low prevalence of pulmonary impairment.

Reduced spinal mobility and chest expansion made the largest contributions to explaining the variance in pulmonary function, and AS patients with restrictive impairment were characterized by reduced spinal mobility and reduced chest expansion. This result is in accordance with several previous studies, reporting that the restrictive disorder seen in AS patients are associated with increased stiffness and ankylosing of the spine and costovertebral joints (12;57;58). This supports the assumption of an association between musculoskeletal limitations and restrictive pulmonary impairment, underlining the importance of maintained spinal flexibility in the management of AS.

Earlier reports have differed concerning whether disease duration is associated with restrictive pulmonary impairment in AS or not. This is interesting, because AS is a chronic, progressive

disease. If pulmonary restrictivity is related to musculoskeletal limitations progressing with time, a logical consequence would be a parallel deterioration in pulmonary parameters. In this study, patients with restrictive pattern were, in agreement with these expectations, older (p=0.054) and had significantly longer disease duration (0=0.02) than patients with normal pulmonary function (data not shown). However, these differences must be interpreted with caution due to lack of data on 30% of cases, and because disease duration was based on the patients' subjective assessments of onset of disease.

Smoking is recognized as having a negative impact on patients with pulmonary restrictions, independent of the etiology of the restriction (10). Yet, in the present study, no differences in restrictive involvement were found between lifelong non-smokers/ex-smokers and smokers, and 56% of the patients with a restrictive pattern were lifelong non-smokers, indicating that the restrictive involvements is not affected by smoking in the patient group. Furthermore, no associations were found between smoking and disease related variables, nor measures of pulmonary function, which is consistent with earlier reports (6-8;10-12;15;16). However, smokers reported significantly higher occurrence of pulmonary disease (p=0.04) and demonstrated a significantly lower VO_{2peak} (p=0.004) than current non-smokers.

When comparing AS patients who never smoked (n=74) with ex-smokers/current smokers (n=73), we found, surprisingly, statistically significant differences (ex-smokers/smokers worse health) in measures of disease activity (BASDAI, ASDAS, ESR, CRP). Additionally, chest expansion and cardio-respiratory fitness (VO_{2peak}) were poorer in the group of smokers and ex-smokers. These findings may indicate that smoking is connected to measures of disease activity, flexibility and cardiorespiratory fitness, but probably not directly to measures of pulmonary function in AS.

A weakness of this study is the lack of data on radiological changes in skeletal structures. Previous reports have recognized relationships between radiographic manifestations and BASMI (especially lumbar flexion and lumbar lateral flexion), but yet, spinal mobility measures cannot stand proxy for radiographic evaluation in an individual patient (59). Another weakness is the lack of CT imaging, as interstitial lung disease is diagnosed by CT. However, there is little evidence of correlation between lung findings by imaging and abnormalities measures by spirometry (5;9;11;13;13;17). Further, the results of this study and the

representativeness of the sample may be influenced by the fact that we only managed to include 59% of the patients and 37% of the controls; the participants being older and living in a more affluent area compared to the non-responders. The study is, however, strengthened by the relatively large number of subjects included, providing an opportunity to produce more accurate estimates and hopefully a more representative sample than previous studies. Furthermore, the comparisons with controls randomly drawn from the general population, and a comprehensive clinical examination may also strengthen the results.

Conclusively, this study showed that patients with AS were more likely to have restrictive pulmonary impairment compared to controls, and the restrictivity was closely related to reduced spinal- and chest wall mobility. The results emphasize the importance of maintaining spinal flexibility in the management of AS. However, the effects of mobility and aerobic exercise on pulmonary function in AS remain to be explored. The study exposed a need for further examination of the relationships between the disease specific changes and pulmonary function in AS, and the effects of biological (anti-TNF-α) treatment on these changes. Further, patients with severely reduced spinal mobility should be referred to pulmonary function examination and relevant follow-up treatment.

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5 Extended results

This chapter begins with presenting the extended results from the bivariate correlation analysis of pulmonary function and clinical measures in the patient group. Then, descriptive data on the influence of smoking in the patient group will be provided.

Mainly, this chapter will focus on the results from the analyses of gender differences. First, a characterization of the demographic features of the male and female AS patients will be presented. Then, the characteristics of the male and female patients will be compared to that of the population controls. Subsequently, pulmonary function in male and female AS patients will be compared, followed by comparisons to controls of same gender. The same procedure will be followed for clinical and laboratory measures.

5.1 Bivariate associations between pulmonary function and clinical measures

Table 4 shows bivariate correlations (r/r_s) between pulmonary function measures and clinical measures in the total patient group (n=147). Disease activity (ASDAS, BASDAI; r=0.07, ESR; r_s=-0.17) correlated poorly with FVC%; the key parameter in restrictive pulmonary defects. Weak correlations were also found between the disease activity measures and the other PFT variables.

Table 4 Bivariate Correlations (r/r_s) between pulmonary function measures and clinical measures in AS-patients (n=147)

	ASDAS	BASDAI	BASFI	BASMI	CE	TWD	LF	LLF	IMD	DD (n=104)	VO_2peak	ESR
FVC %	r=-0.07	r=0.07	r_s=-0.17*	r=-0.57**	r=0.48**	r_s=-0.48**	r=0.50**	r=0.52**	r_s=-0.20*	r_s=-0.21*	r=0.25**	r_s=-0.17*
FEV_1 %	r=-0.16	r=-0.005	r_s=0.27**	r=-0.52**	r=0.44**	r_s=-0.43**	r=0.47**	r=0.47**	r_s=-0.19*	r_s=-0.27**	r=0.43**	r_s=0.27**
PEF %	r=-0.14	r=-0.11	r_s=-0.18*	r=-0.20*	r=0.15	r_s=-0.11	r=0.16	r=0.22**	r_s=0.03	r_s=0.09	r=0.25**	r_s=-0.15
FEV_1/ FVC %	r=-0.07	r=0.05	r_s=-0.13	r=0.09	r=-0.12	r_s=-0.12	r=-0.07	r=-0.09	r_s=-0.001	r_s=-0.14	r=-0.44**	r_s=-0.07

Pearson's Correlation Coefficient (r). Spearman's Correlation Coefficient (r_s). ASDAS: Ankylosing Spondylitis Disease Activity Score: Back pain +Duration morning stiffness + Peripheral pain /swelling (=BASDAI Q2, Q6 and Q3)+ Patient Global + CRP: Low score <1.3, moderate score: 1.3<2.1, high score: 2.1>3.5, very high score>3.5. BASDAI:The Bath Ankylosing Spondylitis Disease Activity Index (0-10, 10 worst). BASFI: The Bath Ankylosing Spondylitis Functional Index; sumscore 0 (easy)-10 (impossible). BASMI: The Bath Ankylosing Spondylitis Metrology Index; sumscore 0-10; high value indicating functional impairment. CE: Chest expansion. TWD: Tragus to wall distance. LF: Lumbar flexion (modified Shober's test). LLF: Lumbar lateral flexion. IMD: Intermalleolar distance. IMD: Inter malleolar distance. DD: Disease duration. VO_{2peak}: Peak oxygen uptake (aerobic capacity). ESR: Erythrocyte Sedimentation Rate. FEV_1: Forced Expiratory Volume in one second. FVC: Forced Vital Capacity. PEF: Peak Expiratory Flow. Predicted percentages (FEV1%, FVC%, PEF%) adjusted to age, sex and height measured at time of testing. *Significant (p<0.05), ** Significant (p<0.001) (Sig. 2-tailed).

The BASFI-scores, representing self reported physical function, also correlated poorly (r_s=0.17) with FVC%, and showed small correlations with the remainder PFT parameters. On the other hand; the BASMI-scores, incorporating the anthropometric test results, showed quite large negative correlations with FVC% (r=-0.57, p<0.001). Chest expansion also showed a quite large, positive correlation (r=0.48, p<0.001)) with FVC% (Table 4).

The scatterplots (Figure 10 and 11) provides graphic illustrations of the bivariate association between BASMI and FVC%, and between chest expansion and FVC%, respectively:

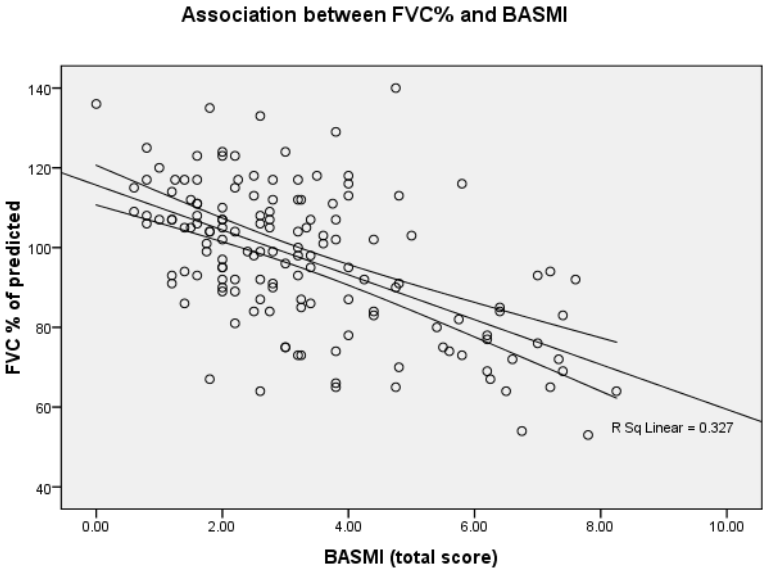


Figure 10 Distribution of BASMI and FVC% scores (curves: mean, 95% confidence interval)

A low BASMI score expresses approximately normal function and correlates well with a large FVC% score, expressing absence of restrictive pulmonary impairment. Correspondingly a large BASMI score expresses reduced spinal (and hip) mobility, and correlates well with a low FVC% score as an expression of a possible presence of restrictive pulmonary impairment.

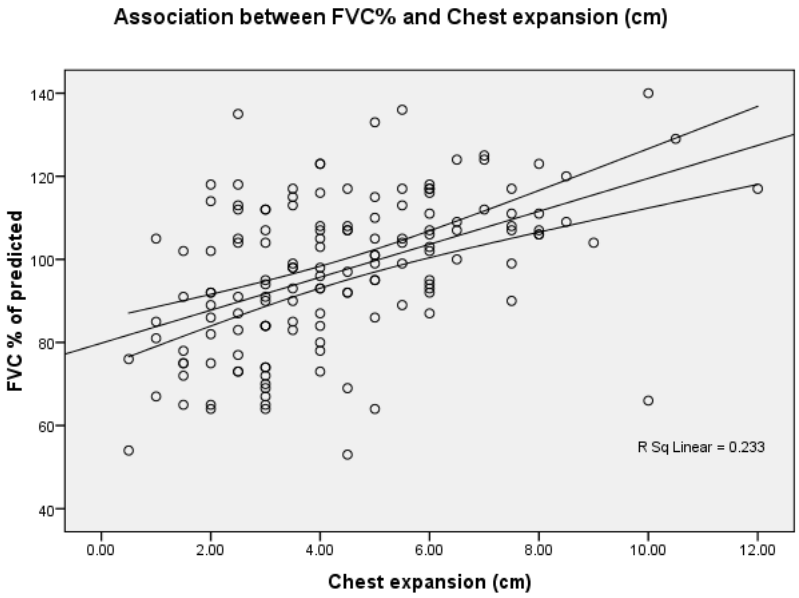


Figure 11 Distribution of Chest expansion and FVC% scores (curves: mean, 95% confidence interval)

Figure 11 indicates a positive, linear relationship between chest expansion and FVC%, implying a connection between low thoracic expansion and a possible presence of restrictive defect. Correspondingly, large thoracic expansability is associated with large FVC% values; which is incompatible with restrictive pulmonary function.

Large correlation coefficients was also present for the relationships between FVC% and the BASMI components TWD (r_s=0.48), Lumbar flexion (r=0.50) and Lumbar lateral flexion (r=0.52), but smaller for hip mobility (IMD; r_s=0.20). Disease duration correlated weakly with FVC% (r_s=0.21), and unfortunately there were missing data on 43 cases concerning this variable. VO_{2peak} did correlate significantly with all PFT parameters, but with a rather small coefficient with respect to FVC% (r=0.25) (Table 4).

5.2 Smoking – pulmonary function and clinical measures in the AS patients

The majority of the patients demonstrated a normal pulmonary function, and this finding was present in lifelong non-smokers, ex-smokers and smokers. Most of the patients with restrictive impairment were non-smokers (82%). Patients with obstructive impairment were mainly smokers and ex-smokers (60%) (Figure12).

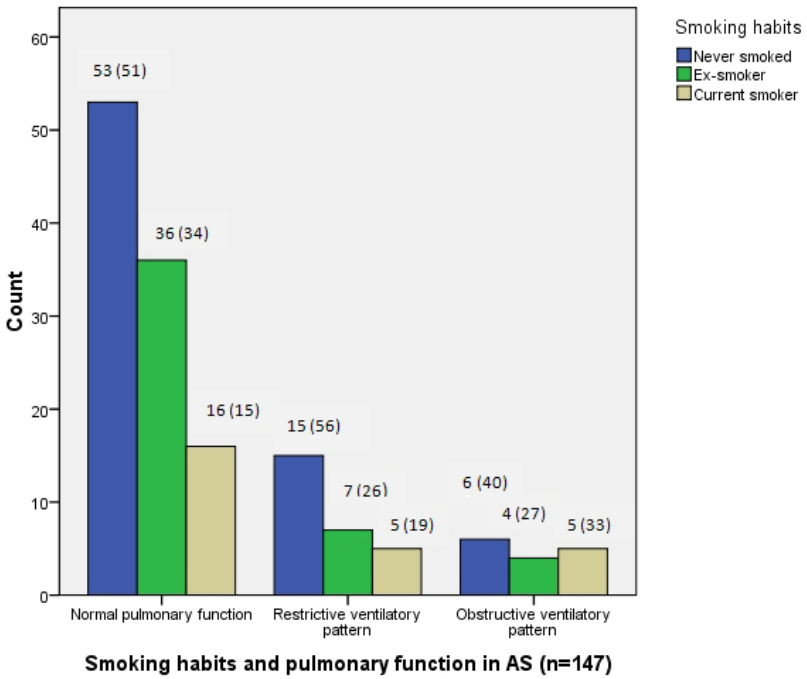


Figure 12 Smoking habits and results of PFTs in AS patients (n=147), counts (%).

When comparing AS patients who never smoked with ex-smokers and current smokers, we found, surprisingly, statistically significant differences regarding disease activity. These findings were present in all the clinical measures defining disease activity; the self reported questionnaire BASDAI (p=0.04), the laboratory measures ESR (p=0.05) and CRP (p=0.02), and even more obvious in the ASDAS (p=0.004) (Table 5). There were no significant differences between the groups in physical test results or, again surprisingly, in any of the pulmonary function test parameters. Additionaly, there were no significant differences in the prevalence of self reported pulmonary disease between the two groups. These findings might

indicate that smoking is of less importance regarding pulmonary impairment in AS, but it is connected to disease activity.

Table 5 Comparisons of PFT and clinical test results for two sub-groups of the AS sample (n=147): Lifelong Non-Smokers (n=74) and Ex-Smokers plus Current smokers (n=73)

Test	**Lifelong Non-Smokers (n=74)**	**Ex-smokers + Current Smokers (n=73)**	**p-value**
Age[a] (yr)	47.8 (11.8)	51.1 (10.1)	0.07[c]
Disease duration[b] (yr)	21.5 (7-55)	23 (8-47)	0.64[d]
Self reported pulmonary disease (yes/no) n (%)	6 (8.1)	10 (13.9)	0.53[e]
FEV_1 (litres)[a]	3.2 (1.0)	3.0 (0.9)	0.18[c]
FEV_1%[a]	89.9 (15.7)	89.6 (16.5)	0.90[c]
FVC (litres)[a]	4.1 (1.2)	3.9 (1.1)	0.45[c]
FVC %[a]	95.7 (17.4)	98.6 (18.8)	0.33[c]
PEF (litres/min)[a]	469.3 (128.5)	458.8 (114.7)	0.60[c]
PEF%[a]	93.6 (18.0)	96.7 (17.1)	0.28[c]
FEV_1/FVC%[a]	77.5 (7.4)	75.4 (7.6)	0.09[c]
ASDAS[a]	2.1 (0.9)	2.5 (0.9)	0.01[c]
BASDAI[a]	3.8 (2.0)	4.5 (2.0)	0.004[c]
ESR[b]	12 (1-90)	19 (2-67)	0.05[d]
CRP[b]	3 (1-57)	5 (1-52)	0.02[d]
BASFI[b]	1.8 (0-10)	2.3 (0-8.5)	0.66[d]
BASMI[a]	3.3 (1.8)	3.2 (1.8)	0.74
Chest Expansion (cm)[a]	4.8 (2.3)	3.9 (2.0)	0.02*[c]
Lumbar flexion (m-Schober)[a]	4.0 (1.7)	4.0 (1.7)	0.90[c]
Lumbar lateral flexion[a]	12.9 (6.0)	13.6 (6.3)	0.53[c]
Tragus to wall distance[b]	13.1 (7.8-38.0)	12.0 (8.0-43.5)	0.33[d]
VO2peak[a]	40.9 (8.4)	38.0 (7.4)	0.04[c]
MET-min/$week_{summer}$[b]	3787 (0-13351)	4638 (0-14438)	0.14[d]
MET-min/$week_{winter}$[b]	3062 (0-16354)	3571 (0-13478)	0.37[d]
Interpretation of PFT	**Lifelong non-smokers (n=74)**	**Ex-smoker + Smokers (n=73)**	**p-value**
Normal (n) (%)	53 (71.6)	52 (71.2)	1.00[e]
Restrictive pattern (n) (%)	15 (20.3)	12 (16.4)	0.67[e]
Obstructive pattern (n) (%)	6 (8.1)	9 (12.3)	0.43[e]

[a] Mean (SD). [b] Median (min-max). [c]Independent Sample T test. [d] Mann Whitney U test. [e] Chi Square Test for Independence. FEV_1: Forced Expiratory Volume in one second, FVC: Forced Vital Capacity, PEF: Peak Expiratory Flow, Predicted percentages (FEV_1 %, FVC %, PEF %) adjusted to age, sex and height measured at time of testing. FEV1/FVC %: Absolute FEV1/FVC ratio derived from observed values. ASDAS: Ankylosing Spondylitis Disease Activity Score; Low score <1.3, moderate score: 1.3<2.1, high score: 2.1>3.5, very high score>3.5 BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index (0-10, 10 worst). BASFI: The Bath Ankylosing Spondylitis Functional Index (0 (easy)-10 (impossible)). BASFI: The Bath Ankylosing Spondylitis Functional Index (0 (easy)-10 (impossible)). BASMI: The Bath Ankylosing Spondylitis Metrologi Index (0-10, low score indicates normal function). CRP: C-Reactive Protein. ESR: Erythrocyte Sedimentation Rate. Chest expansion: Circumference of the chest (cm) measured at the level of proc xiphoideus. VO_{2peak}: Peak Oxygen Uptake. MET-min/week: Total physical activity score across 4 different domains during a week in summer/winter= sum of Total Work + Total Transport + Total Domestic and Garden + Total Leisure-Time-MET-minutes-week-scores.

5.3 Demographic features – gender comparisons

This cross sectional study included 147 AS patients, 93 men and 54 women, aged 30-70 years. The demographic characteristics of the AS patients are presented in Table 6a. Median age was 48.5 years, and median disease duration was 22 years, ranging from 7 to 55 years. There were no significant differences in age and in disease duration between male (n=93) and female (n=54) patients. However, median age of the female patients was almost 9 years larger than median age of the males. With regard to smoking habits, 74 (50 %) of the total AS patient sample were lifelong non-smokers, 48 (32%) were ex-smokers and 26 (18%) were current smokers. There were no significant gender differences in smoking habits, but more men were lifelong non-smokers (53%) compared to women (32%), and the prevalence of current smokers was twice as high in women (26%) compared to men (13%). The education levels of both female and male patients were quite high; 66 individuals (44%) reported more than 4 years of university education. With regard to employment; 77 (82%) of the men were currently employed compared to 34 (63%) of the women, and this difference was significant ($p=0.002$). Further, a significantly higher number of women; 31 (59 %), compared to men; 26 (29 %), reported to receive social security benefit ($p<0.001$). Approximately 68% of the patients were married or living with a partner, but significantly more female patients were divorced or widowed, and significantly more male patients reported to be single ($p<0.001$).

Table 6a Demographic characteristics of the AS patients, gender comparison

Characteristics	AS Patients Total (n=147)	AS Patients Male (n=93)	AS Patients Female (n=54)	Gender difference p-value
Age (yr), median (range)	48.5 (30-70)	46.5 (31-70)	55 (30-68)	0.11[a]
Disease duration (yr)	22 (7-55) (n=101)	23 (7-55) (n=59)	21.5 (9-46) (n=42)	0.87[a]
Smoking habits				
Lifelong non-smoker (n) %	74 (50,0)	51 (54.3)	17 (31.5)	
Ex-smoker (n) %	48 (32.4)	31 (33.0)	23 (42.6)	0.06[c]
Current smoker (n) %	26 (17.6)	12 (12.8)	14 (25.9)	
Education level completed				
College (12 yr) or less (n) %	43 (29.5)	25 (26.6)	18 (33.3)	
< 4 yr University (n) %	37 (25.3)	20 (21.3)	17 (31.5)	0.16[c]
> 4 yr University (n) %	66 (44.2)	47 (50.0)	19 (35.2)	
Employment				
Currently employed (n) %	111 (76.6)	77 (81.9)	34 (63)	0.002[d]
Social security benefit (n) %	58 (39.4)	26 (28.6)	31 (58.5)	<0.001[d]
Marital status				
Married / cohabitant (n) %	99 (67.8)	62 (66)	37 (68.5)	
Divorced /widowed (n) %	19 (13.0)	6 (6.4)	13 (24.1)	<0.001[c]
Single (n) %	28 (18.9)	24 (25.5)	4 (7.4)	

[a] Mann Whitney U test. [b] Independent Sample T test. [c] Chi-square test for independence (χ). [d]Chi-square test for independence (χ) with Yates Correction for Continuity (2x2 table).

This study also included 121 population controls, 68 men and 53 women. The control group was randomly selected to match stratification of the patient group for age, sex and place of residence. Table 6b shows comparisons of demographic features for the AS patients and the population controls of same gender. There were no significant differences between the groups in age, anthropometrics, smoking habits or education levels, although male controls tended to be older (median age 55 years) than the male patients (median age 46.5). Significantly fewer female AS patients were currently employed compared to controls (p=0.02). The AS patients reported to receive social security benefit to a significantly larger extent than the controls, and this difference was present for both males (p=0.01) and females (p<0.001).

Table 6b Demographic characteristics of AS patients and population controls – comparisons of same gender

Characteristics	Male AS patients (n=93)	Male Controls (n=68)	P-value	Female AS patients (n=54)	Female controls (n=53)	P-value
Age (yr) median (range)	46.5 (31-70)	55 (30-69)	0.06[a]	55 (30-68)	57 (33-70)	0.13[a]
Height (cm) mean (SD)	178.2 (8.5)	178.9 (6.2)	0.56[b]	167.0 (7.7)	169.5 (6.2)	0.43[b]
Weight (kg)	82.5 (11.5)	83.5 (11.7)	0.59[b]	68.6 (12.7)	69.3 (12.0)	0.79[b]
BMI (kg/cm^2)	26.0 (3.3)	26.1 (3.3)	0.88[b]	24.4 (3.7)	25.2 (4.3)	0.40[b]
Smoking habits						
Never smoked (n) (%)	51 (54.3)	33 (48.5)		23 (42.6)	26 (49.0)	
Ex-smoker (n) (%)	31 (33)	21 (30.9)	0.41[c]	17 (31.5)	16 (30.2)	0.75[c]
Current smoker (n) (%)	12 (12.8)	14 (20.6)		14 (25.9)	11 (20.8)	
Education level completed						
≤ College (12 yr) (n) (%)	25 (27.2)	26 (39.4)		18 (33.3)	25 (47.2)	
< 4 yr University (n) (%)	20 (21.7)	15 (22.7)	0.20[c]	17 (31.5)	8 (15.1)	0.11[c]
> 4 yr University (n) (%)	47 (51.1)	25 (37.9)		19 (35.2)	20 (37.7)	
Employment						
Currently employed (n) (%)	77 (84.6)	55 (82.1)	0.84[d]	34 (63.0)	44 (84.6)	0.02[d]
Social security benefit (n) (%)	26 (28.6)	7 (10.4)	0.01[d]	31 (58.5)	8 (15.4)	0.001[d]
Marital status						
Married/cohabitant n (%)	62 (67.4)	45 (67.2)		37 (68.5)	26 (51.0)	
Divorced/widowed n (%)	6 (6.5)	12 (17.9)	0.04[c]	13 (24.1)	16 (31.4)	0.13[c]
Single n (%)	24 (26.1)	10 (14.9)		4 (7.4)	9 (17.6)	

[a] Mann-Whitney U test. [b] Independent Sample T-test. [c] Chi-square test for independence (χ). [d] Chi-square test for independence (χ) med Yates Correction for Continuity (2x2 table).

5.4 Pulmonary function – gender comparisons

Male AS patients had lower PFT scores than female patients after adjustments to age, sex and height, indicating a presence of more extensive pulmonary function impairments in males. The mean FVC% for males was 94%, varying from 53% to 136%, and correspondingly the mean FVC% for females was 102%, varying from 64% to 140% of predicted values. The mean FEV_1% for males was 89% of predicted values, varying from 52% to 126%, and the mean FEV_1% for females was 91%, varying from 61 to 121% of predicted values. When comparing PFT results in male and female AS patients (Table 7a), we found a significant

difference (p=0.007) only for FVC%; the marker parameter of restrictive pulmonary impairment. Accordingly, a larger proportion of the male patients; 21 (23%), compared to the female patients; 6 (11%), was categorized with restrictive ventilatory pattern, but the differences in the proportions of pulmonary impairment in male and female patients was not significant. Figure 13 illustrates the lower part of Table 7a.

Table 7a Results of pulmonary function test for the AS patients, gender comparison

Spirometry	**Male (n=93)**	**Female (n=54)**	**p-value**
FVC % (SD)(range)	94.1 (17.7) (53-136)	102.4 (17.9) (64-140)	0.007
FEV_1 %	89.1 (16.7) (52-126)	90.9 (14.9) (61-121)	0.53
PEF %	95.7 (18.6) (48-135)	94.2 (15.8) (58-124)	0.63
FEV_1/FVC %	76.6 (6.7) (61-93)	76.1 (8.8) (54-99)	0.66
Interpretation of PFT	**Male (n=93)**	**Female (n=54)**	**p-value**
Normal (n) (%)	66 (71.0)	39 (72.2)	1.00
Restrictive pattern (n) (%)	21 (22.6)	6 (11.1)	0.12
Obstructive pattern (n) (%)	6 (6.5)	9 (16.7)	0.09

FVC: Forced Vital Capacity, FEV_1: Forced Expiratory Volume in one second, PEF: Peak Expiratory Flow. Predicted percentages (FVC%, FEV_1%, PEF%) are adjusted to age, sex and height measured at time of testing. FEV_1/FVC %: derived from observed measures. Independent Sample T-test for comparison of mean values (continous variables), Chi-Square for counts

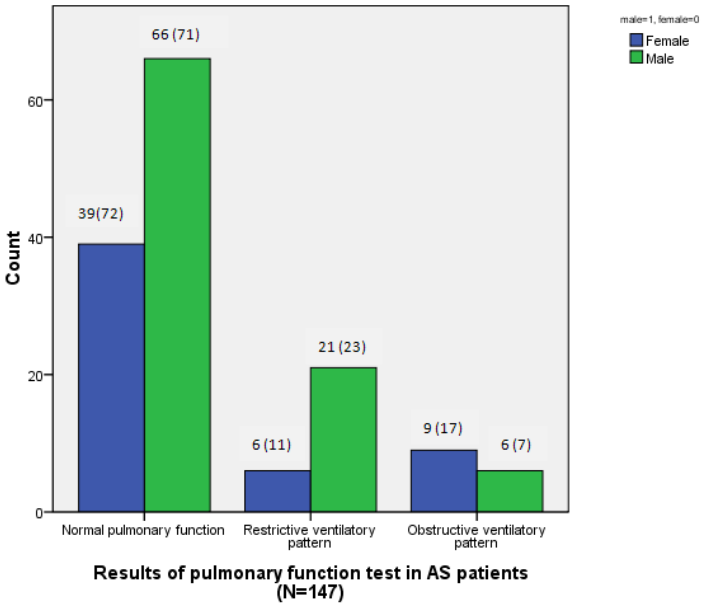


Figure 13 Pulmonary function in female (n=54) and male (n=93) AS patients, presented as counts (%). The majority of the male and female patients demonstrated a normal pulmonary function (71%). The prevalence of restrictive ventilatory pattern was twice as high in males (23%) compared to females (11%), and the prevalence

of obstructive ventilatory pattern was more than twice as high in female patients (17%) compared to male patients (7%).

Comparisons of PFT scores between AS patients and controls of same gender showed significant differences for males in all PFT parameters; FVC% (p=0.02), FEV_1% (p<0.001), and PEF% (p=0.04), except for the FEV_1/FVC% ratio, indicating a weaker pulmonary condition (not obstructive) in male AS patients compared to male controls. The proportion of restrictive ventilatory pattern was significantly higher (p<0.001) in male AS patients (n=21) compared to male controls (n=0). For females the comparisons of same gender showed significant differences in FVC% (p=0.008) and in FEV_1% (p=0.005) scores. 6 female AS patients presented a restrictive ventilatory pattern compared to 0 in the control group, and this difference was significant (p=0.03). There were no significant differences in the occurence of obstructive ventilatory pattern between patients and controls of same gender. The results are displayed in Table 7b.

Table 7b Results of pulmonary function tests for AS patients and population controls, same gender comparison

Spirometry	Male AS patients (n=93)	Male Controls (n=68)	p-value	Female AS patients (n=54)	Female controls (n=53)	p-value
	Mean (SD) (range)	Mean (SD) (range)		Mean (SD) (range)	Mean (SD) (range)	
FVC%	94.1 (17.7) (53-136)	100.3 (14.0) (62-130)	0.019	102.4 (17.9) (64-140)	110.9 (14.7) (71-138)	0.008
FEV_1%	89.1 (16.7) (52-126)	98.3 (15.3)(57-136)	<0.001	90.9 (14.9) (61-121)	98.8 (13.5)(66-127)	0.005
PEF%	95.7 (18.6) (48-135)	101.9 (18) (41-136)	0.037	94.2 (15.8) (58-124)	96.2 (14.1) (69-130)	0.483
FEV_1/FVC%	76.6 (6.7) (61-93)	78.4 (6.3) (59-93)	0.096	76.1 (8.8) (54-99)	75.7 (6.2) (60-90)	0.770
Interpretation of PFT	**Male AS patients (n=93)**	**Male Controls (n=68)**	**p-value**	**Female AS patients (n=54)**	**Female controls (n=53)**	**p-value**
Normal (n) (%)	66 (71.0)	63 (92.6)	0.001[a]	39 (72.2)	47 (88.7)	0.050[a]
Restrictive pattern (n) (%)	21 (22.6)	0	<0.001[b]	6 (11.1)	0	0.027[b]
Obstructive pattern (n) (%)	6 (6.5)	5 (7.4)	1.000[b]	9 (16.7)	6 (11.3)	0.579[a]

FEV_1: Forced Expiratory Volume in one second, FVC: Forced Vital Capacity, PEF: Peak Expiratory Flow. Predicted percentages (FEV_1 %, FVC %, PEF %) are adjusted to age, sex and height measured at time of testing. FEV_1/FVC % is derived from observed values. An Independent Sample T-test was conducted for comparison of mean values for continous variables, a [a]Chi Square test and a [b]Fisher's Exact test for counts.

Pulmonary comorbidity was recorded from self reported statements (yes/no). When comparing these data with the PFT results, we found that 85% of the AS patients with restrictive ventilatory pattern reported negatively to the question of having a pulmonary disease (Figure 14).

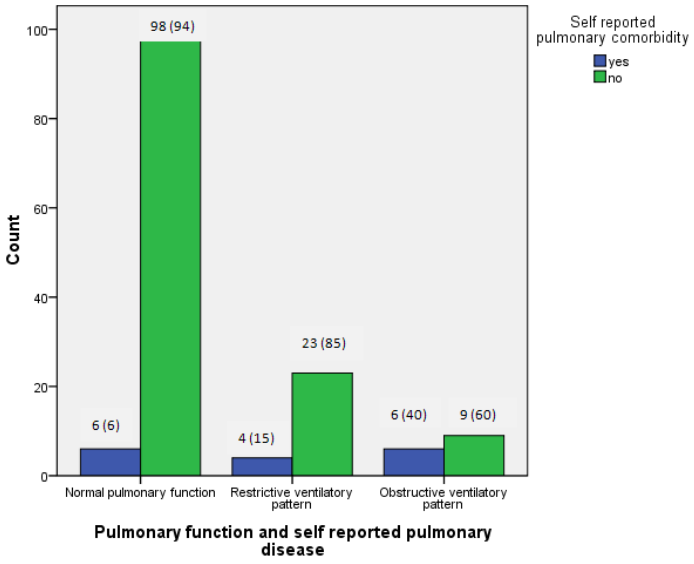


Figure 14 Self reported pulmonary disease and results of PFTs in AS patients (n=147), presented as counts (%).

5.5 Clinical features – gender comparisons

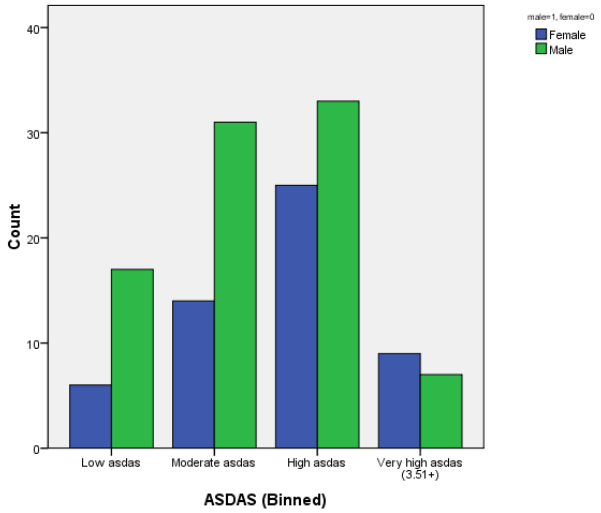
Table 8a shows gender comparisons of clinical test scores in the AS sample. Female patients reported significantly poorer health in terms of disease activity (ASDAS; p=0.02, BASDAI; p=0.002, ESR; p=0.009) and physical function (BASFI; p=0.02) compared to male patients. Nevertheless, most of the disease specific anthropometric measures (BASMI, Lumbar flexion, Lumbar lateral flexion and Chest expansion) showed no significant differences between the sexes, except for the Tragus to wall distance (p<0.001), the latter expressing that male patients were significantly more marked by increased dorsal kyphosis; a core feature in the AS disease. Further, as expected; males demonstrated a higher VO_{2peak} value than females. There were no significant gender differences in self reported physical activity (MET-min/week), although women reported a slightly higher activity level during a typical week in the summer, compared to men, and men reported a higher activity level during winter, compared to women.

The ASDAS scores for male and female patients are presented as both a continous measure (Table 8a) and in four categories (Figure 15); both variables showing a tendency to higher disease activity scores in female patients compared to male patients, the continous measure being significantly different (p=0.02).

Table 8a Results of clinical and laboratory tests for the AS patients, a gender comparison

Test	Total AS (n=147)	Male (n=93)	Female (n=54)	p-value
Age (yr), median (range)	48.5 (30-70)	46.5 (31-70)	55 (30-68)	0.11[a]
Disease duration (yr)[b]	22 (7-55) (n=101)	23 (7-55) (n=59)	21.5 (9-46) (n=42)	0.87[d]
ASDAS[a]	2.3 (0.9)	2.1 (0.9)	2.5 (0.9)	0.02[c]
BASDAI[a]	4.1 (2.0)	3.7 (1.9)	4.8 (2.1)	0.002[c]
CRP[b]	3.0 (1-57)	3.0 (1-57)	3.0 (1-52)	0.75[d]
ESR[b]	16.5 (1-90)	14 (1-90)	21.5 (3-67)	0.009[d]
BASFI[b]	2.1 (0-10)	1.8 (0-10)	2.6 (0-8)	0.02[d]
BASMI[a]	3.3 (1.8)	3.4 (2.1)	3.1 (1.4)	0.24[c]
Lumbar flexion (cm)[a]	4.0 (1.7)	3.9 (1.9)	4.2 (1.3)	0.18[c]
Lumbar lateral flexion (cm)[a]	13.2 (6.2)	13.0 (6.7)	13.6 (5.1)	0.60[c]
Tragus to wall distance(cm)[b]	12.3 (7.8-43.5)	14.0 (9-43.5)	10.6 (7.8-24.5)	<0.001[d]
Chest exspansion[xip] (cm)[a]	4.4 (2.2)	4.5 (2.1)	4.2 (2.3)	0.22[c]
VO_{2peak}[a]	39.4 (8.0)	41.9 (7.6)	35.3 (6.9)	<0.001[c]
MET-min/$week_{summer}$[b]	4292 (0-14438)	4217 (0-14438)	4470 (320-13278)	0.60[d]
MET-min/$week_{winter}$[b]	3210 (0-16355)	3396 (0-16355)	3015 (0-12078)	0.32[d]

[a]Mean (SD). [b]Median (range). [c]Independent Sample T-test. [d]Mann Whitney U test.
ASDAS: Ankylosing Spondylitis Disease Activity Score: Back pain +Duration morning stiffness + Peripheral pain/swelling (=BASDAI Q2, Q6 and Q3)+ Patient Global + CRP: Low score <1.3, moderate score: 1.3<2.1, high score: 2.1>3.5, very high score>3.5. BASDAI:The Bath Ankylosing Spondylitis Disease Activity Index (0-10, 10 worst). CRP: C-Reactive Protein. ESR: Erythrocyte Sedimentation Rate. BASFI: The Bath Ankylosing Spondylitis Functional Index (0 (easy)-10(impossible)). BASMI: The Bath Ankylosing Spondylitis Metrologi Index (0-10, low score indicates normal function). Chest expansion: Circumference of the chest (cm) measured at the level of proc xiphoideus; difference between maximum inspiration and expiration. VO_{2peak}: Peak Oxygen Uptake MET-minute/week: A total physical activity score across 4 different domains during a week in the summer/winter = sum of Total Work+ Total Transport +Total Domestic and Garden + Total Leisure-Time-MET-minutes/week -scores



ASDAS	Male	Female	p
Low (n) (%)	17 (19.3)	6 (11.1)	
Moderate	31 (35.2)	14 (25.9)	0.16[a]
High	33 (37.5)	25 (46.3)	
Very high	7 (8.0)	9 (16.7)	

[a]Chi Square Test

Figure 15 The ASDAS scores of the male and female AS patients. ASDAS=Ankylosing Spondylitis Disease Activity Score: Back pain +Duration morning stiffness + Peripheral pain/swelling (=BASDAI Q2, Q6 and Q3)+

Patient Global + CRP (C-Reactive Protein).); Low score <1.3, moderate score: 1.3<2.1, high score: 2.1>3.5, very high score>3.5.

The male AS patients scored significantly lower ($p<0.001$) on all clinical tests except for VO_{2peak} and self assessed physical activity, compared to population controls of same gender. When comparing female patients to female controls, the results where similar, but with slightly larger p-values on Chest expansion ($p=0.01$) and Lumbar flexion ($p=0.002$), and with a near significant difference ($p=0.052$) in median TWD values. The female patients had significantly poorer aerobic capacity (VO_{2peak}; $p=0.04$) compared to female controls, this in opposition to the findings in the male subset. There were no differences in self reported physical activity (MET-scores) (Table 8b).

Table 8b Results of clinical tests for AS patients and population controls, same gender comparison

Test	Male AS patients (n=93)	Male Controls (n=68)	p-value	Female AS patients (n=54)	Female controls (n=53)	p-value
Age (yr) median (range)	46.5 (31-70)	55 (30-69)	0.06[a]	55 (30-68)	57 (33-70)	0.13[a]
ASDAS[a]	2.1 (0.9)	-	-	2.5 (0.9)	-	-
BASDAI[a]	3.7 (1.9)	1.5 (1.2)	<0.001	4.8 (2.1)	2.1 (2.0)	<0.001[c]
CRP[b]	3.0 (1-57)	1 (1-37)	<0.001	3.0 (1-52)	1 (1-103)	<0.001[d]
ESR[b]	14(1-90)	6 (1-70)	<0.001	21.5 (3-67)	10 (2-67)	<0.001[d]
BASFI[b]	1.8 (0-10)	0.1 (0-3.4)	<0.001	2.6 (0-8)	0.3 (0-6.3)	<0.001[d]
BASMI[a]	3.4 (2.1)	1.6 (0.9)	<0.001	31.1 (1.4)	1.8 (0.9)	<0.001 [c]
Lumbar flexion (cm)[a]	3.9 (1.9)	5.1 (1.8)	<0.001	4.2 (1.3)	4.9 (0.8)	0.002[c]
Lumbar lateral flexion (cm)[a]	13.0 (6.7)	20.2 (4.1)	<0.001	13.6 (5.1)	18.8 (4.9)	<0.001[c]
Tragus to wall distance (cm)[a]	14.0 (9-43.5)	10.1 (8.8-25.0)	<0.001	10.6 (7.8-24.5)	9.8 (7.8-17.5)	0.052[d]
Chest expansion(cm)[a]	4.5 (2.1)	6.2 (2.3)	<0.001	4.2 (2.3)	5.2 (2.0)	0.01[c]
VO_{2peak}[a]	41.9 (7.6) (n=88)	42.1 (7.7)	0.31[c]	35.3 (6.9) (n=53)	38.1 (6.5)	0.04[c]
MET-min/$week_{summer}$[b]	4217 (0-14438)	4638 (0-17130)	0.52[d]	4470 (320-13278)	5274 (170-13518)	0.23[d]
MET-min/$week_{winter}$[b]	3396 (0-16355)	3155 (0-15423)	0.70[d]	3015 (0-12078)	3250 (120-10806)	0.69[d]

[a]Mean (SD).[b] Median (range). [c]Independent Sample T-test. [d]Mann Whitney U test.

ASDAS: Ankylosing Spondylitis Disease Activity Score: Back pain +Duration morning stiffness + Peripheral pain/swelling (=BASDAI Q2, Q6 and Q3) + Patient Global + CRP; Low score <1.3, moderate score: 1.3<2.1, high score: 2.1>3.5, very high score>3.5. BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index (sum score 0-10, 10 worst). BASFI: The Bath Ankylosing Spondylitis Functional Index (sumscore 0 (easy)-10 (impossible). CRP: C-Reactive Protein. ESR: Erythrocyte Sedimentation Rate BASMI: The Bath Ankylosing Spondylitis Metrologi Index (sumscore 0-10, 0= normal function). Chest expansion: Difference(cm) in circumference of the chest between maximum inspiration and expiration measured at the level of proc. xiphoideus. Lumbar flexion: modified Shober. VO_{2peak}: Peak Oxygen Uptake. MET-min/week: Total physical activity score across 4 different domains during a week in summer/winter= sum of Total Work + Total Transport + Total Domestic and Garden + Total Leisure-Time-MET-minutes-week-scores.

6 General discussion

A distinctive function of statistics is this: it enables the scientist to make a numerical evaluation of the uncertainty of his conclusion.

Snedecor, 1950 (154)

The discussion in this chapter will found on two major topics; *methodological aspects* and the *extended results*. Initially, an examination of potential strengths and sources of bias concerning the study sample, study design, methods for data collection and statistical procedures will be provided. Then, the previously presented extended results will be evaluated.

6.1 Methodological aspects

6.1.1 Study samples

The sample size influences the statistical conclusion validity. A large sample is more likely to be representative of the population, and tend to produce more accurate estimates than smaller samples (129). This study is strengthened by a relatively large sample size compared to previous studies of AS (Table 2, 1.2.1).

Selection of study samples influence the characteristics of samples, which in turn influence the generalizability, or external validity of studies. Sampling bias emerges with systematic over-representation or under-representation of some segment of the population in terms of characteristics relevant to the research question (129;156). The quality of the sample depends on how typical, or representative, the study participants are of the population to which one hope to generalize the results. For most human attributes, homogeneity is the exception rather that the rule, and variation in the population should therefore ideally be reflected in the sample. *External validity* concerns the persons, settings or times to which or across which the results of the study can be generalized, and threats to external validity can influence both the believability and utility of research (156). Selection bias is also one of the most frequently

encountered threats to the *internal validity* of studies not using an experimental design because preexisting differences between the attending groups may disrupt the results. When there is sampling bias, there is always a possibility that the results could be misleading or incorrect, and it should therefore be avoided (129;154;157).

6.1.2 The AS patients

The patients with AS in this study were recruited from a hospital based register in Oslo. The register was previously evaluated as representative according to a commonly reported prevalence of AS (0.1%) (3). A potential disadvantage of recruiting from hospital registers is that one may fail to include patients with mild disease, as patients with mild symptoms may not be enrolled in a hospital system. Another potential short-coming is that one may fail to incorporate the patients with the most severe disease symptoms, because of poor health. However, the ASDAS (Ankylosing Spondylitis Disease Activity Score) results in this study show that the patient cohort scores throughout the whole range of the disease activity scale, from low to very high disease activity.

A representative sample usually implies that the participants have a composition that reflects the study population to a great degree with regard to background variables like age, sex and social belonging (157). Although there are some differences between participants in this study and other study samples, especially concerning sex-ratios (67;77;109), smoking history and pulmonary comorbidity (71;77;78;83;109), the demographic characteristics, disease severity and disease duration of the present sample are comparable with cohort features in other relevant studies (71;75;77;78;85;104).

The patients in this study reside in an urban or sub-urban setting, which may influence the results, but the effect of this is uncertain. We made a rough examination of the non-responding AS patients with respect to the variables age, sex and place of residence, which showed that the non-responders were predominantly younger, male and were more likely to live in the eastern part of Oslo compared to the responders.

A strength of this sampling method is that all the included patients had their diagnoses confirmed by a rheumatologist according to the New York criteria. This improves the basis

for comparison with other patient cohorts. In the light of the given information, we presume that the results of this study can be generalized to AS patients in similar cohorts.

6.1.3 The population controls

The population controls without arthritis were randomly selected from the national register by Statistics Norway to match stratification of the patients for age, sex and place of residence on a group level. Stratified sampling is utilized when certain subgroups must be represented in adequate numbers within the sample, or to preserve the proportions of sub-groups within the sample (156). Random selection secures equal probability of participation in the study for potential subjects (158), and was used to produce a random distribution of the population controls' characteristics. However, the controls turned out to be significantly younger than the AS patients (Table 1, Paper). This may affect the results by reducing the differences between patients and controls; for example in PFT variables that are influenced by aging.

There is likely to be less willingness among healthy people to participate in a study than among patients, and this may possibly introduce a bias. Factors like self-interest, reward, strain in terms of waste of time, physical dislikes and perhaps financial costs, as well as attitudes about the importance of the research subject, may influence the potential participants' willingness to contribute. The prospect of having a thorough health examination may contribute to increase the attendance (158). We found that the non-responders in the control group had the same characteristics as the non-responders in the patient group; they were significantly younger, predominantly male and living in the eastern part of Oslo compared to the responders. A similar observation has been done previously in a study of health in Oslo (159) which showed that attendance to the project increased with increasing age, and was higher among women compared to men (158). Nevertheless, the non-responding patients and controls in this study appeared to be similar with respect to basic characteristics. We presume that the test results of the population controls can be considered applicable for use as reference data in this project.

6.1.4 Study design

The study was carried out to investigate the prevalence of pulmonary function disorders in AS patients, describe possible differences between AS patients and population controls with respect to PFT variables and explore associations between PFT variables and disease specific variables in AS patients. To meet the research questions, a cross sectional design with a control group was considered appropriate. The participants were investigated on one occasion only, which means that data were collected at one point in time. Cross sectional studies are suitable for describing the status of phenomena and for describing the relationship among phenomena at a fixed point in time (129;158), and provide a snap-shot view of a single sample measured once (156).

A particular limitation of cross sectional studies investigating associations with disease is that one cannot draw a clear inference of causality because all the information is collected at once (154). A criterion for inferring a causal relationship is that the cause must precede the effect. Further, only prevalent and not incident cases are included. The advantages of cross sectional studies are that they are practical, relatively cost-effective in terms of time and economy and easy to administer, creating large amounts of information fast with moderate resources (129;158).

6.1.5 Methods of data collection

The conclusions in the present thesis are based upon data from self-administered questionnaires (subjective) and observed measures (objective). The different methods of data collection may strengthen the validity of the results. Validity refers to the meaningfulness of test scores as they are used for specific purposes (156). Measurement of variables should be valid, accurate and precise. Errors can be made when measurements are taken, when the data are originally recorded or when being typed into the computer. Random variations in different variables occur naturally in an individual, but sources of systematic bias must be identified and eliminated (160). Internal validity refers to valid inference to the study population; i.e. to the extent to which it is possible to make an inference that the independent variable is truly causing or influencing the dependent variable and that the relationship between the two is not the false effect of a confounding variable (129). Possible information bias, confounding

variables and sampling bias are central concepts in the discussion of the internal validity of a study.

An instrument does not possess or lack validity; it is more a question of degree. Some instruments may be valid for a wide range of uses with different kinds of samples, but each use requires new supporting evidence. The more supporting evidence, the more confidence can be placed in that an instrument is measuring what it is supposed to be measuring (129).

Pulmonary function test

Spirometry has been standardized for application to a wide range of study populations (122), but we are not familiar with any specific validation study for spirometry applied to AS patients. However, standard procedures were followed strictly during data collection (see 3.4.2.2) (122), which increase the accuracy of pulmonary function measures in this project and make them comparable with measures in studies using the same procedures.

Spirometric test results are dependent upon instruction and subject cooperation. Therefore FEV_1 and FVC can only be underestimated, never overestimated (113). FEV_1 is the most repeatable parameter (124), whereas FVC is the most vulnerable to sub-maximal effort and it may also drop because of airway obstruction (89), which in turn may influence the FEV_1/FVC ratio. Inadequate tests may lead to erroneous conclusions; e.g. that the patient has a ventilatory disorder when this is not the case, or the other way around (113).

Spirometry is a test of function, but the most common lung diseases are defined in terms of structure (emphysema) or symptoms (chronic bronchitis), suggesting methodological limitations of spirometry (121). Further, the gold-standard definition of restrictive pulmonary disease requires measurement of total lung capacity (TLC). Spirometry is very effective at excluding a restrictive defect, but a classic restrictive pattern on spirometry does not accurately predict a true restrictive defect because it represents a true restriction in only <60% of cases (120). Thus, measurement of lung volumes (TLC) is necessary to confirm a restrictive impairment (124). A potential criticism of our study is that TLC measurements were not performed. The true prevalence of restrictive impairment in this material is probably even smaller than what appears by the results of the tests we have carried out. Lung volume data would have provided a precise estimate.

In accordance with the literature, we suspected a presence of a restrictive ventilatory defect when FVC was reduced, the FEV_1/FVC ratio was normal or increased and the flow-volume-curve showed a convex pattern (89;120;124) (3.4.2.3, Figure 6 and Figure 7). The cut-off value for FVC% vas set at 80% of predicted, not narrower than cut-off values given in other reports (Table 2), but a cut-off value at 75% would have provided a smaller prevalence of restrictive impairments in this material. In order to make the data statistically manageable we did not categorize the severity of lung function impairment (i.e. mild, moderate, severe), although this would have produced a more nuanced picture of the lung function status in the present sample. However, the standard deviations (SD) and ranges given for the mean PFT measures provide information on the variability of the results.

We did not produce a category for mixed abnormalities in this study. A mixed ventilatory defect is characterized by the coexistence of obstruction and restriction (124), defined by reduced TLC and reduced FEV_1/FVC ratio. There were four cases of possible mixed abnormalities among the AS patients in our sample; all had FVC scores well below 80% of predicted combined with a FEV_1/FVC ratio just below 0.7. Because FVC may be equally reduced in both obstruction and restriction (Figure 7), we evaluated the individual flow-volume-curves before categorization, and we let the FVC% score overrule the ratio. All four cases of doubt were categorized with restrictive ventilatory pattern. A previously published equation to account for the effects of airflow obstruction on the observed FVC (161) found that in patients with an FEV_1/FVC ratio < 70%, obstruction explained 15 to 17% of the variability in FVC% (120;161). A statistical adjustment for the effects of obstruction could further have reduced the prevalence of restrictivity in this material.

A special challenge when measuring pulmonary function in AS patients concerns the parameter height. Lung volumes are related to body size, and standing height is the most important correlating variable (124). Patients with AS often loose height due to increasing dorsal kyphosis as the disease progresses[2]. Two previous studies (74;100) used patients'

[2] We did collect data on original height. All participants were contacted by telephone after the examinations and asked for information on original height. Original height was compared to height measured at time of testing, and the difference calculated. A difference < 2 cm was considered insignificant as measured height may vary at different times of the day. The difference in original and measured height correlated well with the tragus to wall distance (TWD), which expresses increased dorsal kyphosis (r_s= 0.52, p<0.001), indicating a connection between loss of height and increased dorsal curvature.

original height to calculate predicted normal values, and one study calculated height from arm span measurement (162). As the reliability of recalled and stated height may be questionable, we used height measured at time of testing, in accordance with the ATS/ERS guidelines (124), although the consequence may be that we may have failed to discover some cases of restrictive pulmonary impairment.

Information on bronchodilator use was not recorded. The patients' primary diagnosis was rheumatologic, not pulmonary, but some patients reported pulmonary comorbidity. In these cases, if the pulmonary comorbidity was that of COPD, PFT should probably have been performed after administration of a fast-acting bronchodilator drug, in order to improve the conditions for a best possible performance (113). When testing patients with pulmonary disease as primary diagnosis, alternative and more appropriate reference data is required (163;164). The use of NSAIDs, steroids and TNF-blockers in AS patients was recorded. These drugs may indirectly influence the PFT results through reducing pain, inflammation and disease activity, making conditions better for patients with severe functional limitations. The aspect of drugs in relation to spirometry will not be subject to further examinations because it is beyond the scope of this thesis.

Disease specific measures

The disease specific instruments used in this study have been constructed to measure physical limitations (138), disease activity (132;133) and range of motion (140;145;146) in patients with AS. The instruments are included in the core set recommended for research and clinical practice in this patient group (3;165;166). They are all well established and widely used instruments in research on pulmonary function in AS patients, and we considered them appropriate in this project for patient characterization (with an eye to representativeness) and comparative purposes. The use of previously validated questionnaires increases the quality of the study (167).

Numeric rating scales (NRS)

The indexes of the latest version of the Bath Ankylosing Spondylitis (BAS) instruments are made up of NRS results. We used a 0-10 NRS (11-point scale) with ascending numbers in boxes that were anchored with two extremes at either end (Appendix 7, 8). The participants marked their answers by putting a cross through the appropriate number. Original versions of the BAS instruments were completed on VAS (168), but risks of error have been pointed out during measurement on the line, and photocopying the scale may alter its length. Several reports have suggested that the NRS is less time consuming, easier to administer and score than the VAS, and it can therefore be used in a greater variety of patients (169;170). Furthermore, the NRS has been shown to be as sensitive as the VAS because little information is lost when a 101-point NRS is transformed to an 11-point NRS (168). Some reports indicate that the NRS is even more responsive to change than the VAS in patients with chronic back pain (171;172). The primary weakness of the NRS is that it may not have ratio qualities as opposed to the VAS (170), but it does produce interval level data that can be used in parametric analysis (169). Overall, the 0-10 NRS is a simple and robust measurement method that has many advantages over the alternatives for clinical use and research (169;170).

Survey research

The questionnaires used in this study are comprehensive, and completing them properly requires consentration, honesty and mental effort. Questionnaires may fail bacause participants cannot complete them, get bored or offended or dislike how they look (173). When preparing the questionnaire we considered the order and placement of the different questions and instruments, as well as the content of instruments and a simple reader-friendly layout.

The questionnaires were identical in content, but slightly different ordered for patients and controls. To evoke the interest of the patients, we placed the disease-specific instruments first. We did not expect the control group to have problems with back pain, and to arouse their attention we initiated the questionnaire with questions concerning general health. It is possible that the order of the overall and disease specific health status questionnaires may influence the responses, although such evidence was not found in a previous study (174). Demographic

questions may be percieived as highly sensitive, and were placed in the middle of the form to minimize potential threats to participants (175).

Most of the data were recorded by self-completation, but information concerning comorbidity and medication was recorded with help from a health worker. The participants were ensured with privacy and quiet surroundings when they completed the questionnaires, and with anonymity when analysing the responses. Prior to the examinations, the participants were notified with a personal invitation where the objective of the study, the content of the questionnaires and the expected time frame were explained (Appendix 1 and 2). All these factors are shown to increase response rates (173). We experienced very good respons rates to the questionnaires with minimal loss of data, which respresents a strength of this study.

The IPAQ-Long form (Appendix 11) was used to gather information on physical activity. Questions regarding physical activity may be understood differently by different people, in different times and cultures (157), which in turn may influence the generalizability of the results. Huge variations in general population median MET-hours/week-scores have been reported across different European countries; ranging from the lowest 11.6 (Ireland), 18.7 (Sweden), 33.9 (Western Germany) to the highest 39.4 (France). Inconsistence between studies may be connected to measurement problems, as well as conceptual differences in the assessment of physical activity (176). The IPAQ-L is a standarized measure developed for assessing physical activity in different populations (www.ipaq.ki.se), which represents a strength when used in this study, but it has not been clinically validated for the AS patient group, which may be considered a weakness.

Clinical examinations

The clinical examinations in this study included tests that are usually applied in clinical practice and are well known to patients with AS. The tests do normally not involve pain or effort and should therefore potentially measure the ‘true’ range of motion (3). The BASMI and its components have shown good intra- and intertester reliability (128;144;145), and high correlation with radiographic scores (BASMI total; Pearson r=0.74) (141). However, despite that decreased spinal mobility is associated with radiographic damage of the spine in AS

patients, the spinal mobility measures cannot be a proxy for the assessment of spinal structural damage by radiography (143).

We used the newly developed version of BASMI, which show fewer floor effects, i.e. is able to show changes in patients with limited restrictions, compared to the previous version. Further, it is more practical in computer evaluations in clinical trials due to metric advantages because it behaves like a linear continous measure (142).

The laboratory tests (CRP, ESR) have previously shown limited value in the determination of disease activity in AS patients (4;6). In this study, the inflammatory markers showed weak correlations with the pulmonary function variables, which may confirm their restricted relevance.

Aerobic capacity, or cardio-respiratory fitness, was assessed with a recommended and well known field test (The Balke modified protocol; Appendix 10). Possible limitations of a field test may be poorer validity, reliability and accuracy compared to the gold standard test of aerobic capacity, which involves direct measurement of maximal oxygen uptake during maximal work load performed in a laboratory setting. In this project, peak oxygen uptake was estimated based on the work load at the end of the treadmill test. Low accuracy may have complicated the detection of differences between the groups in the present study. However, the face validity of the test may be acceptable since the participants walked the treadmill until exhaustion (RPE).

6.1.6 Statistical issues

Prior to designing the study, a power calculation was performed to establish the number of population controls, based on the distribution of scores (mean, SD) and difference between patients and the general population in a self-reported general health questionnaire (SF-36) (177). According to this calculation, we aimed at recruiting 120 population controls to match the patients, which was estimated necessary to reliably show clinically significant group differences with a significance level of 5% and a statistical power of 80%. We therefore presumed that our sample of 147 AS patients and 121 controls was large enough to reveal clinically valuable findings, if they existed, and to reasonably ensure that no differences

existed, if they were not found. The probability of making a Type II error (a false negative result) is minimized with an acceptable power value (156).

The cut-off level for statistical significance was set at 0.05. In the paper, pulmonary function measures were reported as means with 95% CIs of the differences. The 95% confidence intervals show the uncertainty, or lack of precision, in the estimates, and thus express more useful information than the p-values. The p-value and the CI are related as p will be less than 0.05 (significant) only when the 95% CI does not include zero (the value specified in the null hypothesis). According to Altman (1991), the presentation of both the actual p-value and the CI is desirable (154). In order to decrease the probability of making a Type I error (e.g. rejecting the null hypothesis when it is actually true), the stated significance level could have been more conservative (e.g. 1%) (178). On the other hand, the relatively large sample size contributes to minimize the risk of making a Type I error (157).

Univariate ANCOVAs (analysis of covariance) were performed to explore group differences in pulmonary function measures and to adjust for relevant background variables. ANCOVAs can result in more precise estimates, and can often improve the internal validity of a study (129). In the paper, we used multivariate linear regression analysis to estimate associations between various independent variables and FVC% as the continous dependent variable. Multivariate regression techniques are constructed to analyze complex relationships among different variables (156). When building the model, we used a backward stepwise regression strategy; which implies initially putting all the selected variables (believed to be important explanatory variables) into the equation and then delete them one at a time if their presence does not contribute significantly (154). Stepwise regression involves empirically selecting the combination of independent variables with the most predictive power. The procedure is somewhat controversial because variables are entered into the equation based on statistical, rather than theoretical criteria (129). Alternative types of analysis would be standard multiple regression (all independent variables entered simoultaneously) and hierarchical multiple regression (independent variables entered in order specified by researcher based on theoretical grounds) (179).

6.2 Extended results

6.2.1 Pulmonary function and clinical findings

The literature describes different theories of possible reasons for restrictive pulmonary function in AS, including inflammation or fusion of the thoracic joints resulting in pain and chest wall rigidity (see 1.2 for thorough examination of the subject). The results in this study supports the assumption of a connection between the musculoskeletal limitations in AS and restrictive pulmonary impairment.

The strongest association was observed between FVC% (hallmark of restrictive pattern) and BASMI ($r=-0.57$, $p<0.001$). The BASMI components tragus to wall distance (TWD, $r_s=-0.48$), lumbar flexion (LF, $r=-0.50$) and lumbar lateral flexion (LLF, $r=-0.52$) also correlated well separately with FVC%, while inter-malleolar distance (IMD) correlated poorly ($r_s=-0.20$) with FVC%, indicating that hip mobility is of less importance in this context.

A strong association was noted between FVC% and thoracic mobility (CE, $r=0.48$, $p<0.001$). This finding is in agreement with several other studies (71;73;180;181), and supports the assumptions of restrictive pulmonary impairment being connected with reduced chest wall mobility.

Measures of acute inflammation (ESR) and disease activity (ASDAS, BASDAI) did not correlate with FVC%. This finding is in opposition to previous reports claiming that ongoing inflammation in the thoracic joints, by causing pain and stiffness contribute to reduced pulmonary function (69;77;84;85). The results in the present study favour mechanical rather than inflammatory causes responsible for restrictive pulmonary function in AS (78;79).

6.2.2 Smoking

The prevalence of smokers in the total patient sample (18%) was lower than other reports from general populations in Oslo (182), but smoking habits did not differ between patients and controls in the present sample (Table 1, Paper).

Smoking is associated with increased counts of macrophages and neutrophils in the lung parenchyma, and may worsen existing lung disease in AS patients (69). However, the present

study showed no significant differences in pulmonary function, self reported pulmonary disease or physical function between AS patients who never smoked and current smokers/ex-smokers. This result is in agreement with previous reports (67;70;71;73;77).

Surprisingly, we found significant differences between lifelong non-smokers and smokers/ex-smokers concerning all measures of acute inflammation and disease activity, indicating that smoking is connected to the general inflammatory processes in AS. Further, never-smokers had significantly better chest wall mobility compared to smokers/ex-smokers, and better aerobic capacity. Earlier reports on pulmonary function in AS found no differences in disease activity between smokers and non-smokers (71;77). However, associations between smoking and more rapid disease progression and poor long-term outcome have been described (48;183).

6.2.3 Physical capacity

Aerobic capacity (VO_{2peak}) was significantly reduced in the AS patients compared to the controls ($p=0.002$) (Table 1, Paper), which means that the patients were characterized with a lesser work capacity or exercise tolerance. Exercise tolerance (VO_{2max}) has been reported to correlate directly with changes in vital capacity (VC) (45). Fisher et al found a significant association between VC and chest expansion, and between VC and aerobic capacity in AS patients (74). Sedentary patients (non-exercisers) had significantly lower VC and VO_{2max} compared to active patients (exercisers). The study suggested that patients who took a modest amount of exercise regularly could maintain a satisfactory work capacity despite very reduced spinal and chest wall mobility. The present study confirms earlier findings with respect to significant associations between aerobic capacity and pulmonary function measures (Table 4), although with a small correlation coefficient for FVC% ($r=0.25$, $p<0.001$).

Chest expansion was associated with VO_{2peak} ($r=0.35$, $p<0.001$) in the patient group (data not shown), This is in opposition to earlier reports; which, however, were based on relatively small numbers of participants, 33 and 20 respectively (67;74). We believe that the present study, providing a larger sample of 147 patients, may have produced a more accurate estimate. The results from the present study indicate that aerobic capacity, or work capacity is influenced by limitation of chest wall mobility in AS patients.

6.2.4 Physical activity

Regarding the total sample, there were no significant differences in self reported physical activity (MET-score) between the AS patients and the population controls. Both patients and controls reported very high values, representing very high levels of physical activity across several domains of everyday life. The median value was 4292 MET-min/week during an ordinary week in the summer, which corresponds with 71.5 MET-hours/week, or 10.2 MET-hours/day. This portrays the AS sample as being very physical active.

AS patients often feel urge to move due to stiffness symptoms and tend to feel better after engaging in physical activity. Furthermore, current treatment guidelines for AS recommend exercise as part of the disease management (54-56). The high MET-scores may be products of patients acting in, or responding in ways compliant with health workers recommendations. On the other hand, the controls without arthritis did probably not have such obvious reasons for exercising, other than general health benefits, counterbalancing the results.

Socio economical status (SES) may be relevant here. The tendency to promote a healthy lifestyle including more physical activity is generally more pronounced in people with higher education levels, and physical active lifestyles are reported to be more frequent in affluent areas than in poorer parts of Oslo (184). A previous study showed that well educated (>13 years) patients with rheumatic disease tended to participate in more self-care activities, including regular exercise, than those with lesser education (185). In the present study, the patients had slightly higher levels of education compared to the controls. Better-educated patients may be more likely to optimise their own health status and reduce the impact of their disease (3). Better patient health may lead to a reduction in differences between patients and controls.

There is no formal consensus on a “correct” method for defining levels of physical activity based on self-report population surveys (152). Even though an instrument may demonstrate acceptable measurement properties in a variety of studies, it can be difficult to generalize in new study populations (186;187). We find it likely that physical activity, a socially desirable behaviour, has been over-reported on the IPAQ-questionnaire, by both the patients and the population controls. A corresponding conclusion was reached in a previous health study in Oslo in which very high IPAQ scores were observed (188).

6.2.5 Gender comparisons

AS has always been considered to be a disease that largely affected men, but recent studies have shown that a significant proportion of the patients are women, with a ratio of men to women approaching 2-3:1 (19). There is now much evidence that women, especially those with a negative family history, have been underdiagnosed in former decades (184). Previous studies suggest differences in the expression of the AS disease between the genders. Presumably, women have a later onset of disease, milder disease course, longer asymptomatic periods, more extra-spinal involvement and more peripheral joint involvement (3;4;17). However, we are not familiar with any studies comparing pulmonary function in male and female AS patients. The relatively large sample size in this study provide better conditions for exploring possible differences in sub-groups of the sample, like gender differences. Therefore, to better understand the potential influence of gender in determining pulmonary function in AS, we found it necessary to characterise pulmonary function in male and female AS patients, and compare the results to population controls of similar group characteristics.

Background factors

Female AS patients in this study were older than male patients, and they were more frequently smokers. Both aging and smoking are factors that influence pulmonary function (113;185). PFTs revealed a higher prevalence of obstructive ventilatory impairment in female compared to male patients, but this difference was not significant.

Female patients reported lower participation in working life, larger degree of sickliness and larger consumption of social security benefits compared to males. These findings are in agreement with earlier reports (3;19;24;25;186). However, the employment rate among male patients was rather high (82%) compared to other studies (28), and so was the education level; 50% of the males reported more than 4 years university education. Formal education is one component of socioeconomic status (SES), most often correlated with income, occupation and living conditions. The education level is unlikely to be a causative factor, but may be representative of other variables influencing health, such as work strain, access to medical care, health habits and overall lifestyle (187). Thus, SES may indirectly influence both disease

severity and prognosis in AS, as well as pulmonary function measures (27;126;188;189). In this material, it is uncertain whether and in what way SES may influence gender differences.

When comparing patients and controls of same gender with respect to background variables no significant differences were found in age, anthropometrics, smoking habits or education levels. In the case of the variable age; male controls were approximately 9 years older than the male patients, and the lack of significant difference may be ascribed to lowered power (possible Type II error). This finding reveals a possible sampling bias, as we seem to have failed to include a sufficient number of younger male controls. The older age of the male controls may influence both clinical and pulmonary function measures. Possible existing or 'true' differences between patients and controls may disappear, or appear less prominent. However, the parameters FVC%, FEV_1% and PEF% all showed significant differences between male patients and male controls, and the proportion of restrictive ventilatory impairment was significantly higher ($p<0.001$) in male patients compared to male controls. Likewise, the disease specific clinical measures and laboratory test all showed highly significant differences ($p<0.001$) between male patients and male controls. This indicates clarity in the observed differences between male patients and controls.

Pulmonary function

Several pulmonary disorders have been described in patients with AS, and these can be associated with significant morbidity and mortality (30;45;190). In general, the ability to work and function in daily life is related to pulmonary function, and patients with reduced function have more respiratory complaints. Further, pulmonary function level is associated with prognosis and morbidity, including fatal outcome from heart and lung disease. In several occupational cohorts, the variables FEV_1 and FEV_1/FVC have been independent predictors of all-cause or respiratory disease mortality (124).

Male patients had lower % of predicted PFT scores than female patients, and over twice as many male patients (23%) compared to female patients (11%) were categorized with restrictive impairment, but the differences in proportions were not significant. Possible interpretations of this result may be that we were not able to produce significant results due to

the reduced power of a small sub-group (male=21, female=6), or that the gender differences in pulmonary function are subtle.

The study revealed significant differences in pulmonary function between patients and controls (see Paper), which were maintained through separate gender analysis. When comparing male patients to male controls, the PFT scores showed highly significant differences ($p<0.001$), as male patients were far more likely to have a restrictive impairment (n=21) compared to controls (n=0). Similar results were found for females ($p<0.03$) as more patients (n=6) were categorized with restrictive impairment compared to controls (n=0). Because we have used a cross sectional design, we are not able to explain the cause of these findings, but previous studies have suggested a connection between disease specific characteristics of AS and restrictive pulmonary impairment (46;68;73;74).

Clinical measures

All the disease specific clinical measures and laboratory tests were significantly lower for AS patients compared to controls regarding the total material (Table 1, Paper). This indicates that the disease specific instruments worked well in differentiating healthy subjects from ill, and that the present sample is characterized by typical features representative of the study population.

Female patients reported significantly poorer health in terms of disease activity (ASDAS, BASDAI) and physical function (BASFI) compared to males. There were no significant gender differences in spinal mobility (BASMI and components), but the occurence of increased dorsal kyphosis (TWD) was significantly more prominent in males. These findings are in accordance with previous reports, and corresponds with a general tendency of women to report more impact of chronic disease than men (3). Lee et al (19) conducted a literature review of 27 gender studies in AS from 1966 to 2005 and performed clinical examinations in 302 men and 100 women having AS for ≥ 20 years, and found that women may have more peripheral arthritis and tend to have less thoracic and lumbar spinal radiographic changes, and that men have significantly more severe radiographic changes in spite of similar disease duration. Further, at any given level of radiographic damage, women reported worse functional outcome (BASFI). The discrepancy between radiographic damage and reporting of

function may be a consequence of women having more peripheral arthritis (19). This may also be the case in our study. We did not perform radiographic examinations, but the spinal mobility measures (BASMI and components) were better in women compared to men, indicating less severe spinal involvement in women, although the differences were not significant. Paradoxically, chest expansion was slightly better in men, but not significantly. However, women were almost 9 years older in our patient cohort. When correcting measurements of chest expansion for age and gender; age, but not gender, was exposed as a confounding factor. The variable age is probably influencing more of the clinical test results, making existing gender differences less clear.

Same gender comparisons exposed highly significant differences between male patients and male controls in all clinical test ($p<0.001$). Measures of aerobic capacity deviate from this picture; there was no difference between males in VO_{2peak} , but older age of the controls disturb this result. For females, the results were similar, but with lower p-values, a non (near) significant difference in TWD, and a significant difference in VO_{2peak} . Male patients differed more from controls than female patients differed from female controls. The results suggest that the impact of AS is larger in males, and that increased dorsal kyphosis is a less prominent feature in female patients compared to male patients. Conclusively, these results demonstrate highly significant differences in disease activity, inflammatory markers, physical function, spinal mobility and chest expansability between patients and population controls of same gender.

7 Conclusion

The study exposed significantly reduced pulmonary function in AS patients compared with population controls and with reference data. Restrictive ventilatory impairment measured by spirometry was found in 18% of the patients, but in none of the population controls. The observed prevalence of restrictive impairment was lower compared to earlier reports, but due to a relatively large sample size we think that our estimate is reliable. Obstructive ventilatory impairment was found in 10% of the participants with no significant difference between patients and controls.

The strongest bivariate associations observed were between FVC% (the hallmark of restrictive pulmonary disease) and spinal mobility, and between FVC% and chest expansion. Male sex, spinal- and chest wall mobility explained nearly half of the variation (46%) in pulmonary function in a multiple regression model, whereas measures of disease activity, physical function, VO_{2peak}, smoking and disease duration did not contribute significantly. The results support the assumption of a connection between musculoskeletal limitations and restrictive pulmonary impairment in AS, and suggest that gender is of considerable importance to pulmonary function in this patient group.

Male AS patients generally had lower pulmonary function scores than female patients after adjustments to age, sex and height, and a significant difference between male and female patients was found in FVC%. Accordingly, a larger proportion of the male patients (23%) was categorized with restrictive impairment compared to the female patients (11%), but the difference in proportions was not significant.

Same gender comparisons revealed significant differences in pulmonary function, as both male and female patients were far more likely to have restrictive impairments compared to controls. Further, highly significant differences in disease activity, inflammatory markers, physical function, spinal mobility and chest expansability were found between patients and controls of same gender.

7.1 Clinical implications and further research

The results in the present study support the theory of mechanical, rather than inflammatory, causes responsible for restrictive pulmonary impairment in AS. Reduced spinal- and chest wall mobility was strongly and significantly associated with restrictive impairment. The results therefore emphasize that mobility exercises with focus on maintaining or increasing thoracic and spinal flexibility in patients with AS, still should be important tools in the disease management. However, the effects of mobility exercise and aerobic exercise on pulmonary function in AS patients remain to be explored. In the light of the existing knowledge, there may be reason to further examine different exercise modes on pulmonary function in this patient group.

85 % of the patients with restrictive ventilatory impairment were not aware of having a pulmonary disease. This finding makes visible a need for patient education, or for empowering patients with decision knowledge. Knowledge is an important factor concerning the ability to manage, or limit, the consequences of chronic disease. On the other hand, the finding may also indicate that the patients with restrictive impairment were not severely afflicted by it. Thus, the problem may be less relevant to the clinical situation. However, patients with severely reduced spinal- or chest wall mobility should be referred to examinations of pulmonary function and relevant follow-up treatment.

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9 Appendix

Overview of appendixes

Appendix 1: Enquiry about participation and written patient information for informed consent (Forespørsel, informasjonsskriv og samtykkeskjema for pasienter)

Appendix 2: Enquiry about participation and written information for informed consent, population controls (Forespørsel, informasjonsskriv og samtykkeskjema for kontrollpersoner)

Appendix 3: Recommendation from The National Committee for Medical Research Ethics, Southern Norway, Oslo (Tilrådning fra REK S-02059, 14.03 2002)

Appendix 4: Recommendation from The National Committee for Medical Research Ethics, Southern Norway, Oslo (Tilrådning fra REK S-03066, 08.04 2003)

Appendix 5: Letter from The National Committee for Medical Research Ethics, Southern Norway, Oslo (Brev fra REK S-03066 /S-02059, 19.01 2008)

Appendix 6: Licence to register and store individual health information; The Data Inspectorate, Norway (Konsesjon til å behandle helseopplysninger; Datatilsynet 11.03 2008)

Appendix 7: Form for registration of BASDAI (Q 1-6)

Appendix 8: Form for registration of BASFI (Q 1-10)

Appendix 9: Form for registration of BASMI

Appendix 10: The Balke protocol

Appendix 11: IPAQ Long-form

Appendix 12: Form for registration of pulmonary function test results (spirometry) (example)

Appendix 13: Flow-time curve (example)

Appendix 14: Flow-volume curve (example)

Appendix 1: Enquiry about participation and written patient information for informed consent

Informasjon og forespørsel om deltakelse i forskningsprosjektet:

"Konsekvenser av Bekhterev sykdom"

Hensikten med studien

Du får denne henvendelsen fordi du har Bekhterev sykdom og tidligere er undersøkt/behandlet ved revmatologisk avdeling, Diakonhjemmet Sykehus. Du samtykket den gangen til å stå registrert i Bekhterev-registeret.

Vi vil med dette spørre deg om du vil delta i en oppfølgingsstudie. Hensikten er å kartlegge helsestatus og eventuelle sykdomskomplikasjoner hos en stor gruppe pasienter med Bekhterev sykdom som deltok i en spørreundersøkelse i 2002.

Dersom du IKKE ønsker å delta i studien, så ber vi deg likevel gi beskjed dersom du IKKE ønsker å stå registrert i Bekhterev-registeret til desember 2025. Om du ikke gir slik beskjed vil opplysningene bli brukt til fremtidig forskning innenfor rammen av ditt tidligere samtykke.

Du bestemmer selv

Det er frivillig å delta i oppfølgingsstudien. Dersom du velger å ikke delta, trenger du ikke å oppgi grunn. Om du skulle bestemme deg for ikke å delta, får dette ingen behandlingsmessige konsekvenser for deg nå eller i fremtiden. Du har også mulighet til å forlange og bli strøket fra databasen.

Hvis du sier ja til å delta i studien betyr det at du vil møte på revmatologisk poliklinikk ved Diakonhjemmet Sykehus 2 halve dager og gjennomgå en full klinisk undersøkelse som inneholder:

- svare på spørreskjemaer angående sykdomsaktivitet, fysisk funksjon og vaner for fysisk aktivitet (ca 20 minutter)
- klinisk undersøkelse av ledd og rygg (ca 15 minutter)
- bentetthetsmåling (ca 20 minutter) for å undersøke om du har osteoporose (benskjørhet)

- gjennomføre en kondisjonstest på tredemølle og test av lungekapasitet (ca 20-30 min).
- gjennomføre en test av lungekapasitet (Spirometri) (ca 5 min)

Vi vil ha dessuten et spesielt fokus på kartlegging av mulige sykdomskomplikasjoner knyttet til hjerte og blodkar:

- Spørreskjema over forhold som kan være relatert til forekomst av hjerte-karsykdom hos deg eller din familie (ca 10 minutter).
- EKG undersøkelse hvor man fester elektroder på brystet for å måle hjertets elektriske aktivitet (ca 5 minutter).
- Trykkmåling i håndleddets pulsåre samt i lyske og på halskar. Undersøkelsen utføres ved hjelp av en probe som klemmes lett mot huden (ca 20 minutter).
- Ultralydmåling av diameteren på halsens hovedpulsåre ved hjelp av en probe som holdes mot halsen (ca 15 minutter).
- Måling av blodstrømmen i armens pulsåre etter 5 minutters avklemming ved hjelp av en blodtrykksmansjett som blir pumpet opp rundt overarmen (ca 10 minutter).

I tillegg vil det bli tatt en blodprøve. Alle resultatene vil avidentifiseres før de analyseres forskningsmessig, men de vil også bli en del av din sykehusjournal. På den måten vil resultatene være en status som kan brukes for å undersøke om helsetilstanden endrer seg senere. Påviste forandringer ved undersøkelsen av blodårene vil kunne lede til videre spesialundersøkelser ved hjerteavdelingen på Aker universitetssykehus som er samarbeidsparter for denne delen av prosjektet.

Biobank

Blodprøvene som blir tatt og informasjonen utledet av dette materialet vil bli lagret i en forskningsbiobank ved Diakonhjemmet Sykehus. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Avdelingssjef/avdelingsoverlege Tore K Kvien ved revmatologisk avdeling er ansvarlig for biobanken. Biobanken planlegges å vare til 31. desember 2025. Etter dette vil materiale og opplysninger bli destruert/slettet etter interne retningslinjer.

Slik ivaretas dine prøver og personopplysninger

Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg.
Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.
Opplysningene slettes i 2025.

Vi ønsker å ha muligheten for å kontakte deg igjen senere for oppfølgingsstudier og ber om din

tillatelse til dette.

Kobling til andre opplysninger/registre

Dersom du takker ja til å delta i oppfølgingsundersøkelsen vil dine opplysninger i Bekhterevregisteret kunne kobles til Dødsårsaksregisteret, Kreftregisteret og Leddproteseregisteret. Dette gjelder bare de som aktivt har samtykket i å delta i oppfølgingsundersøkelsen og som fysisk har møtt frem ved sykehuset

Dine rettigheter

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert evt. feil i de opplysningene vi har registrert.

Hvis du senere trekker deg fra studien, kan du kreve at materialet og opplysningene destrueres.

Prosjektansvarlig/Mer informasjon

Hvis du har spørsmål om studien, kan du kontakte forskningskoordinator Tone Omreng tlf 22 45 17 47, eller prosjektsamordner Camilla Fongen tlf 22 45 48 69, som vil formidle kontakt til prosjektansvarlige som er Avdelingssjef/professor Tore K Kvien og forsker/PhD Hanne Dagfinrud.

SAMTYKKE – PROSJEKTDELTAKER

for studien

Konsekvenser av Bekhterev sykdom.

Deltakelse i studien er basert på ditt frivillige, informerte samtykke etter å ha mottatt skriftlig informasjon om studien og fått anledning til å innhente den informasjon som du har behov for. Dersom du ønsker informasjon utover det som framkommer i dette informasjonsskrivet og den muntlige informasjonen du har mottatt/vil få, har du full anledning til å be om dette.

Jeg, _____(navn med blokkbokstaver)

Kryss av

|__| *er villig til å delta i studien og samtykker til at nye opplysninger samles inn fra Kreftregisteret, Dødsårsaksregisteret og Leddproteseregisteret*

|__| *er ikke villig til å delta i studien, men samtykker til at tidligere innsamlede opplysninger fortsatt kan brukes til forskningsformål og samtykker til at nye opplysninger samles inn fra Kreftregisteret, Dødsårsaksregisteret og Leddproteseregisteret*

|__| *er ikke villig til å delta i studien og ønsker å bli strøket fra Bekhterev-registeret*

*Signatur*_____*Dato*_____

(sign. prosjektdeltaker) *(datert av prosjektdeltaker)*

Hvis du ønsker å delta i undersøkelse, vennligst oppgi det eller de telefonnumre som vi kan bruke for å gjøre avtaler om tidspunkt for undersøkelsene:

Fasttelefon…… Mobil……

Denne siden returneres i vedlagte svarkonvolutt

Appendix 2: Enquiry about participation and written information for informed consent, population controls

Informasjon og forespørsel om deltakelse som kontrollpersoner i forskningsprosjektet: "Hjerte-karsykdom hos pasienter med revmatisk sykdom".

Bakgrunn og hensikt

Dette er en forespørsel til deg om å delta i et forskningsprosjekt hvor du vil bli undersøkt for hjerte-karsykdom og risikofaktorer for å få slik sykdom. Du får denne henvendelsen gjennom et søk i Folkeregisteret som er foretatt av Statistisk Sentralbyrå. Det er ingen spesiell grunn til at du får denne henvendelsen, en gruppe mennesker er helt tilfeldig valgt.

Det har vist seg at mennesker med revmatiske sykdommer har økt sjanse for å utvikle hjerte-karsykdom. 275 mennesker med tidlig leddbetennelse, etablert leddgikt eller Bekhterev sykdom har det siste året deltatt i studier ved Diakonhjemmet sykehus i Oslo hvor vi har målt graden av åreforkalkning ved flere forskjellige enkle, ufarlige, ikke-invasive, undersøkelser. I tillegg har vi målt fysisk kapasitet og lungefunksjon hos Bekhterev-pasientene. For å undersøke i hvilken grad mennesker med revmatisk sykdom har økt risiko for hjerte-kar sykdom er det behov for å sammenligne resultater fra pasientene med funn fra den generelle befolkningen. Resultatene fra undersøkelsen av kontrollpersoner vil dermed bli brukt til sammenligning med resultater fra 4 andre studier. Diakonhjemmet Sykehus AS er ansvarlig for studien.

Hva innebærer studien?

Hvis du sier ja til å delta i studien betyr det at du vil møte på revmatologisk poliklinikk ved Diakonhjemmet Sykehus en eller to ganger til undersøkelser som totalt vil ta ca 4 timer. Deltagelse innebærer også at det blir tatt en blodprøve samt at du blir stukket en gang i fingeren. Det er nødvendig å faste i 3 timer før undersøkelsene. I tillegg vil du bli bedt om å svare på et spørreskjema vedrørende forhold som kan være relatert til forekomst av hjerte-karsykdom hos deg eller din familie. Vi håper på en størst mulig oppslutning fordi en høy svarprosent gir større vitenskapelig verdi.

Mulige fordeler og ulemper

Den største ulempen for deg blir tidsbruken, undersøkelsen totalt vil ta ca 4 timer, og at det blir tatt to blodprøver. Blodtrykksmansjetten kan gi et visst ubehag i form av klem rundt overarmen. Fordelen vil være at du får en grundig undersøkelse av hjertet og eventuelle funn kan føre til tidlig behandling eller forebygging av fremtidig sykdom. Du får også et mål på din fysiske kondisjon. Hvis man avdekker hjerte-karsykdom sykdom eller alvorlige risikofaktorer for slik sykdom vil du få tilbud om en oppfølgningsundersøkelse ved den hjertemedisinske poliklinikken som er etablert ved revmatologisk poliklinikk.

Hva skjer med prøvene og informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Navnelisten slettes senest 31. desember 2025. Vi ønsker å ha muligheten for å kontakte deg igjen senere for oppfølging og ber om din tillatelse til dette. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i studien. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere, når som helst og uten å oppgi noen grunn, trekke tilbake ditt samtykke uten at det får noen konsekvenser for deg. Dersom du ønsker å trekke deg eller har spørsmål til studien kan du kontakte forskningskoordinator Tone Omreng tlf 22 45 17 47.

Ytterligere informasjon om studien finnes i kapittel A.

Ytterligere informasjon om dine rettigheter, økonomi og forsikring finnes i kapittel B

Kapittel A- utdypende forklaring om hva studien innebærer

Revmatologisk avdeling ved Diakonhjemmet Sykehus har ansvar for spesialisthelsetilbudet til pasienter med leddgikt og beslektede sykdommer i Oslo. I denne forbindelse drives et omfattende klinisk forskningsarbeid. Diakonhjemmet Sykehus har fra 1992 etablert flere registre over pasienter med leddbetennelse, leddgikt og Bekhterevs sykdom bosatt i Oslo. Formålet med disse registrene er å kartlegge forekomst av leddgikt og Bekhterevs sykdom i Oslo og å følge endring i sykdomsaktivitet og funksjonsnivå over tid.

Mennesker fra disse registrene har deltatt i undersøkelser hos oss. Studiene heter:

- Konsekvenser av Bekhterevs sykdom. Fysisk funksjon og egenrapportert helse
- Leddgikt i Oslo - forekomst, sykdomsforløp og prognose. Oppfølgningsundersøkelse i leddgiktsregisteret i Oslo
- Kronisk sykdom: Mestring, sosialt nettverk og livskvalitet- en prospektiv forløpsundersøkelse (Euridiss-prosjektet)
- Artritt (leddbetennelse) av mindre enn 16 ukers varighet – diagnoser og sykdomsforløp.

Studien du er invitert til er den del av disse 4 studiene. Den har som mål å kartlegge både forekomst av og tidlige tegn til hjerte-karsykdom hos pasienter med, tidlig leddbetennelse, leddgikt, Bekhterev sykdom og sammenligne disse funnene med den generelle befolkningen. Vi søker dermed etter tilfeldig utvalgte kontrollpersoner. Resultatene fra kontroll-undersøkelsene vil bli koblet i statistiske analyser til data fra de fire studiene som er nevnt ovenfor.

Hva skjer i studien?

For at undersøkelsen skal være mest mulig korrekt er det er viktig at du faster de siste 3 timene før undersøkelsen (vann er lov). Man må også unngå, nikotin, alkohol og svært fettrike måltider på undersøkelsesdagen av samme grunn.

Følgende undersøkelser vil bli utført:

- Hjertemedisinsk undersøkelse, inkludert måling av blodtrykk, høyde, vekt og livvidde, samt EKG undersøkelse (man fester elektroder på brystet for å måle hjertets elektriske aktivitet).
- Målinger av blodstrømmen i begge pekefingre før, under og etter 5 minutters avklemming av armens pulsåre ved hjelp av en blodtrykksmansjett. Undersøkelsen utføres vha en hette som tres på pekefingeren og gir et mål på åreveggens stivhet, et tidlig tegn på åreforkalkning
- Ultralydmåling av halsens hovedpulsåre ved hjelp av en probe som holdes mot halsen. Dette er et mål for kolesterolavleiring i åreveggen.
- Ultralyd undersøkelse av hjertet ved at det holdes en probe mot brystveggen for å bedømme hjertets funksjon og klaffenes beskaffenhet.
- Måling av trykket i åreveggen i håndleddet, lysken og på halsen.
- Test av fysisk kondisjon på tredemølle med laktatmåling utført ved stikk i fingertupp.
- Måling av bentetthet.
- Blodprøvetaking for analyse av lipidverdier, laktat, betennelsesmarkører og markører for hjerte-karsykdom.

Kapittel B – Dine rettigheter, biobank, økonomi og forsikring

Overføring eller utlån av materiale/opplysninger til andre
Forskningsgruppen ved revmatologisk avdeling Diakonhjemmet Sykehus samarbeider med andre forskningsgrupper i utlandet. Derfor kan noen av de opplysninger som samles inn også brukes i internasjonale forskningsprosjekt. I slike tilfelle vil dataene være anonymisert, dvs at koden som knytter dataene til navnet ditt er fjernet.

Biobank
Blodprøvene som blir tatt og informasjonen utledet av dette materialet vil bli lagret i en forskningsbiobank ved Diakonhjemmet Sykehus. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Avdelingssjef/avdelingsoverlege Tore K. Kvien ved revmatologisk avdeling, Diakonhjemmet Sykehus er ansvarlig for biobanken. Biobanken planlegges å vare til 31. desember 2025. Etter dette vil materiale og opplysninger bli destruert/slettet etter interne retningslinjer.

Økonomi
Denne studien er finansiert gjennom forskningsmidler fra Helse Sør-Øst og fra Diakonhjemmet Sykehus. Prosjektansvarlig og andre som arbeider med prosjektet har ingen form for økonomisk vinning knyttet til prosjektet.

Forsikring
Du er dekket av Norsk pasientskadeerstatning mens du oppholder deg hos oss.

Prosjektansvarlig/Mer informasjon
Hvis du har spørsmål om studien/biobanken, kan du kontakte forskningskoordinator Tone Omreng (prosjektsykepleier) tlf 22 45 17 47 , som vil formidle kontakt til:

avdelingssjef/professor Tore K Kvien (prosjektansvarlig) eller til Sella Aarrestad Provan (doktorgradsstipendiat).

Dine rettigheter
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert evt. feil i de opplysningene vi har registrert. Hvis du senere trekker deg fra studien, kan du kreve at materialet og opplysningene destrueres. Opplysninger som allerede har inngått i analyser eller blitt brukt i vitenskapelige publikasjoner kan ikke trekkes tilbake.

SAMTYKKE – PROSJEKTDELTAKER

for studien

”Hjerte-karsykdom hos pasienter med revmatisk sykdom”

☐ Jeg har mottatt skriftlig informasjon og er villig til å delta i studien.

☐ Jeg har mottatt skriftlig informasjon og er ikke villig til å delta i studien

Dato:_____

Navn:_____ (navn med blokkbokstaver)

Sign.:_____

Hvis du ønsker å delta i undersøkelse, vennligst oppgi det eller de telefonnumre som vi kan bruke for å gjøre avtaler om tidspunkt for undersøkelsene:

Fasttelefon. . . . . Mobil.. . . . . .

Ferdig utfylt samtykkeerklæring returneres i vedlagte svarskonvolutt til:

Tone Omreng
Forskningskoordinator Revmatologisk avdeling
Diakonhjemmet Sykehus
PB23 Vindern
0319 Oslo

Appendix 3: Recommendation from The National Committee for Medical Research Ethics, Southern Norway, Oslo

REGIONAL KOMITE FOR MEDISINSK FORSKNINGSETIKK

Helseregion Sør

Cand.san.
Hanne Dagfinnrud
Seksjon for helsefag
Universitetet i Oslo
Pb. 1153

Deres ref.: 210102 **Vår ref.:** S-02059 **Dato:** 14.03.02

Konsekvenser av Bekhterev sykdom. Fysisk funksjon og egenrapportert helse.
Prosjektleder: Cand.san. Hanne Dagfinnrud, Seksjon for helsefag, Universitetet i Oslo

Komiteen behandlet prosjektet i sitt møte torsdag 28. februar 2002 og gjorde slikt vedtak:

"Komiteen går ut i fra at henvendelsen til pasientene sendes ut fra behandlende lege.

Komiteen vil be om at første setning i pasientinformasjonen formuleres slik e.l.: Vi henvender oss til deg som tidligere pasient ved Diakonhjemmets sykehus for å spørre om du er villig til å delta i et forskningsprosjekt om Bekhterev sykdom".

Dersom det skal hentes opplysninger fra pasientjournal, må det opplyses i informasjonen.

Det må opplyses at man kan trekke seg fra prosjektet når som helst uten å oppgi grunn.

Da komiteen er et rådgivende organ og ikke et forvaltningsorgan, vil komiteen be om at uttrykket "godkjent" strykes i omtalen av komiteens behandling av prosjektet. Uttrykket "godkjent av" vil kunne oppfattes som en godkjennelse i rettslig forstand. Videre må betegnelsen "helseregion øst" rettes til "helseregion sør".

Under disse forutsetninger tilrår komiteen at prosjektet gjennomføres. Revidert pasientinformasjon bes sendt komiteen til orientering."

Vi ønsker lykke til med prosjektet.

Med vennlig hilsen

Annetine Staff (sign)
overlege dr.med.
nestleder

Ola P. Hole
avdelingsleder
sekretær

Kopi: Professor Tore K. Kvien, Diakonhjemmets Sykehus

Postboks 1130 Blindern, 0318 Oslo, tlf 22 84 46 66, faks 22 84 46 61, e-post: rek-2@medisin.uio.no
Besøksadresse: Frederik Holsts hus/Ullevål terrasse, Ullevål sykehus

Appendix 4: Recommendation from The National Committee for Medical Research Ethics, Southern Norway, Oslo

Regional komite for medisinsk forskningsetikk Sør-Norge (REK Sør)

Cand.san. Hanne Dagfinrud
Seksjon for helsefag
Universitetet i Oslo
Postboks 1153 Blindern

Deres ref.: **Vår ref.:** S-03066 **Dato:** 08.04.03

Konsekvenser av Bekhterev sykdom. Fysisk funksjon og egenrapportert helse
Prosjektleder: Cand.san. Hanne Dagfinrud, Seksjon for helsefag, Universitetet i Oslo

Komiteen behandlet prosjektet i sitt møte torsdag 27. mars 2003 og gjorde slikt vedtak:

"Når det gjelder forskningsetikk og søknadsinnhold, finner komiteen at prosjektsøknaden framstår som klar og gjennomtenkt.

Det forutsettes avklaring med Rikstrygdeverket dersom blodprøver for forskningsformål er tenkt finansiert gjennom trygderefusjon.

Når det gjelder pasientinformasjon, ønsker komiteen at skrivet "Informasjon om forskningsprosjekt: Konsekvenser av Bekhterev sykdom" innarbeides i skrivet med overskrift "Forespørsel om å delta i forskningsprosjektet ---". I sistnevnte skriv bør siste setning innledes med "Dersom du er villig til å delta, ber vi deg vennligst besvare ---" da informasjon/forespørsel om deltakelse skal ha en nøytral form

Komiteen vil be om at nei-alternativet strykes i samtykkeerklæringen. En person som er forespurt og ikke ønsker å delta i et forskningsprosjekt, skal ikke behøve å gi det aktivt tilkjenne.

Konklusjon:
Forutsatt at prosjektleder tar hensyn til disse merknadene, tilrår komiteen at prosjektet gjennomføres."

Vi ønsker lykke til med prosjektet.

Med vennlig hilsen

Sigurd Nitter-Hauge (sign)
Professor dr.med.
Leder

Ola P. Hole
Avdelingsleder
Sekretær

Postboks 1130, Blindern, 0318 Oslo tlf 22 84 46 66 Faks 22 84 46 61
E-post: rek-2@medisin.uio.no, **Besøksadresse: Frederik Holsts hus, Ullevål terrasse, Ullevål sykehus**
http://www.etikkom.no/

Appendix 5: Letter from The National Committee for Medical Research Ethics, Southern Norway, Oslo

Regional komite for medisinsk forskningsetikk Sør-Norge (REK Sør-Øst A)

Cand.san. Hanne Dagfinrud
Seksjon for helsefag
Universitetet i Oslo
Postboks 1153 Blindern

Deres ref.: **Vår ref.:** S-03066 / S-02059 **Dato:** 19.01.08

S-03066 Konsekvenser av Bekhterev sykdom. Fysisk funksjon og egenrapportert helse
Prosjektleder: Cand.san. Hanne Dagfinrud, Seksjon for helsefag, Universitetet i Oslo

Vi viser skjema for protokolltillegg og endringer datert 8.108 med revidert informasjonsskriv og samtykkeerklæring vedlagt.

Komiteen har ingen innvendinger mot de endringer som foreslås i studien

Komiteen har følgende merknader til informasjonsskriv med samtykkeerklæring:
I samband med "dine rettigheter": presiser at retten til å kreve opplysninger slettet m.v. ikke gjelder dersom disse alt er inngått i vitenskapelige publikasjoner.

Kopi av søknad om opprettelse av forskningsbiobank foreligger ikke.

Vedtak i saken utsettes. Kopi av skjema for opprettelse av forskningsbiobank må sendes komiteen. Etter behandling og eventuell tilråding videresendes skjema for opprettelse av forskningsbiobank og informasjonsskrivet samt komiteens vedtak til Sosial- og helsedirektoratet for endelig behandling av opprettelse av forskningsbiobanken.

Med vennlig hilsen

Kristian Hagestad
Fylkeslege cand.med., spes. i samf.med
Leder

Jørgen Hardang
Sekretær

Postboks 1130, Blindern, 0318 Oslo tlf 22 84 46 66 Faks 22 84 46 61
E-post: rek-2@medisin.uio.no, **Besøksadresse: Frederik Holsts hus, Ullevål terrasse, Ullevål sykehus**
http://www.etikkom.no/

Appendix 6: Licence to register and store and individual health information; The Data Inspectorate, Norway

Datatilsynet

Diakonhjemmet Sykehus AS
v/Tore Kvien
Postboks 23 Vinderen
0319 OSLO

Deres referanse	Vår referanse (bes oppgitt ved svar)	Dato
	08/00165-2 /sve	11. mars 2008

Konsesjon til å behandle helseopplysninger

Datatilsynet viser til Deres søknad av 24.01.2008 om konsesjon til å behandle helseopplysninger.

Datatilsynet har vurdert søknaden og gir Dem med hjemmel i helseregisterlovens § 5, jf. dødsårsaksregisterforskriftens § 3-5, jf. kreftregisterforskriftens § 3-5, jf. personopplysningslovens § 33, jf. § 34, konsesjon til å behandle helseopplysninger til følgende formål: *"Oppfølgingsundersøkelse - Konsekvenser av Bekhterev sykdom - Fysisk funksjon og egenrapportert helse"*.

Databehandlingsansvarlig er Diakonhjemmet Sykehus AS ved øverste leder. Gjennomføringen av det daglige ansvaret kan delegeres.

Konsesjonen er gitt under forutsetning av at behandlingen foretas i henhold til søknaden og de bestemmelser som følger av helseregisterloven med forskrifter.

Dersom det skjer endringer i behandlingen i forhold til de opplysninger som er gitt i søknaden, må dette fremmes i ny konsesjonssøknad. Det presiseres at konsesjonen, i samsvar med søknaden, er tidsbegrenset til **31.12.2025**. Personidentifiserbare data må da slettes eller anonymiseres.

I medhold av helseregisterlovens § 5, jf. § 36, jf. personopplysningslovens § 35, fastsettes i tillegg følgende vilkår for behandlingen:

1. Den databehandlingsansvarlige skal hvert tredje år sende Datatilsynet bekreftelse på at behandlingen skjer i overensstemmelse med søknaden og helseregisterlovens regler.

Datatilsynet tar forbehold om at konsesjonen kan bli trukket tilbake eller at nye og endrede vilkår kan bli gitt dersom dette er nødvendig ut fra personvernhensyn.

Postadresse: Postboks 8177 Dep 0034 OSLO | Kontoradresse: Tollbugt 3 | Telefon: 22 39 69 00 | Telefaks: 22 42 23 50 | Org.nr: 974 761 467 | Hjemmeside: www.datatilsynet.no

Dette vedtak kan påklages til Personvernnemnda i medhold av forvaltningslovens kapittel IV. Eventuell klage må sendes til Datatilsynet senest tre uker etter mottaket av dette brev.

Med hilsen

Knut B. Kaspersen
avdelingsdirektør

Sverre Engelschiøn
seniorrådgiver

Kopi: Ullevål universitetssykehus HF - Konsern IT, Heidi Thorstensen, 0407 OSLO

Appendix 7: Form for registration of BASDAI (Q 1-6)

SPØRSMÅL OM FUNKSJON, SMERTE, TRETTHET, SYKDOMSAKTIVITET OG ANDRE PLAGER

Spørsmålene nedenfor gjelder hvordan du følte deg den siste uken. Marker ditt svar med å krysse i en rute.

1. **Hvordan vil du beskrive den generelle graden av utmattelse/tretthet du har erfart?**

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

2. **Hvordan vil du beskrive den generelle graden av smerter i nakke-, rygg eller hofter i forbindelse med Bekhterev sykdom?**

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

3. **Hvordan vil du beskrive det generelle nivået av smerter/hevelse du har hatt i andre ledd enn nakken- ryggen eller hoftene?**

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

4. **Hvordan vil du beskrive den generelle graden av ubehag du har hatt på eventuelle steder som gjør vondt ved berøring eller trykk?**

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

5. **Hvordan vil du beskrive den generelle graden av stivhet du har opplevd om morgenen fra det tidspunktet du våkner?**

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

6. **Hvor lenge varer morgenstivheten fra det tidspunktet du våkner?**

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

0 timer — 1 time — 2 timer eller mer

2

Appendix 8: Form for registration of BASFI (Q 1-10)

SPØRSMÅL OM FUNKSJON, SMERTE, TRETTHET, SYKDOMSAKTIVITET OG ANDRE PLAGER

Spørsmålene nedenfor gjelder hvordan du følte deg den siste uken. Marker ditt svar med å krysse av i en rute.

1. Ta på strømper eller strømpebukser uten assistanse eller ved bruk av hjelpemidler (for eksempel strømpe påtrekker)

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

2. Bøye deg fremover fra midjen for å plukke opp en penn fra gulvet uten å bruke et hjelpemiddel

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

3. Nå opp til en høythengende hylle uten bruk av hjelpemidler (for eksempel gripetang)

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

4. Reise deg fra en spisebordsstol uten armlener eller annen hjelp

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

5. Reise deg opp fra liggende stilling på gulvet uten hjelp

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

6. Stå oppreist uten støtte i 10 min. uten å få ubehag

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

7. Gå opp 12-15 trappetrinn uten å bruke rekkverk eller gåstøtte. En fot på hvert trinn

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

3

SPØRSMÅL OM FUNKSJON, SMERTE, TRETTHET, SYKDOMSAKTIVITET OG ANDRE PLAGER

Spørsmålene nedenfor gjelder hvordan du følte deg den siste uken. Marker ditt svar med å krysse av i en rute.

8. Se deg over skulderen uten å vri kroppen

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

9. Utføre fysisk krevende aktiviteter (for eksempel fysioterapiøvelser, hagearbeid eller sport)

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

10. Utføre en hel dags aktiviteter enten hjemme eller på arbeid

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Lett — Umulig

1. Hvor alvorlig var din smerte i ryggsøylen i gjennomsnitt den siste uken?

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

2. Hvor aktiv var din sykdom i gjennomsnitt den siste uken?

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

3. Hvor mye smerte hadde du grunnet din sykdom om nettene i gjennomsnitt den siste uken?

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Ingen — Svært høy

Appendix 9: Form for registration of BASMI

APPENDIX

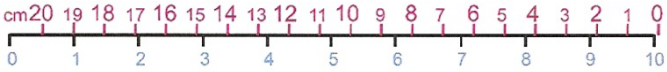
BASMI

Bath Ankylosing Spondylitis Metrology Index, a combined index to assess the spinal mobility in patients with ankylosing spondylitis

Name: _____

Date: _____

1 **Lateral lumbar flexion:** Patient stands with heels and buttocks touching the wall, knees straight, shoulders back, hands by the side. The patient is then asked to bend to the right side as far as possible without lifting the left foot/heel or flexing the right knee, and maintaining a straight posture with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when patient bends to the side, is subtracted from the distance when patient stands upright. The manoeuvre is repeated on the left side.

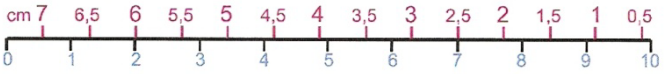


Mean of right/left ☐

2 **Tragus-to-wall distance:** Maintain same starting position as above. The distance between tragus of the ear and wall during maximal effort to draw the head back without raising the chin above its usually carrying level is measured on both sides to the nearest 0.1 cm, using a rigid ruler. Ensure no cervical extension, rotation, flexion or side flexion occurs.

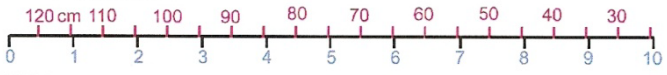
Mean of right/left ☐

3 **Lumbar flexion (modified Schober):** Set marks in upright position at the level of the spinous process of L5 (found as the first process below the projected line across the back at the level of the top of the iliac crest) and 10 cm above above the first mark. Measure distraction of the marks when the patient bends forward as far as possible, keeping the knees traight.



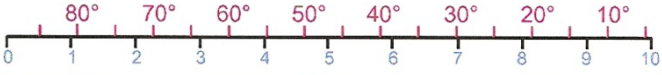
☐

4 **Intermalleolar distance:** Patient supine on the floor or a wide plinth, with the knees straight and the feet pointing straight up. Patient is asked to separate legs along the resting surface as far as possible. Distance between medial malleoli is measured.



☐

5 **Cervical rotation:** Patient supine on plinth, head in neutral position, forehead horizontal (if necessary head on pillow or foam block to allow this, must be documented for future reassessments). Gravity goniometer placed centrally on the forehead. Patient rotates head as far as possible, keeping shoulders still, ensure no neck flexion or side flexion occurs. Rotational angle to the right and to the left is measured.
If you do not have a gravity goniometer: Patient sits with shoulders to the wall. Place goniometer to the wall above the patient's head. Patient rotates head as described above. Examiner aligns goniometer branch parallel to sagittal plane of the head.



Mean of right/left ☐

BASMI: (Average of 5 scores) ☐

Appendix 10: The Balke protocol

KONDISJONSTEST (BALKEPROTOKOLL)

Forsøkspersonen går på tredemølle til utmattelse (18 på Borg CRP skala), med konstant ganghastighet. Oppvarming og tilvending til mølle 5 minutter, 2,5 % helling
Hastighet 5.3 km/h, lavere hastighet kan velges dersom pasienten har behov for dette.
Dersom testpersonen klarer ytterligere belastninger økes hastigheten hvert minutt.

TESTLEDERE ☐ CF ☐ CT

Kontraindikasjoner ☐ Ja ☐ Nei

☐ Nylig hjerteinfarkt ☐ Ustabil angina ☐ Ustabil rytme ☐ Kjent anerysme
☐ Hjerte eller hjertesekkbetennelse ☐ Kjent alvorlig stenose ☐ Akutt infeksjon (feber, kroppsverk mm) ☐ Kronisk infeksjon (mononucleosis, hepatit, AIDS)
☐ Fysisk funksjon ☐ Hevelse i ledd ☐ Annet

Bruk av blodtrykksregulerende medisin? ☐ Ja ☐ Nei

VEKT (kg) ☐☐☐ **HØYDE (cm)** ☐☐☐

ALDER ☐☐ **ALDERSPREDIKERT MAKSPULS** (220-alder) ☐☐☐

FART (km/h) (☐ 4.3) ☐ **4.8** ☐ **5.3** **Annet** ☐.☐

MINUTT	VINKEL STIGNING %	BORG	PULS	KOMMENTAR
1	4.5			
2	6.0			
3	7.5			
4	9.0			
5	10.5			
6	12.0			
7	13.5			
8	15.0			
	FART			
9	+ 0,3 ☐.☐			
10	+ 0,3 ☐.☐			
11	+ 0,3 ☐.☐			
12	+ 0,3 ☐.☐			
13	+ 0,3 ☐.☐			
14	+ 0,3 ☐.☐			
15	+ 0,3 ☐.☐			
16	+ 0,3 ☐.☐			
17	+ 0,3 ☐.☐			
TESTTID	☐☐ min ☐☐ s	☐☐	☐☐☐	
GRUNN TIL Å AVSLUTTE TEST	☐ Generell anstrengelse	☐ Lokal slitenhet	☐ Pust	☐ Andre symptom Hva:

6

Appendix 11: IPAQ-Long form

SPØRSMÅL OM FYSISK AKTIVITET, MOSJON OG TRENING

Vi vet i dag lite om folks aktivitets og mosjonsvaner og er interessert i informasjon om ulike former for fysisk aktivitet som folk driver med i dagliglivet. Spørsmålene gjelder tiden du bruker på alle former for fysisk aktivitet i en vanlig uke om sommeren og i en vanlig uke om vinteren. (IPAQ-L)

Når du svarer på spørsmålene,
Meget anstrengende - er fysisk aktivitet som får deg til å puste *mye* mer enn vanlig.
Middels anstrengende - er fysisk aktivitet som får det til å pust *litt* mer enn vanlig

1. FYSISK AKTIVITET I ARBEIDET

Dette omfatter alt arbeid utenfor hjemmet, betalt eller ubetalt (inkluderer sysselsettingstiltak og frivillig arbeid, men ikke husarbeid, hagearbeid, vedlikeholdsarbeid i hjem eller familieaktiviteter).

1.1 Har du en jobb eller utfører ubetalt arbeid utenfor hjemmet?
☐ **Ja** ☐ **Nei**

Hvis "Nei" gå til 2: TRANSPORTAKTIVITETER

De neste spørsmålene omhandler alle former for fysisk aktivitet du gjør som en del av betalt eller ubetalt arbeid i en vanlig uke. Du skal ikke regne med hvordan du forflytter deg til og fra arbeid. Du skal bara tenke på aktiviteter som varer i minst 10 minutter om gangen.

1.2 Hvor mange dager i en vanlig uke gjør du meget anstrengende fysisk aktivitet som tunge løft, tungt byggearbeid, bære tunge ting eller gravearbeid på jobb?
Om sommeren: ☐ dager per uke
Om vinteren: ☐ dager per uke

1.3 På en vanlig dag på jobb hvor du utfører meget anstrengende fysisk aktivitet, hvor lang tid bruker du totalt på dette?
Om sommeren: ☐☐ timer ☐☐ minutter
Om vinteren: ☐☐ timer ☐☐ minutter

1.4 Hvor mange dager i en vanlig arbeidsuke gjør du middels anstrengende fysisk aktivitet som å bære lette ting på jobb?
Om sommeren: ☐ dager per uke
Om vinteren: ☐ dager per uke

1.5 På en vanlig dag på jobb hvor du utfører middels anstrengende fysisk aktivitet, hvor lang tid bruker du totalt på dette?
Om sommeren: ☐☐ timer ☐☐ minutter
Om vinteren: ☐☐ timer ☐☐ minutter

SPØRSMÅL OM FYSISK AKTIVITET, MOSJON OG TRENING

1. FYSISK AKTIVITET I ARBEIDET (fortsettelse)

1.6 Hvor mange dager i en vanlig arbeidsuke går du minst 10 minutter i strekk på jobb? Ikke ta med gåing til og fra jobb!

Om sommeren: ☐ dager per uke

Om vinteren: ☐ dager per uke

1.7 Hvor lang tid bruker du totalt på å gå på de dagene hvor du utfører en slik aktivitet på jobb?

Om sommeren: ☐☐ timer ☐☐ minutter

Om vinteren: ☐☐ timer ☐☐ minutter

1.8 Når du går som en del av din jobb, i hvilket tempo går du vanligvis?

I raskt tempo ☐ I middels tempo ☐ I rolig tempo ☐

2. TRANSPORTAKTIVITETER

Dette omfatter dine vanlige måter å komme fra et sted til et annet på, inkludert hvordan du kommer deg til og fra jobb, butikker, kino o.l

2.1 Hvor mange dager i en vanlig uke reiser du med et motorisert transportmiddel som tog, buss, bil eller trikk?

Om sommeren: ☐ dager per uke

Om vinteren: ☐ dager per uke

2.2 På en vanlig dag hvor du reiser med motorisert transportmiddel, hvor lang tid bruker du da totalt i transportmiddelet?

Om sommeren: ☐☐ timer ☐☐ minutter

Om vinteren: ☐☐ timer ☐☐ minutter

Nå skal du **bare** tenke på når du sykler eller går til og fra arbeidet, for å gjøre ærend eller bare komme fra et sted til et annet.

2.3 Hvor mange dager i en vanlig uke sykler du minst 10 minutter i strekk for å komme fra et sted til et annet?

Om sommeren: ☐ dager per uke

Om vinteren: ☐ dager per uke

2.4 På en vanlig dag hvor du sykler for å komme det fra et sted til et annet, hvor lang tid bruker du da totalt på å sykle?

Om sommeren: ☐☐ timer ☐☐ minutter

Om vinteren: ☐☐ timer ☐☐ minutter

2.5 Når du forflytter deg fra et sted til et annet på sykkel, i hvilket tempo sykler du vanligvis?

I raskt tempo ☐ I middels tempo ☐ I langsomt tempo ☐

SPØRSMÅL OM FYSISK AKTIVITET, MOSJON OG TRENING

2.6 Hvor mange dager i en vanlig uke går du minst 10 minutter i strekk for å komme fra et sted til et annet?

Om sommeren: ☐ dager per uke

Om vinteren: ☐ dager per uke

2.7 På en vanlig dag hvor du går for å komme det fra et sted til et annet, hvor lang tid bruker du da totalt på å gå?

Om sommeren: ☐☐ timer ☐☐ minutter

Om vinteren: ☐☐ timer ☐☐ minutter

2.8 Når du forflytter deg fra et sted til et annet ved å gå, i hvilket tempo går du vanligvis?

I raskt tempo ☐ I middels tempo ☐ I langsomt tempo ☐

3. AKTIVITET I HJEMMET ELLER I TILKNYTNING TIL HJEMMET

Dette omfatter husarbeid, arbeid på gårdsplassen, hagearbeid, vedlikeholdsarbeid eller ettersyn med familien. Husk; det er kun aktiviteter som varer i minst 10 minutter i strekk som skal rapporteres.

Utendørs aktiviteter

3.1 Hvor mange dager i en vanlig uke gjør du meget anstrengende fysisk aktivitet som å løfte tunge ting, hugge ved, gravearbeid eller snømåking i hagen eller på gårdsplassen?

Om sommeren: ☐ dager per uke

Om vinteren: ☐ dager per uke

3.2 På en vanlig dag hvor du utfører meget anstrengende fysisk aktivitet i hagen eller på gårdsplassen, hvor lang tid bruker du totalt på dette?

Om sommeren: ☐☐ timer ☐☐ minutter

Om vinteren: ☐☐ timer ☐☐ minutter

3.3 Hvor mange dager i en vanlig uke gjør du middels anstrengende fysisk aktivitet som å bære lette ting, feie eller rake i hagen eller gårdsplassen?

Om sommeren: ☐ dager per uke

Om vinteren: ☐ dager per uke

3.4 På en vanlig dag i hagen eller på gårdsplassen hvor du utfører middels anstrengende fysisk aktivitet, hvor lang tid bruker du totalt på dette?

Om sommeren: ☐☐ timer ☐☐ minutter

Om vinteren: ☐☐ timer ☐☐ minutter

Innendørs aktiviteter

3.5 Hvor mange dager i en vanlig uke gjør du middels anstrengende fysisk aktivitet som å støvsuge, vaske gulv eller vinduer eller tunge pleieoppgaver i hjemmet ditt?

Om sommeren: ☐ dager per uke

Om vinteren: ☐ dager per uke

3.6 På en vanlig dag i hjemmet hvor du utfører middels anstrengende fysisk aktivitet, hvor lang tid bruker du totalt på dette?

Om sommeren: ☐☐ timer ☐☐ minutter

Om vinteren: ☐☐ timer ☐☐ minutter

SPØRSMÅL OM FYSISK AKTIVITET, MOSJON OG TRENING

4. REKREASJON, SPORT OG FRITIDSAKTIVITETER

Dette omfatter alle aktiviteter du gjør på fritiden din i en vanlig uke.
Regn med alle fritidsaktiviteter og mosjons- eller treningsaktiviteter som varer minst 10 minutter i strekk. **Du skal ikke regne den aktiviteten som du allerede har regnet med i tidligere spørsmål.**

4.1 Hvor mange dager i en vanlig uke går du turer som varer i mer enn 10 minutter på fritiden?
NB! Du skal skille mellom hverdager og helgedager!

Om sommeren:	**Om vinteren:**
☐ hverdager per uke	☐ hverdager per uke
☐ helgedager per uke	☐ helgedager per uke

4.2 På en vanlig dag hvor du går tur på fritiden, hvor lang tid bruker du totalt på dette?

Om sommeren:		**Om vinteren:**	
Hverdager:	Hverdager:	Hverdager:	Hverdager:
☐☐ timer	☐☐ minutter	☐☐ timer	☐☐ minutter
Helgedager:	Helgedager:	Helgedager:	Helgedager:
☐☐ timer	☐☐ minutter	☐☐ timer	☐☐ minutter

4.3 Når du går tur på fritiden, i hvilket tempo går du vanligvis?

I raskt tempo	I middels tempo	I langsomt tempo
☐	☐	☐

4.4 Hvor mange dager i en vanlig uke utfører du aktiviteter på fritiden din som varer i minst 10 minutter og er meget anstrengende som for eksempel aerobics, gå raskt på ski, sykle fort og svømme fort?

Om sommeren:	**Om vinteren:**
☐ dager per uke	☐ dager per uke

4.5 På en vanlig dag hvor du utfører meget anstrengende aktivitet på fritiden din, hvor lang tid bruker du totalt på dette?

Om sommeren:		**Om vinteren:**	
☐☐ timer	☐☐ minutter	☐☐ timer	☐☐ minutter

4.6 Hvor mange dager i en vanlig uke utfører du aktiviteter på fritiden din som varer i minst 10 minutter og er middels anstrengende som for eksempel å sykle i moderat tempo, svømme i moderat tempo, mosjonstennis, golf, rolige skiturer eller lettere gymnastikk?

Om sommeren:	**Om vinteren:**
☐ dager per uke	☐ dager per uke

4.7 På en vanlig dag hvor du utfører middels anstrengende fysisk aktivitet på fritiden din, hvor lang tid bruker du totalt på dette?

Om sommeren:		**Om vinteren:**	
☐☐ timer	☐☐ minutter	☐☐ timer	☐☐ minutter

SPØRSMÅL OM FYSISK AKTIVITET, MOSJON OG TRENING

5. TID DU TILBRINGER I RO

Dette omfatter alle tid du tilbringer i ro (sittende) på arbeid, hjemme, på kurs og på fritiden. Det kan være tiden du sitter ved et arbeidsbord, hos venner, mens du leser, eller sitter eller ligger for å se på TV. Du skal ikke ta med den tiden du sitter i et motorisert transportmiddel da du allerede har oppgitt dette.

5.1 På en vanlig hverdag hvor lang tid bruker du vanligvis på å sitte?

Om sommeren:		**Om vinteren:**	
☐☐ timer	☐☐ minutter	☐☐ timer	☐☐ minutter

5.2 På en vanlig lørdag eller søndag, hvor lang tid bruker du vanligvis på å sitte?

Om sommeren:		**Om vinteren:**	
☐☐ timer	☐☐ minutter	☐☐ timer	☐☐ minutter

6 DIN FYSISKE AKTIVITET GENERELT

Vennligst les alle alternativene nedenfor. Sett kryss for det alternativet som best beskriver ditt nåværende nivå av fysisk aktivitet eller din interesse for fysisk aktivitet. Tenk på all fysisk aktivitet unntatt aktivitet som er en del av jobben

- For tiden er jeg ikke fysisk aktiv, og har ingen planer om å bli fysisk aktiv i løpet av de neste 6 måneder ☐
- For tiden er jeg ikke fysisk aktiv, men jeg tenker å bli mer fysisk aktiv i løpet av de neste 6 måneder ☐
- For tiden er jeg noe fysisk aktiv, men det er ikke regelmessig ☐
- For tiden er jeg regelmessig fysisk aktiv, men det er først i løpet av de siste 6 måneder at jag har begynt ☐
- For tiden er jeg regelmessig fysisk aktiv, og har vært det lengre enn de siste 6 månedene ☐

Hvor ofte trener du (øket puls og pust) i minst en halv time (30 minutter)? Kryss av bare en gang.

☐ 3 eller flere ganger per uke ☐ 1 – 2 ganger per uke ☐ 1 – 2 ganger/måned

☐ Trener ikke regelmessig ☐ Kan ikke trene pga nedsatt funksjon/handicap

Appendix 12: Form for registration of pulmonary function test results (spirometry) (example)

SPIROMETRIUNDERSØKELSE BEKHTEREV 2008

26.05.2008

ID:		**Alias ID:**			
Namn:					
Ålder:		**Datum:**	07.05.2008 17:58		
Kön:	Man	**Ursprung:**	Kaukasier	**Faktor:**	100
Längd:	168 cm.	**Vikt:**	77.0 kg.	**Rokare:**	0
Remitterad av:		**Yrke:**			

	VC	FEV1	FVC	PEF	VAR	Kvalité	Tid	Datum
Bas		1.64	1.87	437	-5 %	Bra blås	17:58	07.05.2008
Bas		1.74	1.96	458	+0 %	Bra blås	17:58	07.05.2008
+ Bas		**1.74**	**1.96**	**458**	**+0 %**		**17:58**	**07.05.2008**

ATS/ERS Kriteriet (2005): Otillräckligt med blås för att utvärderas, 3 blås eller mer krävs.

Skillnaden baseras på FEV1 + FVC

Index	Bas	%Förv	Post 1	%Förv	Förändr.	[Min	Förv	Max]	Enhet
VC									l
FEV1	1.74	59				2.10	2.94	3.77	l
FVC	1.96	53				2.72	3.72	4.73	l
PEF	458	98				349	468	587	l/min
FEV1/FVC	89					64	76	88	%
FEF25	7.40	107				4.09	6.90	9.72	l/s
FEF50	3.10	76				1.92	4.10	6.27	l/s
FEF75	0.92	64				0.15	1.43	2.72	l/s
FEF25-75	2.37	72				1.58	3.29	5.00	l/s
FET	3.26								s
IC									l
Lungålder	90								År

IC värdena är medel av samtliga tester.

Tolkning: (ATS) Bastest Medel till svår Restriktion.

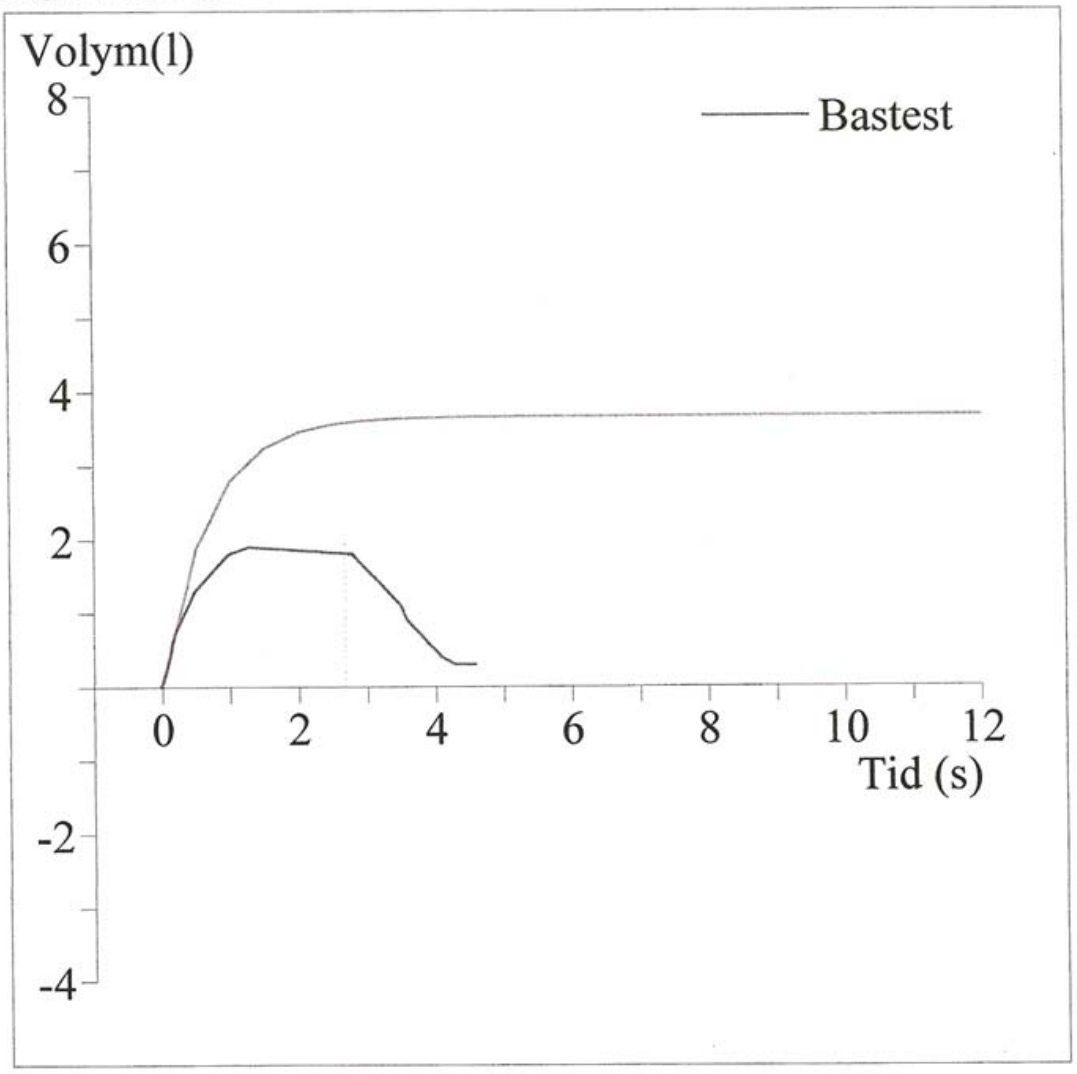
Normalvärden: ECCS (vuxna); Zapletal, Solymar, Cogswell (Barn).
Resultat med BTPS.

237

Appendix 13: Flow-time curve (example)

ID: **Datum:**
Namn:

Diagram, bästa volymtid



Appendix 13: Flow-volume curve (example)

ID: **Datum:**
Namn:

Diagram, bästa flödesvolymslinga