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ASSESSMENT OF WORK DISABILITY IN SERONEGATIVE SPONDYLOARTHRITIS

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ASSESSMENT OF WORK DISABILITY IN SERONEGATIVE SPONDYLOARTHRITIS

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by

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ABSTRACT AND KEYWORDS

Objective: Seronegative spondyloarthritis (SpA), including ankylosing spondylitis (AS) may lead to work disability (WD). We determined the prevalence of WD and limitations in work productivity in SpA using surveys.

Methods: 203 patients with SpA received a questionnaire asking about work status, the WLQ, HAQ, BASDAI, BASFI, BAS-G and FCI. Relationships between WD, WLQ, demographics and disease activity were assessed through bivariate correlations, independent t-tests and multivariable logistic regression.

Results: Response rate was 40%; 18.5% were WD. WD were older than non-WD, had higher scores on BASFI, BAS-G, had worse overall health and more comorbidities. Subjects with AS had less WD than those with other SpA. The decrease in work productivity attributable to health was 8.3%. Productivity loss was correlated with HAQ, BASFI, BASDAI, and BAS-G scores.

Conclusions: WD occurred in 18.5%, and work productivity was also reduced by 8.3%. WD was associated with older age and greater SpA disease activity.

Keywords: work disability, work productivity, spondyloarthritis, ankylosing spondylitis

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LIST OF ABBREVIATIONS

AAWL – arthritis-attributable work limitation

ADLs – activities of daily living

Anti-TNF – anti-tumour necrosis factor alpha medications; "biologics"

AS – ankylosing spondylitis

ASAS – Assessment in AS international working group

BASDAI - Bath Ankylosing Spondylitis Disease Activity Index

BAS-G – Bath Ankylosing Spondylitis Patient Global Score

BASFI – Bath Ankylosing Spondylitis Fuctional Index

BMI – Body Mass Index

CAD – Canadian dollars

CI – confidence intervals

CHF – congestive heart failure

COPD – chronic obstructive pulmonary disease

EA – enteropathic arthritis

ESSG –European Spondylarthropathy Study Group

FCI – functional comorbidity index

GI - gastrointestinal

HAQ – Health Assessment Questionnaire

HAQ-DI – Health Assessment Questionnaire, Disability Index

HLA-B27 – human leukocyte antigen B27

IBD – inflammatory bowel disease

ICF – International Classification of Functioning, Disability and Health

MI – myocardial infarction; heart attack

MIDS – mental-interpersonal demands scale

MRI – magnetic resonance imaging

NHIS – US National Health InterviewStudy

NPHS – Canadian National Population Health Survey

OA – osteoarthritis

ODS – output demands scale

OHIP – Ontario Health Insurance Plan

PDS – physical demands scale

PROs – patient reported outcomes

PVD – peripheral vascular disease

PsA – psoriatic arthritis

RA – rheumatoid arthritis

ReA – reactive arthritis

SD – standard deviation

SERs – standardized employment ratios

SF-36 – Short Form 36, a common outcome measure

SI – sacroiliac

SJHC – St. Joseph's Health Care (London, Ontario)

SpA – spondyloarthritis

SPSS – Statistical Package for the Social Sciences

TIA – transient ischemic attack; mini-stroke

TMS – time management scale

uSpA – undifferentiated spondyloarthritis

UWO – University of Western Ontario

VAS – visual analogue scale

WD – work disability

WHO – World Health Organization

Chapter 1: Introduction

1.0. Ankylosing Spondylitis(AS) and Spondyloarthritis (SpA)

Ankylosing spondylitis (AS) is a complex, chronic inflammatory disorder causing disease of the sacroiliac (SI) joints and spine, as well as peripheral joints and extra-articular sites (1). It typically causes progressive pain and stiffness of the spine, with advancement to fusion (ankylosis) of spinal joints (1). With ongoing active disease, the ankylosing process can cause complete fusion of the spinal column, into a rigid "bamboo spine" in some patients (1). Extraarticular symptoms include, but are not limited to, inflammation of the insertion of tendons into bones (enthesitis), eyes and aorta (1). It has a distinct association with the major histocompatibility complex HLA-B27 (1). AS is often thought of as the prototypical form of spondyloarthritis.

Spondyloarthritis or spondyloarthropathy (SpA) refers to a group of related inflammatory disorders which include spinal arthritis (spondylitis), arthritis of the peripheral joints and enthesitis (2). Diseases that are included in the spondyloarthritis family include AS, reactive arthritis (ReA), psoriatic arthritis (PsA) and arthritis associated with inflammatory bowel disease such as ulcerative colitis and Crohn's disease (enteropathic arthropathy, EA) (2). Some may have an unspecified SpA, with features of some of the typical SpAs, but not meeting full classification criteria (2). Indeed, it has been proposed that AS is only one clinical manifestation of a broader group of disease entities (Figure 1) (3). Due to the overlap in clinical presentations, SpAs are frequently studied together.

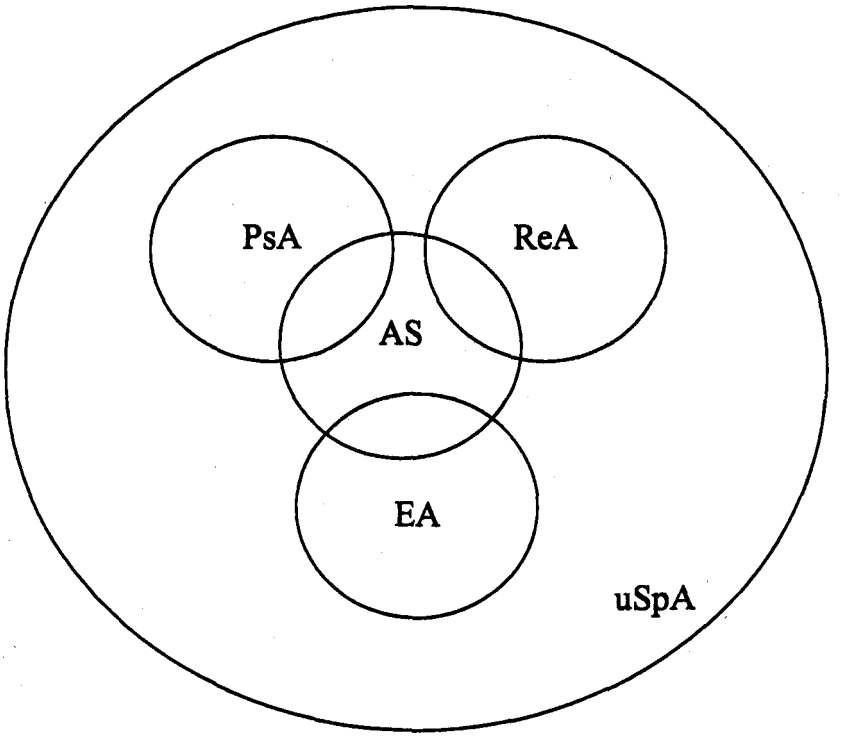


Figure 1: Proposed classification of seronegative spondyloarthritis. AS = ankylosing spondylitis, PsA = psoriatic arthritis, ReA = reactive arthritis, EA = enteropathic arthritis, uSpA= undifferentiated spondyloarthritis. Adapated from (3).

AS and SpA are diseases that affect young adults, classically occurring in the second or third decade of life, with a mean age of onset of 26 years (1). Since SpA affects patients during their working years, work disability (WD) is an important disease outcome.

A meta-analysis of European and American studies has shown variable rates of WD in AS, ranging from 3-50% (4). This WD contributes significantly to the cost of care for AS in Canada, $3 422/year (CAD), about 38% of total annual cost of AS (5).

Areas of impact include reduced income, early retirement, and increased sick leave (5).

Resource utilization and costs of AS have been recently studied in a Canadian cohort (5). Mean annual costs of AS, per patient, were estimated at $9 008 (Canadian dollars), with indirect costs representing 38% (5). Half of the direct costs were attributed to patients' out of pocket expenses, such as over the counter medication and informal care (5). Notably, the study found that the costs of AS were not normally distributed. A small number of patients with high levels of functional impairment and very active disease increased costs substantially (5). Functional impairment was a stronger driver of costs than disease activity (5). The difference in cost from the lowest level of functional impairment to the highest was $ 25 000 (5). Increasing age was also associated with increasing costs, but sex was not (5). Of note, age and disease duration are correlated. The overall costs of AS in Canada were found to be similar to those in the United States, but lower than those reported in European studies, which reported annual costs per patient of about $15 000 (5).

Despite an economic impact of WD in AS, its characteristics have not yet been extensively studied in a Canadian cohort.

1.0.1. Epidemiology

The incidence of AS has been variably reported to be between 0.5-8.2 per 100 000 population (6). Incidence rates are higher in populations with a higher prevalence of HLA-B27 (6).

Prevalence of AS in a given population is also highly dependent on the baseline population prevalence of HLA-B27 (6). Prevalence is generally estimated at between 0.1 to 1.4%, largely on the basis of European studies (7). Of note, HLA-B27 is more prevalent in northern countries, and in certain aboriginal ethnic groups (7).

AS affects young individuals, with a mean age of onset in the third decade of life (1,6,7). Men are more frequently affected than women, at a ratio of approximately 2 to 1 (7). Symptoms develop early, but patients are unfortunately diagnosed on average 5-10 years after the onset of complaints (6). In our rheumatology clinics, there are more referrals of male patients. We have observed that this may be because male patients often have more severe disease, with earlier onset, contributing to a referral bias for specialist care.

Discussion of the epidemiology of AS is further complicated by the fact that other seronegative arthritides can include AS along with other spondyloarthropathies, such as psoriatic arthritis (Figure 2). When one considers the full spectrum of spondyloarthropathies, arriving at epidemiologic estimates becomes increasingly difficult.

1.0.2. Clinical Features

The hallmark of AS is the presence of inflammatory back pain caused by inflammation at the sacroiliac (SI) and other joints in the axial skeleton (7). This presents as low back or gluteal (buttock) pain or stiffness, which is often worse after

periods of inactivity (8). Other classical features of inflammatory back pain include morning stiffness of greater than 30 minutes duration, improvement with exercise, nocturnal wakening and alternating buttock pain (7). Due to the high prevalence of mechanical back pain in the general population, the back pain of AS is frequently misdiagnosed. Other skeletal manifestations include arthritis of the girdle joints (hips and shoulders), and less frequently of the peripheral joints (8). When it does occur, the peripheral arthritis tends to be oligoarticular (involving 3 or fewer peripheral joints) and gravitates toward joints of the lower extremities (7). Another classic skeletal clinical feature of AS is inflammation of the site of insertion of tendon into bone, called enthesitis (8). Osteoporosis and vertebral fractures occur commonly (8).

Like many rheumatic diseases, AS also has characteristic extra-skeletal manifestations, which may be as troublesome as the arthritis. Acute anterior uveitis is an inflammatory disorder of the eye, affecting 25-40% of AS patients at some point during their disease course (8). It is frequently recurrent and may result in decreased vision if not promptly treated (8). Cardiac manifestations, such as aortitis that can give aortic valvular insufficiency and conduction abnormalities, may also occur (8). Restricted chest expansion may lead to extra-parenchymal restrictive lung disease and pulmonary fibrosis at the apices of the lungs can occur (8). Gastrointestinal inflammation has also been reported, consistent with the well-known entity of inflammatory bowel disease (IBD) related spondyloarthropathy (8). Interestingly, inflammatory gastrointestinal lesions have been found on endoscopy of AS patient who were asymptomatic from a bowel point of view (8). Neurologic involvement may occur from compression of the spinal cord, spinal fractures and atlanto-axial subluxation (8).

1.0.3. Diagnostic And Classification Criteria For AS and SpA

A number of classification systems have been proposed for AS (8). The 1984 Modified New York criteria are frequently referenced (Table 1) (9).

The presence of HLA-B27 is not included in either the classification or diagnostic criteria for ankylosing spondylitis (8). However, it is often used to aid in the diagnosis of cases that are equivocal, in which case HLA-B27 positivity increases suspicion of AS (8). HLA-B27 is present in 90-95% of patients with AS, but also fairly prevalent in the general population (about 8%) (8). As previously mentioned, prevalence of HLA-B27 also varies according to the patients' country of origin and ethnicity (8).

Modified New York Criteria For Ankylosing Spondylitis, 1984

Criteria

1. Low back pain for at least 3 months' duration improved by exercise and not relieved by rest
2. Limitation of lumbar spine motion in sagittal and frontal planes
3. Chest expansion decreased relative to normal values for age and sex

4a. Unilateral sacroiliitis grade 3-4
4b. Bilateral sacroiliitis grade 2-4

Definite AS if

(4a or 4b) AND any clinical criterion (1-3)

Table 1: Modified New York criteria for the diagnosis of AS (9).

Diagnostic criteria for the identification of seronegative SpA have not been formally defined, though a preliminary classification scheme was proposed in the early 1990s by the European Spondylarthropathy Study Group (ESSG) (10). Figure 2

outlines the proposed classification criteria, which had a sensitivity and specificity of 87% each, but were not evaluated in diverse clinical settings (10).

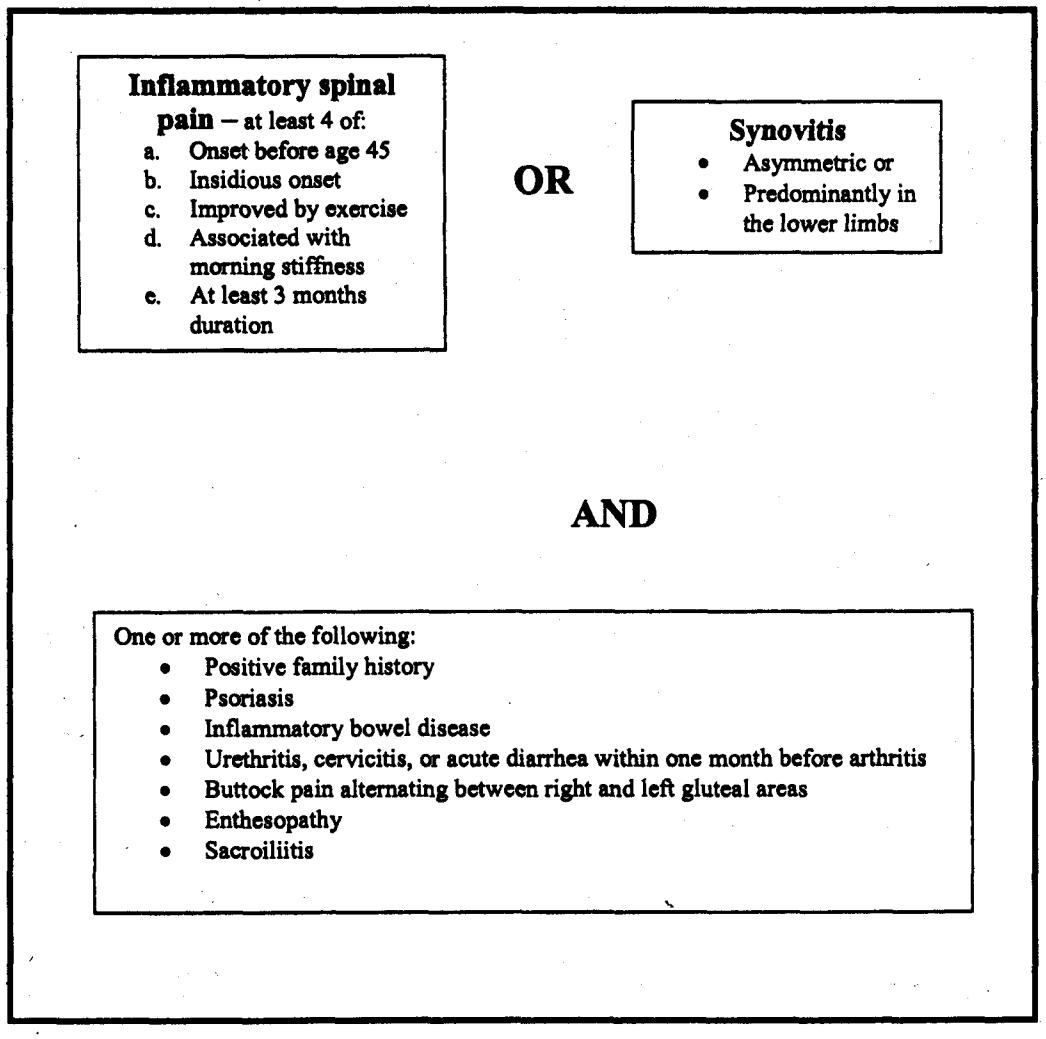


Figure 2: Proposed preliminary classification criteria for spondyloarthritis, modified from (10).

The classical radiographic lesion of AS is sacroiliitis, and its high prevalence in AS has lead to its inclusion in most sets of AS diagnostic criteria (7, 8). The degree of involvement of the SI joints is graded on a scale of 0 to 4 (normal to complete ankylosis) (7, 8). Sacroiliitis is typically bilateral and symmetric (8). Notably, SI joints may appear normal on early plain radiographs, leading to false negatives in diagnosis (7). In symptomatic individuals with apparent normal SI films, MRI may be useful in detecting the inflammatory changes that precede structural damage (7).

Inflammation in the vertebral column affects the outer layers of the annulus fibrosus where they attach to the vertebral bodies, the apophyseal joints and interverterbral ligaments (8). Bony erosions develop, and the superficial layers of the annulus fibrosus begin to ossify, eventually forming bony bridges between vertebrae, called syndesmophytes (8). Syndesmophytes usually begin forming at the thoracolumbar junction before spreading caudally and cranially (8). Eventually, the entire spinal column can become fused, leading to the appearance known as "bamboo spine" (8). Loss of bone density can lead to osteoporosis and spinal fractures (8).

1.0.5. Outcome Measures

1.0.5.1. The Health Assessment Questionnaire (HAQ)

The HAQ can be found in Appendix A.

The HAQ was published in 1980, and is considered to be the gold standard of patient reported outcomes (PROs) for arthritis (11). It enables users to evaluate health outcomes in a manner that produces data which is valid, reliable and sensitive to change (12, 13). The HAQ was founded on 5 generic outcomes which were found to be important to patients: death, disability, discomfort, drug toxicity and dollar costs

(12, 13). These 5 outcomes were then subdivided into a more detailed hierarchy (12, 13). The HAQ was designed to be used largely for longitudinal follow-up of patient outcomes in chronic disease (12, 13). The HAQ is frequently used in two forms, a full version and an abbreviated short version, called the HAQ Disability Index (HAQ-DI) (13). In this study, the traditional HAQ was used to assess relevant aspects of disability (13). It asks patients questions about their ability to perform usual activities over the past week (12). The HAQ assesses impairments in dressing, arising, eating, hygiene, walking, reach, grip and outside activity (12, 13). It also asks patients to complete visual analogue scale (VAS) assessments of pain and global health (12, 13).

The metric properties of the HAQ have been intensively studied (13). Each item set included in the questionnaire has been comprehensively validated using correlation matrices, item-total correlations and correlations with measured gold standards (13). It has been shown to have good face and criterion validity (13). The HAQ has been shown reliable through multiple studies, as well (13). Test-retest correlations for reproducibility are very high (13).

The disability portion of the HAQ consists of 20 questions in 8 functional categories (dressing, arising, eating, hygiene, walking, reach, grip and outside activity) (12). Each item is scored on a scale of difficulty from 0-3 (12). The category scores are averaged and reported on a scale of 0-3, with a higher score representing greater disability (12). Pain is assessed on a double anchored horizontal VAS scored from 0 (no pain) to 100 (severe pain) (12). Global health is also assessed on a horizontal VAS, similar to that used for pain (12).

The HAQ is an important tool to include in the assessment of WD as it is known to correlate significantly with WD as well as other work-related measures, including work capacity, work task performance, and occupation (13).

The HAQ is almost always reported in any arthritis trial, and has been used in numerous arthritic conditions, including AS (13). Furthermore, it is used outside of rheumatology in a wide number of conditions and in general population surveys (13). For these reasons, it is important to compare results of the HAQ with those of the other survey tools used in this study.

1.0.5.2. The Bath Indices

Historically, consensus on appropriate outcome measurements specifically for AS were difficult to achieve, until the development of the Bath AS indices in the mid-1990s (14,15). The Bath Ankylosing Spondylitis Funtional Index (BASFI) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) are now considered to be "gold standards" of outcome measurement in AS, and are used in virtually every AS clinical trial.

Other outcome measures in rheumatology commonly focus on the peripheral joints, thereby ignoring the predominantly axial involvement that is the hallmark of AS. The Bath Indices were some of the first outcome measures designed to specifically address limitations experienced by patients due to spinal disease. Additionally, generic outcome measures are likely not suitably sensitive to detect changes in patients with AS (14).

An assembly of experts in AS have formed the Assessment in AS International working group (ASAS), and has proposed core sets of measurements which should be recorded and followed clinically by rheumatologists (Table 2) (16). The ASAS core set includes both the full BASFI and components of the BASDAI, emphasizing that these measurements are important for daily clinical assessment as well as clinical trials (16).

Domain	Instruments
Patient global assessment	VAS in the last week
Spinal pain	VAS, average overall spinal pain due to AS in the last week *and* VAS, average nocturnal pain due to AS in the last week
Spinal stiffness	VAS, morning stiffness
Spinal mobility	Chest expansion *and* Modified Schober index, *and* occiput-to-wall distance, *and* lateral spinal flexion, *or* Bath Ankylosing Spondylitis Metrology Index
Physical function	Bath Ankylosing Spondylitis Functional Index, *or* Dougados Functional Index
Peripheral joints and entheses	Number of swollen joints (44 swollen joint count), validated enthesitis score
Acute phase reactants	ESR

Table 2: ASAS core sets for clinical record keeping in ankylosing spondylitis. VAS: visual analogue scale; ESR: erythrocyte sedimentation rate. Modified from (16).

Outcome measures such as the Bath Indices are particularly important in AS, since traditional clinical measures and lab values are known to poorly predict radiographic damage (14, 15). The utility of the Bath Indices is further supported by the fact that they have good known content, face, criterion, discriminant and construct validity (14, 15). Furthermore, they are quick and easy self-administered tools that are not cumbersome to patients or clinicians (14, 15). Both the BASFI and BASDAI have also been shown to be reliable, reproducible and applicable to the entire spectrum of AS (from mild to severe disease) (14, 15).

1.0.5.2.1. The Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI can be found in Appendix B.

The BASFI was developed with the input of rheumtologists, physiotherapists, researchers and patients with AS (14). The inclusion of a multidisciplinary team distinguishes the BASFI from other AS functional indices (14). The BASFI consists of 8 questions regarding functional anatomy and 2 questions that assess patients' abilities to cope with everyday life; this allows the questionnaire to fully assess activities of daily living (ADLs) (14). The tasks asked about on the BASFI are specific enough to avoid confusion, yet they are also common tasks that almost all individuals would be familiar with (14). Patients are also specifically asked to exclude the use of aids or assistive devices (14). Patients are asked to rate their responses to each question on a 10 cm VAS that has no distinguishing marks except for "easy" and "impossible" at either end of the scale (14).

The BASFI score is easily calculated by taking the mean of the 10 individual scores (14). When developed, the BASFI was extremely quick for patients to complete, with a maximal completion time of 100 seconds (14).

Validity of the BASFI was established through comparison with a previously published AS functional index, the Dougados functional index (17). The BASFI was found to have better score distribution than the Dougados (14). The BASFI was both reproducible and consistent when administered 24 hours apart (14). External validation between patient and observers scores were also reliably consistent (14).

Importantly, the BASFI showed a greater sensitivity to small treatment changes than the Dougados functional index (14). Specifically, an intensive three-week course of treatment improved BASFI scores significantly, but produced no significant change on the Dougados functional index (14).

1.0.5.2.2. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI may be found in Appendix C.

As with the BASFI, the BASDAI was developed with input from a multidisciplinary health care team that included rheumatologists, physiotherapists, researchers and patients (15). The BASDAI consists of 6 questions in regards to 5 areas of commonly cited disease activity in AS: fatigue, spinal pain, joint pain/swelling, localized tenderness (assessing enthesitis) and morning stiffness (15). Morning stiffness is assessed by 2 questions, thus ascertaining both quality and quantity of the stiffness (15). The complete BASDAI can be found in Appendix C.

As with the BASFI, responses to the first 5 BASDAI questions are recorded on a 10 cm VAS with no distinguishing marks other than descriptive markers at the extreme ("none" to "very severe") (15). The last question, which assesses duration of morning stiffness, is anchored with "0 hrs" and "2 or more hrs" with marks at 15 minute intervals (15).

The BASDAI score is calculated by taking the average of the last 2 questions (relating to morning stiffness). This value is then added to the remaining scores, and the total divided by 5 to create an aggregate (15). In this way, the morning stiffness

question has equal weighting as the others, despite the fact that it is assessed twice (15).

The BASDAI is quick to complete, taking a mean time of one minute (range 30-120 seconds) (15). Reliability was assessed though completion of the BASDAI at the same time of day on two consecutive days of an inpatient treatment program (15). Using this technique, the BASDAI was found to be highly reliable and consistent (15). The BASDAI was to accommodate a wide range of responses, with a good score distribution (15). The BASDAI was sensitive to change during a relatively short (18 day) treatment period (15). None of the individual symptoms asked about on the BASDAI correlated well with each other, with the exception of the two questions about morning stiffness (15). The BASDAI also correlated well with a previous version of the index (Bath DAI) (15).

Importantly, the BASDAI was one of the first questionnaires to include assessment of patient fatigue as an outcome measure (15).

1.0.5.2.3. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G)

The BAS-G may be found in Appendix D.

The BAS-G is a single-item, patient administered global assessment score that reports patients' well-being over a certain period of time (18). It is comprised of 2 questions. On each, the patient is asked to indicate the effect of their disease on a 10 cm VAS. The first question covers the last week, and the second asks about the last six months. The mean of the two VAS scores gives the final BAS-G score, on a scale

of 0-10, with higher numbers indicating a greater perceived effect on the patient's overall well being (18).

The BAS-G has been formally assessed for face, discriminant, predicitive and construct validity (18). Responses to the BAS-G have been found to cover the full range of scores (0-10) for both the week and six month components (18). The BAS-G has been shown to correlate well with both BASDAI and BASFI, suggesting that both disease activity and functional ability play significant roles in patients' perceived well-being (18). In particular, the spinal pain and fatigue components of the BASDAI were highly correlated with the BAS-G, suggesting that these issues play a significant role in patients' perceptions of well-being (18). Interestingly, the BAS-G did not correlate as well with metrology outcomes (18). The BAS-G was also shown to be significantly sensitive to change (18).

Importantly, for studies of WD, BAS-G was not associated with occupational status (18).

1.0.5.3 The Functional Comorbidity Index (FCI)

The FCI may be found in Appendix E.

Patients with AS may have comorbid conditions which could also affect outcomes in WD. Adjusting for these comorbidities is important if the WD is to be relevant specifically for AS. For this reason, it is important to collect data regarding comorbidities in any disability research. The tool used in this study was a quick self-administered questionnaire called the Functional Comorbidity Index (FCI) (19).

The FCI was developed by determining factors associated with physical function through literature review and focus groups (19). Similar diagnoses were grouped together, resulting in 40 remaining diagnoses (19). The authors of the FCI chose a diagnosis-based system rather than a symptom-based system to avoid subjective and vague responses regarding comorbidities and to simplify data extraction through existing databases (19). Two large national (Canadian) databases were used (19). Multiple linear regression was then used to identify variables that were significantly associated with the SF-36 physical function score; 18 such variables were ultimately found (19). These 1 variables were: arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease (COPD), angina, congestive heart failure (CHF), prior heart attack (myocardial infarction, MI), neurologic disease (multiple sclerosis, Parkinson's disease), prior stroke or transient ischemic attack (TIA), peripheral vascular disease (PVD), diabetes, upper gastrointestinal disease (ulcers and gastroesophageal reflux disease), depressed mood, anxiety, visual impairment, hearing impairment obesity and back pain (19). The FCI is scored as a simple count of the present diagnoses, which was found to be equivalent to a weighted count, that is, a count in which subjectively more "important" conditions were given more weight (19).

The FCI was found to correlate well with the SF-36 physical and role function subscales (19). It also accounted for more variation in physical function scores than other commonly used measures of comorbidity, such as the Charlson and Kaplan-Feinstein indices (19).

Importantly, the FCI was developed with physical function as the main outcome, rather than mortality (19). Other comorbidity tools were not developed with

function as an outcome, and thus would be less appropriate choices for a study of WD.

1.1. Work Disability

In our study, we defined WD as not able to work, due to arthritis. However, there are many ways of defining WD.

1.1.1. Defining Disability

Disability is a difficult concept to define, since its characterization depends upon the viewpoint of the observer. From a medical or disease viewpoint, disability is frequently defined as the consequences or impact of a disease condition (20). From a rehabilitation or disability perspective, the patient's health and functioning are not simply a consequence of disease, but are associated with disease itself, and are placed in the context of personal and environmental factors (20). Both of these perspectives are equally important to the clinician when assessing their patients.

1.1.2. Conceptual Frameworks In Disability

The most commonly used current framework of disability is the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF). The ICF measures health and disability at both individual and population levels (21). The ICF classifies health and health domains that describe body function, body structure, activities and participation and environmental factors

(22). It takes a holistic approach to disability, and the individual domains are classified from body, individual, and societal perspectives (22). Figure 3 illustrates the WHO ICF framework (22).

In the ICF framework, disability is an interaction between diseases and contextual factors that lead to impairment, limitations in activity and reduced participation (20). The interaction between disability and functioning is viewed as dynamic.

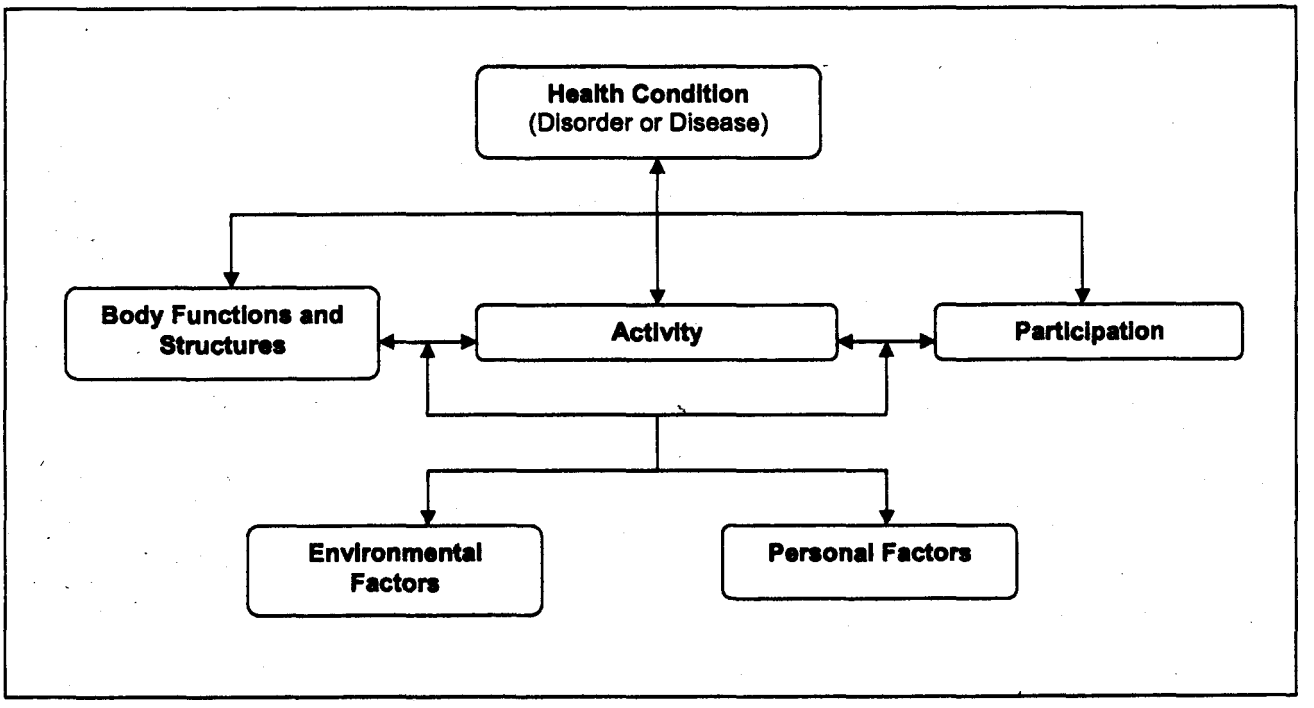


Figure 3: The WHO International Classification of Functioning, Disability and Health (ICF) (22).

1.1.2.1. The WHO ICF As Applied To Arthritis

The WHO ICF can easily be applied to inflammatory arthritis in general, and to AS in particular. Impairments are defined as significant loss of body structure and function, or both (20). The body functions and structures that are affected include not only the peripheral and axial joints, but in many cases other organ systems. For example, ocular involvement in AS is not typically thought of as an arthritic problem, but could lead to significant functional impairment through reduced visual acuity. Participation affected could include work/employment, but also participation in hobbies or personal relationships. Such limitations in participation are referred to as restrictions (20). These restrictions are compared to levels of participation acceptable for the general population.

Practical lists of affected areas for a particular disease are gathered into ICF Core Sets (20). The goal of developing the ICF Core Sets is to provide lists of domains that may help physicians when dealing with individual patients and may aid in rehabilitation (20).

The ICF framework has previously been applied to patients with AS, specifically, through a series of interviews (23). Patients with AS found 76% of the ICF categories to be relevant on an extended checklist (23). Of these categories, 35% were related to mobility or movement (with in the components "body functions and structures" and "activities and participation" (23). The interviews also found that AS had a significant impact on patients' vitality, with large numbers reporting impairments in emotional, energy/drive, and sleep functions (23). Additionally,

patients frequently reported restricted participation in leisure and recreational activities (23).

Of note, patients also reported that environmental factors behaved as either facilitators or barriers to their function (23). Conceivably, environmental factors in the workplace could significantly impact levels of functioning in AS, such as a job requiring heavy labor compared to a sedentary job.

1.1.3. Defining Work Disability (WD): Methodology

Numerous methods have been used to define productivity loss at work due to chronic medical conditions. Terms that have been applied include work disability (WD), work disability days, work loss, work limitation and work instability (24).

WD has been defined as the state in which the affected individual has had to leave their jobs, or forced to work fewer hours (24). WD is the most commonly investigated outcome in rheumatic diseases, with most research focusing on rheumatoid arthritis (RA) (24).

One issue that complicates the WD literature is the variable methodology that has been used in WD studies. For example, some studies rely exclusively on patient self-report, while others use administrative databases or economic outcomes (24). Additionally, literature searches of previous research in WD are complicated by the lack of standardized terminology. Searches on "work capacity", "absenteeism", "sick leave" and "occupational health" may all recover relevant articles but not identical results from the searches.

An additional challenge is the definition of employment outcome measures (25). Surrogate outcome measures, such as days off from work likely underestimate the full impact of disease on employment (25). More holistic outcomes, such as career satisfaction, advancement and quality of life while at work are difficult to measure (25).

Another methodological issue in WD literature is the lack of research on unpaid work. Restrictions in caring for children or the elderly, volunteer and community activities are undoubtedly important endpoints that are difficult to quantify by traditional WD assessments (25).

The easiest employment outcome to measure is days or hours missed from work, but not all WD leads to absenteeism. Recently, the concept of *presenteeism*, or decreased work performance due to health conditions, has emerged in the WD literature (26). Presenteeism includes decreased productivity due to time not spent on task, decreased quality of work, decreased quantity of work and personal factors (26). Several self-reported workplace productivity instruments have been developed, and measure elements of presenteeism (26). For the purposes of this study, WD will be defined as the inablility to do paid work due to AS and the extent of limitations at work will be studied using standardized questionnaires as defined elsewhere.

1.1.4. Outcome Measures In WD: The Work Limitations Questionnaire (WLQ)

See Appendix F for the Work Limitations Questionnaire.

The WLQ was developed in 2001 in order to determine the on-the-job impact of chronic conditions, and their treatment (27, 28). It was specifically designed to fill

gaps left by previous employment measurement tools, specifically losses in productivity (27, 28). It consists of a 25-item, self-administered questionnaire that asks respondents to rate how their health problems interfere with performing job roles over the previous 2 weeks (27, 28).

The 25 items included in the WLQ were chosen for four specific reasons, outlined by the authors in the technical report that accompanies it (29). The reasons include: demands are required in a range of jobs; demands can be affected by a number of different physical and emotional health problems; demands are considered important by employees; and losses in work productivity are often related to the ability to perform the demands (29).

The 25 items contained in the WLQ assess 4 dimensions of work disability (27, 28). These include: limitations handling Time, Physical, Mental-Interpersonal and Output Demands (27, 28). A detailed schematic of the domains and items contained assessed by the WLQ can be found in Figure 4. Figure 5 details levels of data assessed by the WLQ.

The WLQ was developed using patients with several different chronic diseases, including asthma, Crohn's disease, liver disease, depression, generalized anxiety and epilepsy (27, 28). Patients were excluded if they had a history of substance abuse or a pending work disability claim (27, 28). Validity testing also included patients with chronic headaches, rheumatoid arthritis, and epilepsy (27).

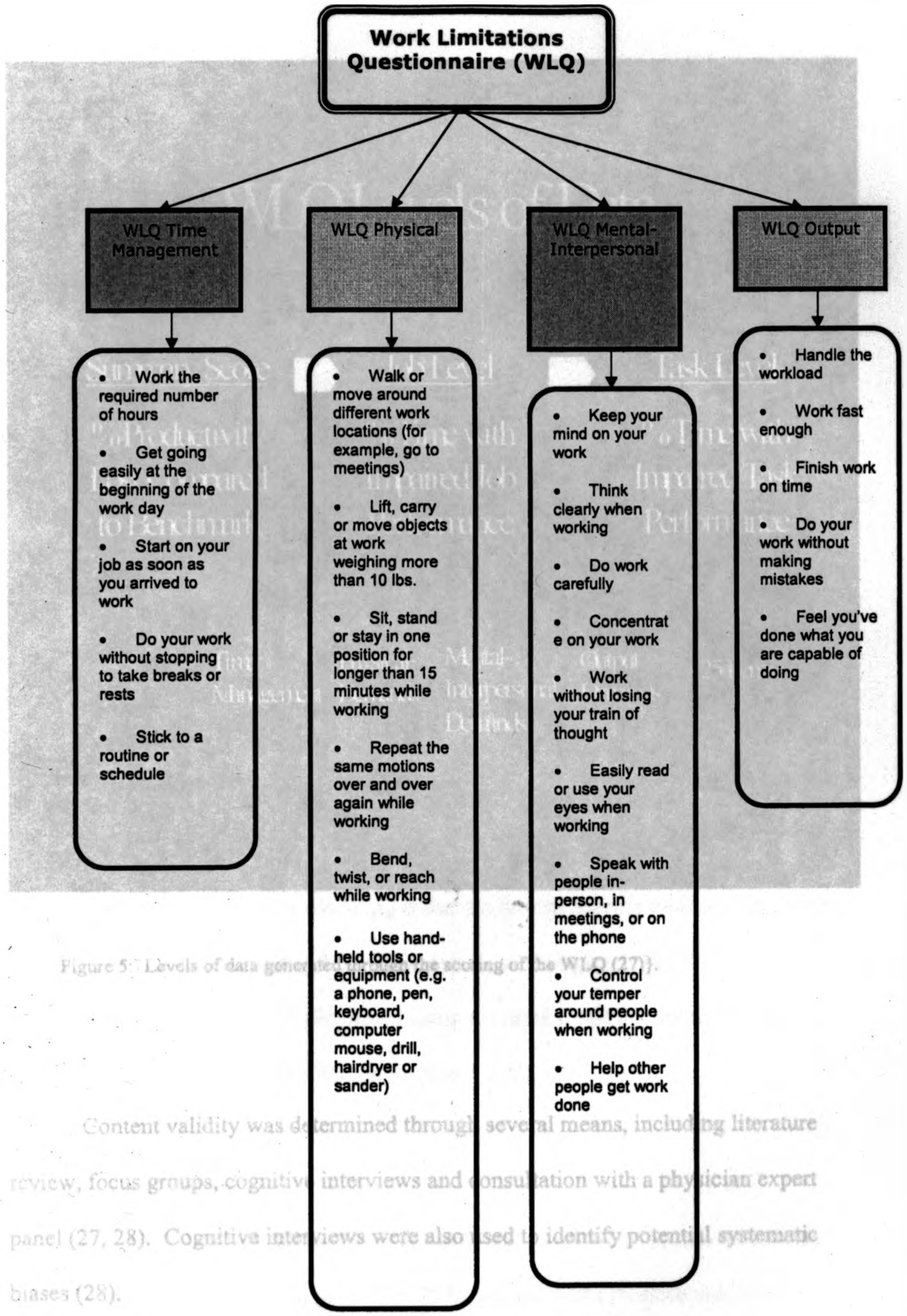


Figure 4: Domains and question content of the Work Limitations Questionnaire (WLQ) (27)

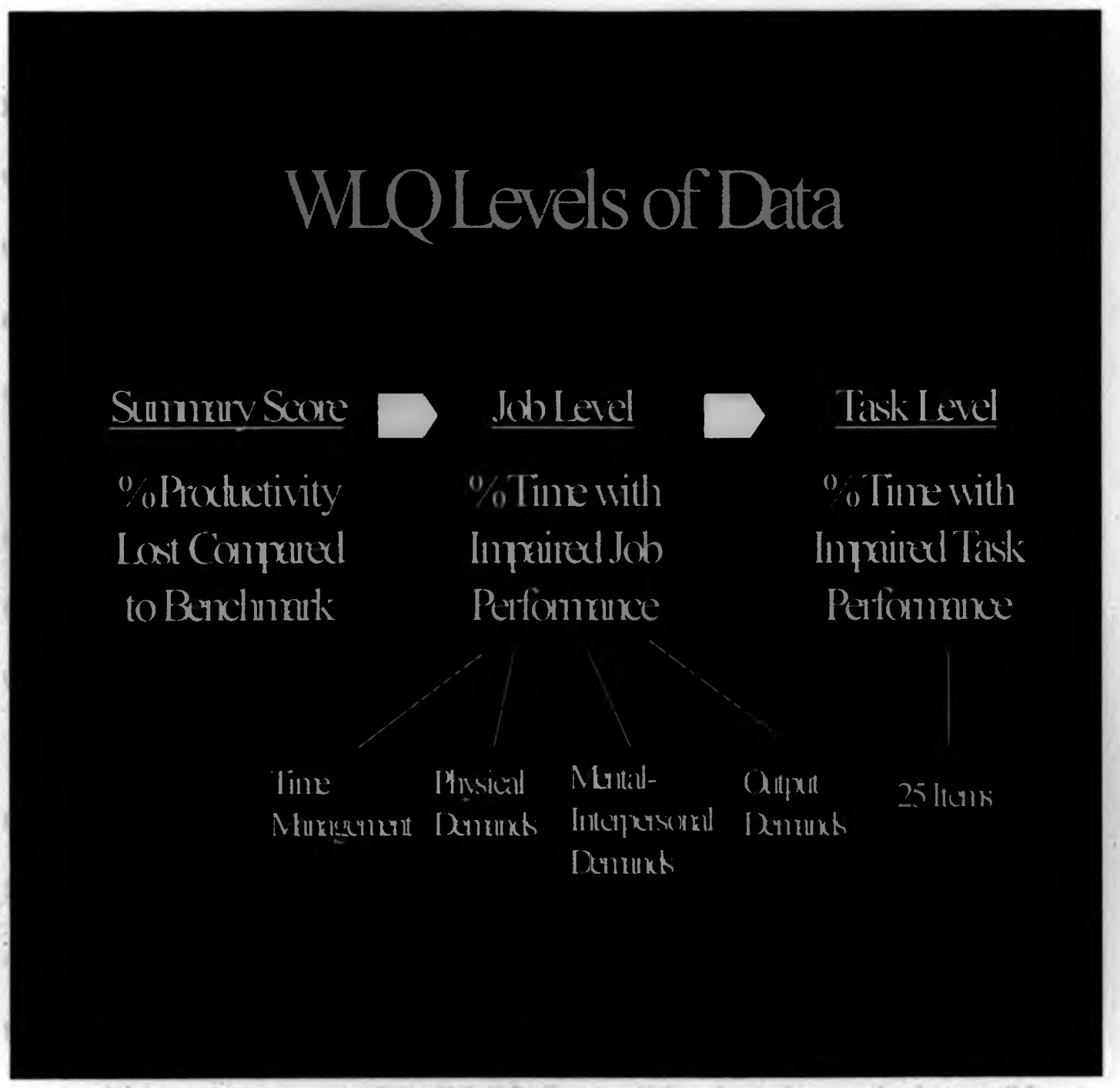


Figure 5: Levels of data generated through the scoring of the WLQ (27)}.

Content validity was determined through several means, including literature review, focus groups, cognitive interviews and consultation with a physician expert panel (27, 28). Cognitive interviews were also used to identify potential systematic biases (28).

Inter-rater reliability was determined through triangulation of the responses given to the WLQ by a worker with a chronic health condition, a control worker and observations by a trained expert (28). Intra-rater reliability and recall error were determined through the use of 3 different question formats, each with slightly different wordings (27, 28). Scaling tests revealed that Cronbach's α statistics were all above 0.70 and had good item-to-total correlation (27, 28).

Construct validity was determined through comparison of WLQ scores to scores from the SF-36 role limitation scales (27, 28). Criterion validity was tested in employees whose productivity was monitored electronically, who were then asked to complete the WLQ (28).

Recall error and bias was evaluated by asking both chronically ill and job-matched healthy controls to complete diaries of their work limitations (27, 28). Subjects were also asked to complete the WLQ at either the end of 2 and 4 weeks, or 4 weeks alone. These results were compared to the diaries, which were considered the "gold standards" for assessment of work limitations (27, 28).

An important aspect of the WLQ is that traditional scoring methods treat "does not apply" responses as missing data, though it may be imputed (30, 31).

Scoring of the WLQ is performed using a template that is provided by the survey authors (29). This is detailed in Section 1.1.4.1.

1.1.4.1. Scoring The WLQ

The WLQ produces three types of scores: summary scores, job level scores and task level scores (Figure 5) (29). The 25 individual items produce task level scores for limitations in performing a specific task for the preceding two weeks (29).

The items are combined to create four job level scores: time management, physical demands, mental-interpersonal demands and output demands (29). The job level scores provide a score for the degree of impairment each subject experienced for each of the four domains in the two weeks prior to responding to the WLQ (29). These job level scores then combine to form an overall summary score, which estimates the percentage of productivity lost due to ill health (29). The authors of the WLQ state that the summary score "reflects the percent difference in output between 'limited' employees and a benchmark group of employees that have no limitations" (29).

The confidential technical report that accompanies the WLQ provides specific instructions as to how to deal with missing data (29). Minimum numbers required to calculate summary scores, and methods to impute missing values are described in detail (29). Formulas are also provided for computing the scale scores and productivity loss scores (29). As the scoring report is confidential (at the authors' request), the details will not be included in this thesis, but are available upon request of the WLQ authors at wlq@tufts-nemc.org (phone 617-636-8149).

1.2. WD In The Rheumatic Diseases

1.2.1. WD In Arthritis In General

1.2.1.1. WD In Arthritis In General: Canada

Previous research has demonstrated that arthritis is frequently cited as a reason for WD, with high economic costs (32). Additionally, people with musculoskeletal conditions have been shown to have higher WD rates than those with other chronic

medical conditions (32). Another factor likely to impact WD rates is the fact that estimates suggest increasing numbers of individuals with arthritis in working age groups (45-64 years) over the next few decades (32).

A large population-based survey in Ontario found that those with self-reported arthritis were more likely to be out of the labor force, and one in 6 of those with arthritis reported disability (32). Other factors associated with not being in the labour force included older age, female gender and low education level (32). Additionally, family composition differentially affected men and women (32).

Data from the 1994 Canadian National Population Health Survey (NPHS) was used to calculate working life expectancy for those with and without arthritis and rheumatism (33). In this study, tables were used to calculate the expected number of future years a person would be in the workforce. A study of the NPHS data found that the working life expectancy of those with arthritis at all ages was reduced in comparison to the total population (33). The differences in working life expectancy were largest at younger age groups (33). On average, women with arthritis lost 4 years of work, and men with arthritis lost 3 years in comparison to the general population (33). The study authors noted that premature departure from the workforce has a multitude of outcomes, including social, psychological and economic effects (33).

It is more difficult to study *work transitions* that those with arthritis make to remain employed. These work transitions are changes in work pattern or job type without a necessary reduction in hours of overall employment. A recent study has examined the frequency of arthritis-related work transitions made by those with inflammatory and degenerative arthritis in order to remain employed (34). In this

small, interview-based study, work transitions were common, including inability to accept a promotion, inability to accept projects, change of work duties and use of vacation time in lieu of sick leave (34).

1.2.1.2.WD In Arthritis In General: Worldwide

WD has been examined worldwide, and many of these international studies can shed light on WD in a Canadian cohort.

Recently, data from the large US National Health Interview Study (NHIS) has been examined for the prevalence and correlates of Arthritis-Attributable Work Limitation (AAWL) (35). The results showed that the population prevalence of AAWL for adults 18-64 was quite high at 5.3% (6.9 million US adults) (35). The age-adjusted AAWL prevalence was found to be higher among women, those with lower education and income, and non-Hispanic blacks (35). Nearly one third of those with self-reported arthritis described some AAWL (35).

An in-depth German study, with large numbers of participants, examined employment across chronic inflammatory rheumatic diseases in comparison with the general population (36). This study had the advantage of adjusting for other reasons for nonparticipation in the workforce, including labor market conditions and subjects' level of education (36). The authors found that standardized employment ratios (SERs) were significantly reduced in those with RA, and less so in those with AS (36). SERs decreased as disease duration increased for all inflammatory rheumatic conditions (36). This study also found that a lower level of education was an independent risk factor for unemployment (36). The authors proposed, "Education

may be a surrogate marker for type of work, income, and self-management abilities" (36).

1.2.2 WD In AS

Although WD is most often studied in RA, some studies of AS-specific WD do exist. Boonen *et al.* completed a systematic review of the WD in AS literature, encompassing data published between 1980 and March 2000 (4). Notably, numbers for high-quality studies on this topic were poor (4). The studies included in the systematic review included a wide range of figures on employment, from 96-34% in patients with 5-45 years of disease duration (4). Half of the reviewed studies reported an employment rate less than 70% (4). As with employment, figures for WD encompassed a wide range, from a minimum of 3% to a maximum of 50% (4). Half of the included studies reported WD in greater than 20% of the studied AS patients (4). As with employment rates, WD figures appeared to be related to disease duration, though a multivariate analysis did not bear this out (4). All of the studies included in the systematic review reported substantial patient use of sick leave, from 12-46 days per working patient per year (4).

A retrospective cohort study of 234 patients with AS showed that patients altered the type of work that they did due to their AS (37). Patients tended to move from more to less physically active jobs over time (37). 26 % of the cohort reported leaving a job due to their AS (37). With long-term follow-up, 84% of patients were still working at 30 years of disease duration, and 77% at 40 years (37). This retrospective cohort analysis also used multivariate analysis to show the risk of permanent work disability was higher in those with older age of onset, lower

education level, and physically active jobs (37). Risk of permanent WD in AS increased by a remarkable 5% with each year of age of onset of AS (37). The authors concluded that although permanent WD was not common, temporary WD or changes at work occurred in nearly one third of the patient cohort (37). In comparison, WD in RA is reported at rates of 30-50%.

A Dutch study demonstrated that both men and women with AS had decreased employment in comparison to the general population (age and sex adjusted, 11% lower) (40). However, this decrease was only statistically significant for men (40). Patients with AS also took, on average, an additional 10.1 days of sick leave per year than the general population (40). The overall estimate of age and sex adjusted WD in the AS patients was increased by 15% in comparison to the general Dutch population (40).

Another Dutch study, authored by the same group, looked at a cross-sectional sample of 658 AS patients (41). In this patient sample, the age and sex adjusted risk of workforce withdrawal was 3.1 (95% CI 2.5-3.7) times greater than the general Dutch population (41). Rates of workforce withdrawal increased with time from diagnosis of AS, and was more pronounced in younger and male patients (41). The study was also unique in that it examined specific psychosocial and coping mechanisms in regards to their impact on WD. Patients with unfavorable coping strategies fared worse than those with favorable coping (41). Patients without a job because of WD had higher frequencies of psychopathology, worse physical function, higher disease activity, worse perceived health and higher levels of fatigue than those who were still working (41). In summary, the risk of WD causing work withdrawal

resulted in one third of patients having left the workforce by 20 years after diagnosis, and an overall threefold increase in WD (41).

A Canadian cohort was recently studied using patients largely from Alberta and Ontario (5). In this mail-based survey, 20% of patients reported that they had retired from their jobs due to AS (5) Other alterations in work patterns included a reduction in working time (9.5% of patients) or change in work (8% of patients) (5). Annual sick leave use was only marginally higher than that of the general population (8 days/year vs. 7.5 days/year) (5).

A summary of a literature review of WD in AS studies can be found in the following table, Table 3.

Citation	Population And Study Design	Definition Of WD	Results	Risk Factors For WD
Lehtinen K. Scand J Rheumatol 1981; 10263-265	76 patients from hospital sample; cohort study; Finnish study	Employment rates	96% employed at 5 yrs disease duration, 95% at 10 yrs, 87% at 15 yrs, 65% at 25 yrs, 34% at 45 yrs; 17% had to change occupation due to AS	
Chamberlain MA Int Rehabil Med 1981; 3:94-99	56 patients from hospital sample; cross-sectional; UK study	Employment rates	84% employed	
Chamberlain MA Int Rehabil Med 1983; 5:149-153	50 patients with AS (25 male and 25 female); UK study	Employment rates	60% employed	Fatigue accounted for much of the disability
Nissila M et al. Scand J Rheumatol	84 patients with SpA; Finnish study	Employment rates	89% employed; disability due	

1983;12:33-38			to AS 9%	
McGuigan LE et al. Ann Rheum Dis 1984; 43:604-606	84 patients with AS; New Zealand	Patient report of inability to work due to AS	4.8% unable to work due to AS; 80% had full-time jobs which they performed without difficulty	All 4 patients who were WD employed in light manual labour; severe restriction in lumbar spine ROM and symptomatic hip disease impaired work
Urbanek T et al. Czech Med 1984; 7:78-89	170 patients with AS; Slovakia	Patient report of employment status	61.2% of AS patients remained in their original employment; 28.8% received full invalid rent	Labor activity; level of education
Gran JT et al. J Rheumatol 1984; 11:788-793.	100 AS patients; combination of community and hospital; Norway	Employment rates	Overall 69% employed	More community employed (89%) than hospital (63%)
Gran JT et al. J Rheumatol 1985; 12:126-129	44 females and 82 males with AS; combination of community and hospital patients; Norway	Employment rates	Employment rate 69%	
Wordsworth BP et al. Br J Rheuamtol 1986; 25:175-180	100 patients with AS; UK	Employment rates	9% unemployed; 9% felt that AS seriously affected employment; 2% retired due to AS; >2 months sick leave in 32.9%	
Kaarela K et al. Scand J Rheumatol 1987; 16:403-406	20 patients with AS; cohort study with retrospective	Employment rates	After 8 years, 85-90% of AS patients were employed; 15% reported	

	assessment; community patients; Finland		disability due to arthritis	
Guillemin F et al. Arthritis Rheum 1990; 33:1001-1006	182 patients with AS; France			
Edmunds L et al. J Rheumatol 1991; 18:696-8	1332 patients with seronegative SpA; comparison of AS with PsA and IBD related SpA age and sex controlled; UK	Self-report of working status	PsA vs AS: 65% and 68% working respectively; IBD AS vs AS: 55% and 56% working respectively	
Ringsdal VS et al. Dan Med Bull 1991;38:282-284	248 patients with AS; cross-sectional; Danish study	Responses to questionnaire regarding employment status	85% able to work after 20 or more years of illness; 41 reported reduced ability to manage full-time work; 85 changed occupation or educational status due to AS; 31 retired as invalids	
Roussou E et al. J Rheumatol 1997; 24:908-911	1044 patients with AS; 1/3 from hospital and 2/3 from patient society; cross-sectional; UK study		85% were fully employed and 15% unemoloyed	Increased disease activity; lower psychosocial well being
Gran JT et al. Br J Rheumatol 1997; 36:766-771.	100 patients with adult-onset primary AS; mean disease duration 16 years; cross-sectional; Norwegian	Employment status; functional outcome through assessment of ADLs	51.5% employed in full-time work; work cessation occurred at a mean disease duration of 15.6 years; loss of	Female sex; low education level; acute anterior uveitis; bamboo spine; co-existence of non-rheumatic disease

	study		function occurred within first 10 years of disease activity	
Boonen A et al. Ann Rheum Dis 2001; 60:353-358	658 patients with AS; cross-sectional; large Dutch study	Inability to perform paid work due to AS	11% decrease in employment, 15% increase in WD, 10.1 days of sick leave due to AS per person per year	Male sex
Boonen, A et al. Ann Rheum Dis 2001; 60:1033-1039	658 patients with AS; cross-sectional; large Dutch study	Inability to perform paid work due to AS	17.3% left the work force due to AS, age and sex-adjusted risk of withdrawal from the work force compared to general Dutch population 3.1 times greater in AS	Older age at diagnosis, manual work, unfavorable coping strategies, longer disease duration, lower social class, presence of comorbidity, extraspinal disease, total hip replacement, psychopathology, higher BASFI, BASDAI and BAS-G scores, higher levels of fatigue
Ward MW et al. J Rheumatol 2001;28:315-21	234 patients with AS, retrospective cohort; 144 patients assessed for risk factors for change in work hours, prospective study	Payments for WD or self-reported WD	13.2% reported permanent WD; 84% of patients still working at 30 yrs of AS and 77% still working at 40 yrs of AS; 24.3% received payments for WD; 14-31% made	Lower level of education, more comorbid medical conditions, smoking, more physically active jobs, older age; Risk of permanent WD increased by 5% with each year of age of onset of AS and decreased by

			significant changes at work due to AS	24% with each additional year of education, female sex more likely to receive payments for temporary WD
Barlow JH et al. Arthritis Rheum 2001; 45:424-429	39 consecutive patients from rheumatology outpatient department and 94 members of the National AS Society; total 133 patients; UK; cross-sectional	Open-ended questions regarding change in work due to AS	31% experienced WD; 46% had to change nature of their job; many patients reduced working hours, changed roles, worked from home, became self-employed, resigned or took early retirement	Older age, longer disease duration, lower level of education, comorbidity, greater physical impairment, fatigue, pain, stiffness, anxiety, depressed mood, lower self-esteem
Boonen A et al. Ann Rheum Dis 2002; 61:429-437	216 patients with AS from three European countries (Netherlands [NL], France [F], Belgium [B]), observational	Officially recognized inability to perform paid work because of AS according to the criteria of each country; productivity costs calculated using friction costs (FC) and human capital approach (HC)	Those reporting AS-related sick leave from a paid job: 52% in NL, 48% in F, 47% B; days of sick leave per working patient per year: 18.5 NL, 6.0 F, 9.2 B; adjusted employment 55% NL, 72% F, 72% B; adjusted WD 41% NL, 23% F, 9% B; higher FC and HC in NL; WD in all countries associated with	Living in NL, manual job, higher BASFI scores, presence of IBD

			poorer QOL	
Boonen A et al. Ann Rheum Dis 2002; 61:658	658 patients with AS, cross-sectional, large Dutch study	Able to participate in a paid job	Overall risk to withdraw from labor force 3.0 times greater in AS than expected in the general population; risk is 4.9 times greater in those with a manual job vs. 2.2 times higher for those with a non-manual job	Observed effect stronger in males (NB smaller number of females in study)
Chorus AMJ et al. Ann Rheum Dis 2002; 61:693-699	658 patients with AS, cross-sectional, large Dutch study	Able to participate in a paid job	11% reduction in work participation compared to general Dutch population; 86.1% due to physical limitations, 77.4% due to fatigue, 73% due to limitations in coping	Longer disease duration, increased disease activity, use of more medications, total hip replacement, coping strategy, decreased global well-being (BAS-G), industrial job, difficulty accessing workplace, increased dependence on colleagues, decreased support
van Tubergen et al. Ann Rheum Dis 2003; 62:140-145	214 patients with AS from 2 separate trials; 117 from an RCT of spa treatment and 97 from a longitudinal observational	World Health Organization Disability Assessment Schedule II (WHODAS II) – a measure of disability across various	Mean WHODAS score of 23.9 (SD 15.5) but large range (0-76)	Scores on WHODAS II significantly correlated with BASFI, BASDAI, DFI, HAQ-S, PGA, spinal pain, ASQoL and all

	study of outcomes	conditions and interventions		domains of SF-36; variables which best predicted disability after 5 yrs were BASFI and BASDAI scores
Chorus AMJ et al. Ann Rheum Dis 2003; 62:1178-1184	658 patients with AS, cross-sectional, large Dutch study; comparison made with 1056 patients with RA	Able to participate in a paid job	Quality of life by SF-36 physical (PCS) and mental (MCS) functioning scales; physical health related QOL in patients with RA worse than AS, but mental health related QOL similar between RA and AS	
Van Der Heijde D et al. Arthritis Rheum 2006;55:569-574	ASSERT Trial (AS Study for the Evaluation of Recominant Infliximab Therapy) – phase III randomized, double-blind, placebo-controlled, multicenter trial designed to assess safety of infliximab vs. standard anti-inflammatory therapy in AS; 279 patients with AS	10 cm VAS self report of perceived impact of AS on daily productivity in past 6 weeks; individual SF-36 questions (answering "yes" to at least 1 from either physical or mental domains constituted impairment in work); self-perceived work ability; workdays lost	At baseline: 70% employable, 58% employed, 23% receiving disability compensation, productivity 3.8 on 10 cm VAS	High BASFI scores, emotional problems based on SF-36 items, those in infliximab group had significant reduction in impact of physical and emotional health on work, had improved productivity and lost fewer workdays compared to placebo group
Kobelt G et al. J Rheumatol 2006; 33:289-	545 patients from rheumatology	Questionnaires with specific questions on	20.2% retired from work due to AS; 9.5%	Higher costs associated with higher BASFI

295	centers in Alberta, members of the Ontario Spondylitis Association and The Arthritis Society (BC branch); cross-sectional retrospective	WD	reduced working time; 8.4% changed their work; mean annual sick days 8 days/yr (vs. 7.5 days general Canadian population); mean annual cost/pt Cdn $9 008	and BASDAI scores
Collantes E et al. Rheumatology 2007; 46:1309-15	National Spondylo-arthropathies Registry (REGISPONS-ER) in Spain, 1379 patients with AS; prospective cohort	Demographic questionnaires	26.5% had some sort of life-long occupational disability; of these, 3.9% temporarily disabled, 4.4% permanently, partially disabled, 5.5% permanently, totally disabled, 11% totally disabled from work of any kind, 0.7% absolutely disabled (required aid in daily life tasks)	
Rkain H et al. Clin Rheumatol 2007; 26:2081-2088	100 consecutive patients with AS hospitalized or seen in clinic at Moroccan hospital	Permanent work stoppage as determined by investigator-administered questionnaire asking about economic consequences of AS	22.9% withdrawn from work; mean timing of withdrawal 43.4 months after AS onset	Higher BASFI scores, higher BASDAI scores, unmarried marital status, lower education level, relationship problems with supervisors, physically

				demanding jobs, lack of health insurance, independent work
Tam L-S et al. J Rheumatol 2007; 34:1032-9.	314 members of Hong Kong AS association and Hong Kong B27 Association	Ever on either temporary or permanent WD resulting from AS	23% reported AS-related WD (7% retired prematurely, 15% unemployed, 1% sick leave); median time to inability to work 11 years; WD rate 2-6 times higher than age- and sex-matched Hong Kong general populations	Work capacity lower in more severe disease (BASFI and BASDAI scores), lower family income
Ward MW et al. Arthritis Rheum 2008; 59:497-503	549 patients seen at US rheumatology clinics; cross-sectional	Self-report of inability to participate in paid work, regardless of cause	13% WD compared to expected population risk of 5.7% WD; 90% attributed WD to AS	Female sex more likely to have withdrawn from labor force (RR 4.0 women vs 2.9 men), AS $\geq$ 20 yrs, age $\geq$ 45 yrs, not college graduate
Kobelt G et al. Value Health 2008; 11:408-15	601 patients; retrospective; Spain	Loss of work capacity including sick leave, reductions in working time because of AS, early retirement; used the human capital approach	53% were working compared to 69% of general population; 24.5% stopped work due to AS; 13% reduced work hours; 19% changed jobs due to AS	Earlier disease less WD than later disease; loss of work capacity with advancing disease of 30%

Table 3: Summary of studies examining WD in AS.

1.2.2.1. Personal Factors Related To WD In AS

Few studies have examined patients' personal reasons for leaving work in AS. Chorus et al. studied employment perspectives in patients with AS in Dutch AS cohort (42). In this study, patients who withdrew from the labor force had longer disease duration, had higher levels of disease activity, had greater general disabilities, used more medications and had more often had a total hip replacement (42). Those who stopped working were also more likely to be employed in the industrial sector rather than as professionals (42). Those who withdrew from the workforce were less likely to have special training for their jobs and more likely to have had a physically demanding job at some point during their working life (42). Work disability was lower for those who worked for larger corporations, as well as for those who had ergonomic work adjustments (42).

AS patients who stopped working also reported difficulty accessing their workplace and reduced transportation resources (42). They were more dependent upon their colleagues in comparison to those who remained employed (42). Those who had left the workforce believed that the attitudes of their coworkers and superiors was negative, with little support (42). In other rheumatic diseases, such as RA, lack of self-efficacy (i.e., increased helplessness) is known to be a risk factor for WD (43).

Those who used pacing (a passive technique) to cope with their limitations at work more accounted for 73% of those who became work disabled. Other factors that increased WD were: "often/very often seeking creative solutions to cope with

limitations", high disease activity, older age, and insufficient support from coworkers (42).

Older age, comorbidity, smoking, and physically active jobs have also been identified as correlated with increased risk of permanent WD in AS patients (37).

1.2.3. Economic Impact Of WD In Arthritis In General

The economic impact of WD due to arthritis will likely become an increasingly important issue as increasingly more expensive treatments are developed. The use of highly expensive treatments will need to be justified to policy makers as cost effective by demonstrating a clear reduction in disease-associated costs such as work loss.

Societal costs for arthritis disability in Canada were estimated at $5.8 billion (0.9% of the Gross Domestic Product), with the majority of costs resulting from decreased productivity (32). From the Canadian NPHS study described above (chapter 1.2.1.1.), the lifetime cost of lost wages due to arthritis was $177 435 for men and $86 296 for women (using age and sex-specific average salaries for Canadians, indexed to the year 2000) (33). The overall cost to Canada was estimated at $208 billion, over the lifetime of the work-disabled individuals (33). This figure likely underestimates total costs, as the study examined only complete and long-term work loss, and not reduction in hours (33). Additionally, it is difficult to attribute an economic value to reduced productivity or presenteeism. The direct medication costs from AS are only a minor portion of these costs, but now that expensive treatments are available for AS, it is likely that the direct costs in AS are increasing (44).

Assessing the economic impact of WD is also difficult in cases where patients are engaged in full-time work, but do not receive pay. Such situations include full-time caregivers (of children, the elderly, or the ill), full-time students and volunteers. Arthritis unquestionably has an impact on these unpaid avenues of work, but it is difficult to quantify for economic analysis. Disability in this "unpaid workforce" would have an economic impact if paid replacements are required to do volunteer or care giving work.

1.2.4. Economic Impact of WD In AS

The economic impact of AS is often divided into direct and indirect costs. Direct costs refer to expenses that result from treatment of the disease, such as visits to a healthcare provider, hospitalizations, treatments, assistive devices and household help (45). Conversely, indirect costs include expenses that are associated with lost productivity, such as loss of ability to work or to participate in leisure activities (45, 46).

A recent study examined resource utilization by AS patients in Canada. Hospitalizations were rare (3% of patients per year), but there was a high number of outpatient visits, most often to rheumatologists (5). Large numbers of radiographs were obtained in conjunction with the frequent specialist appointments (5). Other sources of high resource utilization included visits to general practitioners, physiotherapy and massage therapists (5).

Studies in the US have shown that the greatest annual direct costs in AS are incurred by women and those with greater functional disability (45). European

studies showed an association of longer disease duration, higher disease activity, lower physical functioning, and lower levels of education with higher costs (45). Patients with extra-spinal manifestations of AS were also found to incur greater costs (45). Of note, these studies were performed before the routine use of expensive biologic medications for AS.

1.2.5. WD: Qualitative Studies

There are few qualitative studies of WD in inflammatory arthritis. However, some recent work has revealed important information about the perceptions of those with inflammatory arthritis in regards to problems they faced at work (47). Lacaille *et al.* performed a comprehensive qualitative study examining issues that were meaningful to those with arthritis, and that require greater attention from healthcare professionals (47). This study found 4 categories of problems that patients with inflammatory arthritis identified as making it difficult to continue working: 1) symptoms and characteristics of arthritis, 2) working conditions, 3) interpersonal difficulties at work and 4) emotional challenges (47). Seventy-six individual problems were identified within these 4 larger groups (47).

In terms of specific characteristics of arthritis cited as causing difficulty at work, fatigue was the highest ranking problem identified, even above pain or physical limitation (47). This is an important finding, as the majority of literature on risk factors for work loss emphasizes pain and functional limitation (47). Patients also stated that fatigue was the symptom of their arthritis that was least helped by medications and least accepted or understood by their coworkers (47). Many related

that the quality of their work suffered due to fatigue, or that they had to sacrifice some tasks or personal life due to fatigue (47). Fatigue was identified as an "invisible" disability, along with pain, in that coworkers could not directly visualize the underlying problem (47). Other identified problems included the fluctuating/unpredictable nature of arthritis and problems related to disease managements, such as taking time off work for appointments (47).

Participants also described specific aspects of their working conditions that caused difficulty. Lack of flexibility, such as over working hours, pacing and organization of tasks caused significant problems (47). Specific demands of the job, such as repetitive movements or prolonged standing were also issues (47). Other working conditions that caused difficulty with continuing to work included commuting issues and choosing job that was suitable to arthritis rather than one which was fulfilling (47).

Interpersonal difficulties at work affected some patients more than others, particularly those who worked as part of a team (47). Some worried about resentment from others due to time taken off during arthritis flares (47). Many participants were concerned that their coworkers and employers did not understand the experience of living with arthritis, and feared they may be perceived as being lazy or unmotivated (47). A substantial number of participants had not informed their employer that they had inflammatory arthritis, nor did they use assistive devices at work, for fear of stigmatization (47).

Participants also described emotional issues that contributed to problems at work, such as anxiety regarding flares or guilt regarding absenteeism (47). Many stated that troubles at work affected their interpersonal relationships with family and

friends (47). Patients felt that they had little energy to do anything besides their job due to the fatigue of arthritis (47).

Overall, this qualitative examination of patients with inflammatory arthritis concluded that employment issues were insufficiently addressed by healthcare professionals (47).

1.2.6. Outcome Measures: The WLQ In Arthritis

The WLQ has been studied extensively in terms of reliability and validity for both osteoarthritis (OA) and rheumatoid arthritis (RA) (30, 31). A small abstract recently presented at an international meeting has also reported results of WLQ testing in AS, though it did not specifically address test characteristics (48). These studies shed light on the appropriateness of the WLQ for assessment of WD in AS.

A study of employed OA patients found that they had large differences on their WLQ scores when compared with controls (30). Not surprisingly, given the physical nature of arthritis, those with OA had most difficulty with physical and time demands, and less limitation in regards to mental and interpersonal tasks (30). Patients with OA were found to have 4-5 times more disability in physical and time management areas than control patients (30). Patients with back OA had the most WD overall (30). WLQ subscales correlated well with self-reported arthritis severity (30). The Physical Demands scales correlated well with other survey instruments which measure physical burden of disease (30). Overall, this study provided good support for the reliability and validity of the WLQ in patients suffering from OA, particularly for the assessment of on-the-job disability (30).

The WLQ has also been used in the assessment of work limitations in patients with RA, which is usually thought of as the prototypical inflammatory arthritis (31). In this cross-sectional study, WLQ scales were linked to observed productivity so that individual scores could be interpreted as decreased productivity in comparison to healthy controls (31). The results revealed highly skewed WLQ scores for patients with RA (31). Almost one quarter of respondents indicated that they had no work limitations, and less than 1% indicated high levels of WD (scores > 30) (31). Overall, those with RA had 4.9% decreased work productivity in comparison to their healthy counterparts (31). The study also found that RA patients worked extra hours to compensate for their decreased productivity (31). A notable caveat of the study was the fact that several observations were excluded when respondents indicated that the asked questions did not apply to their jobs, and thus treated as missing data (31). Missing data was associated with age, sex and disease severity (31). This could imply that older, male patients with more severe disease tended to choose jobs with fewer demands (31). An interesting finding of the RA study was that a one-unit change in WLQ corresponded to a change in income of $243 (95% CI 83-570) (31).

The WLQ was compared to similar tests of disability and found to have good construct validity for patients with RA (31). Reliability was also found to be high (31).

AS has not been studied intensively in terms of work disability. However, preliminary results of a study of the WLQ in Canadian AS patients was presented at a recent international rheumatology conference (48). In this study, AS patients were compared with the general population through the calculation of age- and gender-adjusted employment ratios (48). Employment ratios did not differ significantly from

the general population for either male or female AS patients (1.03 [95% CI 0.95-1.13] and 1.08 [95% CI 0.89-1.27], respectively) (48). However, patients with AS did take more sick leave and experienced greater physical and time-pressure demands than the general population (48).

Given the reliability, validity and usefulness of the WLQ, and its demonstrated usefulness in arthritis, it would be a high-quality outcome measure for WD in AS.

Chapter 2: Study Objective And Hypothesis

2.0. Objectives

1. Determine the prevalence of WD in our seronegative SpA patients.
2. Assessment of risk factors for WD such as age, gender, education, physically demanding work, comorbid diseases and high disease activity as assessed by commonly used clinical tools (HAQ, BASDAI, BASFI, FCI).
3. Comparison of the results of WLQ to the above risk factors.

2.1. Hypotheses

We hypothesized that:

1. 10% or more of patients with AS/SpA would be work disabled.
2. Risk factors for WD would include duration of disease, level of disease activity, physically active jobs and level of education.
3. Assessment of disability by currently used tools such as the HAQ, BASDAI and BASFI would correlate highly with the results of the WLQ.
4. Even those who are working will have decreased work productivity.

Chapter 3: Methods

3.0. Overview Of Study Design

This study was designed as a point prevalence study in SpA to determine factors associated with work disability via a mailed survey using a questionnaire that was developed for the project and also including several validated other questionnaires on work, function and pain. The actual study flow / processes can be seen in Figure 6.

The study population consisted of 203 patients with seronegative SpA, confirmed by a rheumatologist, who have attended a rheumatology clinic at St. Joseph's Health Center in London, Ontario. The sampling frame was obtained by searching OHIP billing codes for a diagnosis of 720 (ankylosing spondylitis, other SpA) in all patients seen in the clinic in from March 2007-March 2008 from 6 rheumatologists. Subjects were excluded if they and unable to complete the WLQ. Subjects received a study package by mail, containing a letter of information approved by the Ethics Review Board of the University of Western Ontario, the WLQ, HAQ, BASDAI and BASFI and a stamped returne envelope. Appendix H includes local research ethics board approval and our letter of information. Subjects were also asked to complete the Functional Comorbidity Index (FCI), and to indicate their level of fatigue on a visual analogue scale (Fatigue VAS). In order to determine obesity status for the FCI, patients were asked to give their height and weight and the investigators calculated BMI using the formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight in kilograms/(height in meters)}^2$$

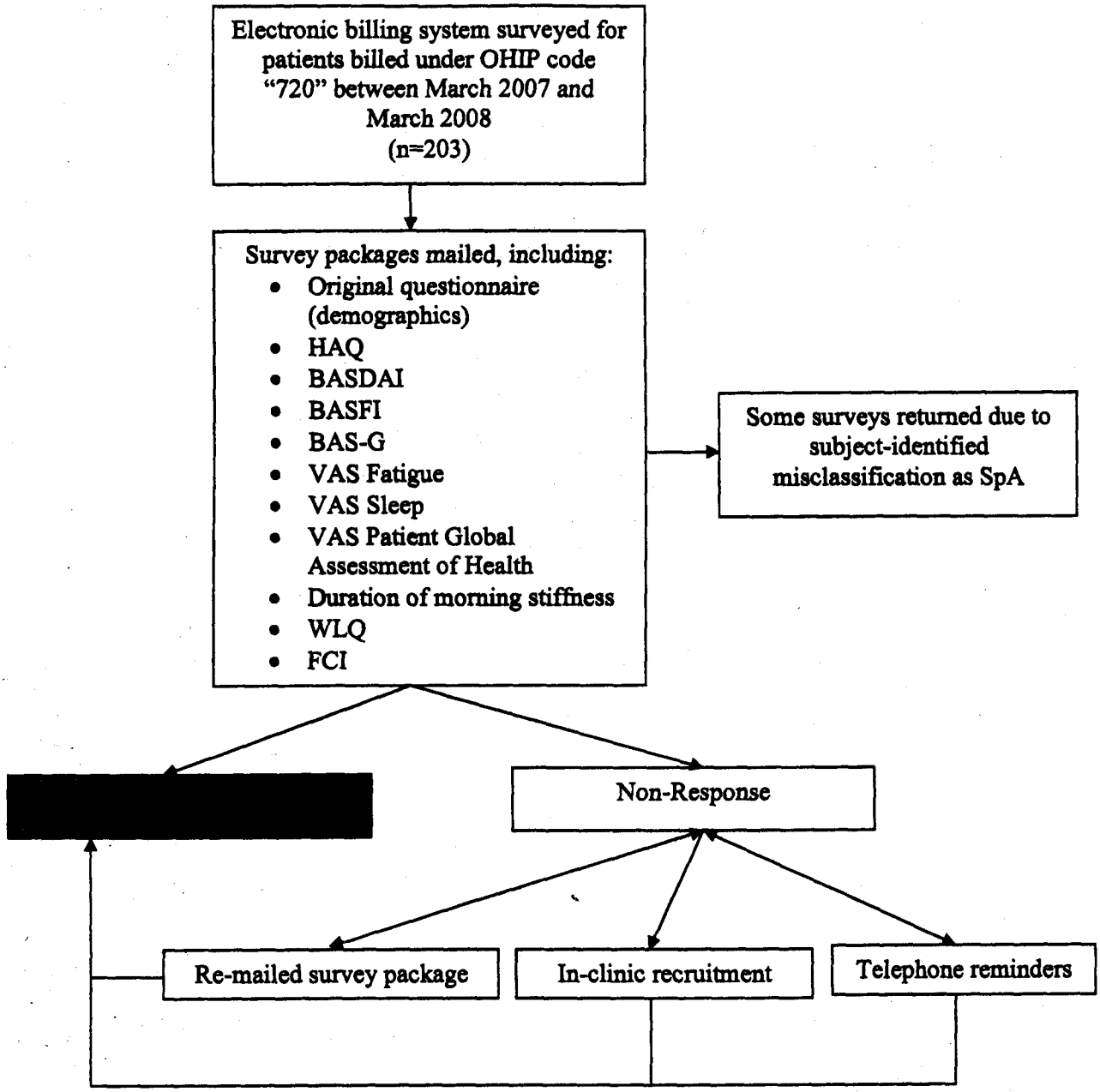


Figure 6: Flowchart demonstrating study process.

The questionnaire that was sent can be seen in Appendix H.

The results of the WLQ were then correlated with those from the HAQ, BASDAI and BASFI using correlation coefficients. The results were also correlated with and adjusted for baseline comorbidities using the FCI. Data obtained from this study was compared to outcomes in the general population and those with RA and OA, determined through literature review.

Subjects were also asked to report basic demographic data. Results were subject to univariate and multivariate regression analysis. Please refer to Section 3.7 below for more detail in regards to the statistical analysis.

To ensure a high response rates, subjects were telephoned to remind them to complete their surveys. New survey sets were sent to those who requested them. In addition, when patients came to clinic for a regular visit, they were given the survey if they had not returned it and were willing to complete it. Repeat surveys were mailed out to non-responders approximately 1 month after the initial mailing. A chart review of the entire sample was done to determine differences in overall group of patients with SpA and the responders to determine if they were similar as in many surveys, younger people and men may be less apt to reply, and baseline data on work were obtained from all charts (if documented at the first visit to the rheumatologist as it was not systematically collected for patients after the initial consult) and comorbidities were documented. The data extraction form used for chart review can be found in Appendix I.

3.1. Sample Size

This study was conducted using a convenience sample of all patients who had been diagnosed with AS by a rheumatologist at St. Joseph's Health Care Center and had attended a rheumatology clinic. The use of a convenience sample was justified as there is little prior research on the prevalence of WD in an AS population, making it difficult to perform a formal sample size calculation.

We did run some models determine what the margin of error would be for WD for various response rates, using online software (49). We assumed a population size of 200, confidence level of 95% and response distribution of 50%. The response distribution of 50% was chosen to provided the most conservative estimate. Using this technique, a 60% response rate would give a margin of error of 5.67%, a 50% response rate a margin of error of 6.95% and 40% response rate a margin of error of 8.42%. To obtain a margin of error of 5%, a sample size of 132 respondents (66% response rate) would be needed.

3.2. Participant Inclusion Criteria

Subjects were included if they had a diagnosis of seronegative spondyloarthropathy, confirmed by a rheumatologist, and had at least one clinic visit at St. Joseph's Health Center and seen over the years 2007-2008. The sampling frame was obtained by searching lists of billing information. All patients of the 6 currently

practicing St. Joseph's rheumatologists for whom OHIP diagnostic codes of 720 (corresponding to AS) were billed were asked to participate. Patients were sent information packages regardless of their current employment status. To clarify the diagnosis of AS, and to ensure a billing code error had not been made, patients were asked to report their own diagnosis. If there were any discrepancies between physician and patient reported diagnoses, the treating physician's diagnosis was verified by chart review.

3.3. Participant Exclusion Criteria

Subjects were excluded if they were less than 18 years of age at the time that they received the survey package, or if they were unable to read or write English.

3.4 Additional Data Gathered

Some additional data was gathered through the use of a brief, original questionnaire, which may be found in Appendix H. The questionnaire asked specific questions about current work status, absences from work, type of arthritis, and demographic information. This questionnaire was included to ensure that we could obtain a full sense of the participants' current work status as well as to gather demographic information. The questions were decided upon through consensus and did not undergo specific psychometric testing.

Additionally, a complete chart review of all patients (both responders and non-responders) with billing code 720 was performed by an independent assessor. This

individual gathered data about employment status from chart data. The data extraction form used for chart review can be found in Appendix I. The chart review was performed to gather information about all patients, even non-responders.

3.5 Independent and Dependent Variables

3.5.1. Work Disability

The primary outcome of this study was determination of the prevalence of WD, defined as not currently working due to arthritis.

3.5.2. Assessment of Risk Factors for Work Disability

Independent variables, which were explored to be related to WD, included:

- HAQ scores
- BASDAI scores
- BASFI scores
- BAS-G scores
- VAS fatigue
- VAS sleep
- VAS patient global assessment of health
- Type of AS (primary versus that associated with other inflammatory disease)
- Presence of comorbidity as assessed by the FCI

Covariates analyzed included:

- Age
- Disease duration

- Level of education
- Income

3.5.2. Assessment of Losses in Work Productivity

To assess work productivity, the outcome measure used was WLQ productivity loss (%) due to arthritis. Independent variables, which were explored to be related to WLQ productivity loss, included:

- HAQ scores
- BASDAI scores
- BASFI scores
- BAS-G scores
- VAS fatigue
- VAS sleep
- VAS patient global assessment of health
- Type of AS (primary versus that associated with other inflammatory disease)
- Presence of comorbidity as assessed by the FCI

Covariates analyzed included:

- Age
- Disease duration
- Level of education
- Income

3.6. Dealing With Responses

Some respondents answered the survey questions incorrectly, particularly the way in which answers were given on VAS. To minimize measurement bias, the same investigator graded responses with uniformity. If instead of a single vertical mark on the VAS, the respondent used a bar, checkmark, or "x", the midpoint of the mark was used as the response. If the respondent drew a number on the VAS, such as "5" near the midpoint of the 10 cm VAS, the midpoint of where the number crossed the VAS was used. If the respondent gave a number that was not on the VAS (for example, "5" written next to the VAS), the number was used. If they made both a mark on the VAS and then provided a written number next to the VAS, the measured point of the mark on the VAS was used.

Missing data was imputed through the instructions provided by the creators of the WLQ (28). For each scale of the WLQ, imputation was permitted if more than one half of scale items had responses. If fewer than half of the items had responses, the entire scale was scored as missing.

3.7. Statistical Analysis

Analysis was performed using SPSS (50). Prevalence of WD was calculated using proportion. The association of each independent variable with WD was calculated using bivariate correlation. Both Pearson and Spearman χ^2 were used in case the results were not normally distributed. Two-tailed tests were used, with a level of significance of $p<0.05$. The association of each independent variable with

losses in work productivity, as assessed by the WLQ, were also determined through $\chi 2$ and bivariate correlation. Two-tailed tests were used with a level of significance of $p<0.05$.

Linear regression was used to determine the impact of various independents on the dependent loss in health related work productivity (%).

Logistic regression was used to predict dependent variables on the basis of continuous and categorical independents, thus allowing the determination of the percent of variance in the dependent that could be explained by the independents. Binomial logistic regression was used for dichotomous dependents (such as work disabled, yes/no).

The enter method was used. Probability for stepwise entry was 0.05, and for removal was 0.10, with 20 maximum iterations.

Chapter 4: Results

4.0. Response Rate

The results presented below are based on an analysis of 81 survey responses. This is a response rate of 40%. Unfortunately a larger sample size of 200 responses was not obtained.

4.1. Descriptive Statistics

4.1.1. Demographics

Eighty-one completed questionnaire packages were returned (response rate 40%), reporting a physician diagnosis of AS most frequently (64.2%), followed by spondylitis associated with IBD (21.0%). A smaller number of subjects reported spondylitis associated with psoriatic skin disease or reactive arthritis occurring after a prodromal genitourinary or gastrointestinal infection. The frequencies of the reported forms of arthritis are summarized in Figure 7. Respondents were largely in the fifth decade of life (mean age 45 years, SD 11.5) with a mean duration of disease activity of 9.9 years (SD 12.1). A frequency distribution of the respondent's ages and disease duration can be found in Figures 8 and 9, respectively. There was no significant gender difference in age of diagnosis. Of note, there was quite a wide range of responses in regards to age (50 years).

The majority of subjects stated that their highest level of education was college and university (40.7%). The next highest proportion of subjects had

completed grade 9-12 (33.3%). A complete summary of the educational achievements of the respondents can be found in Figure 10. Most subjects reported that their average yearly income, before taxes, was between $0-20 000. Figure 11 summarizes the income status of the survey respondents.

There were notable differences in the demographic characteristics of respondents and non-respondents, summarized in Figure 12. Non-responders tended to be younger male subjects (Figure 12).

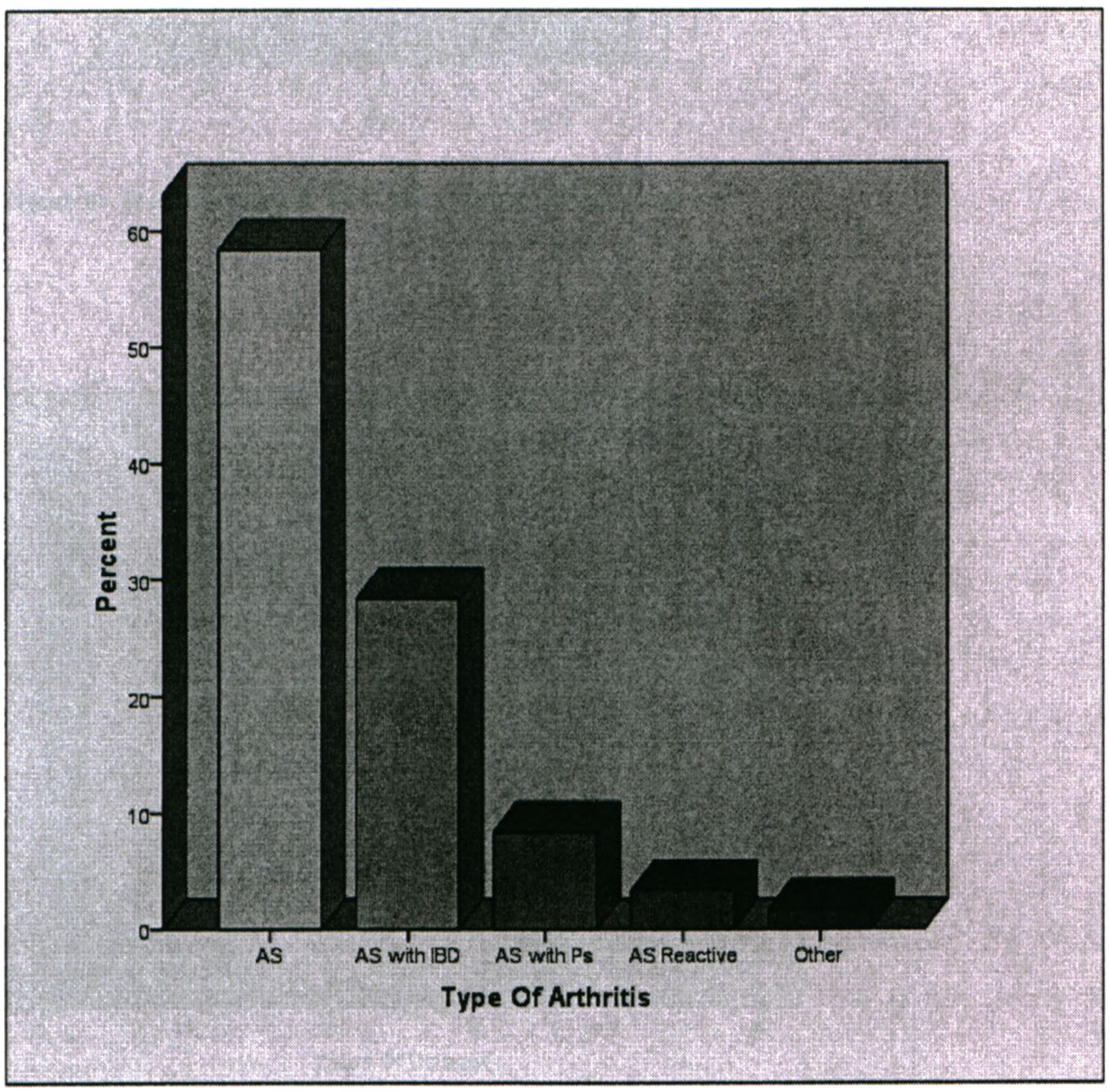


Figure 7: Distribution of types of arthritis affecting study participants.

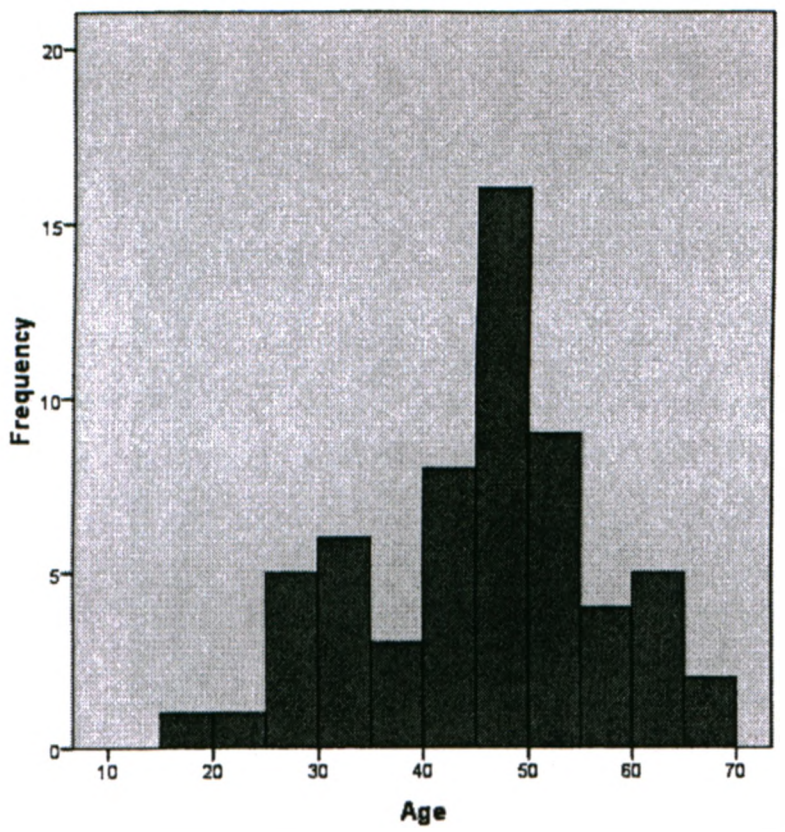


Figure 8: Frequency distribution of the ages of study respondents.

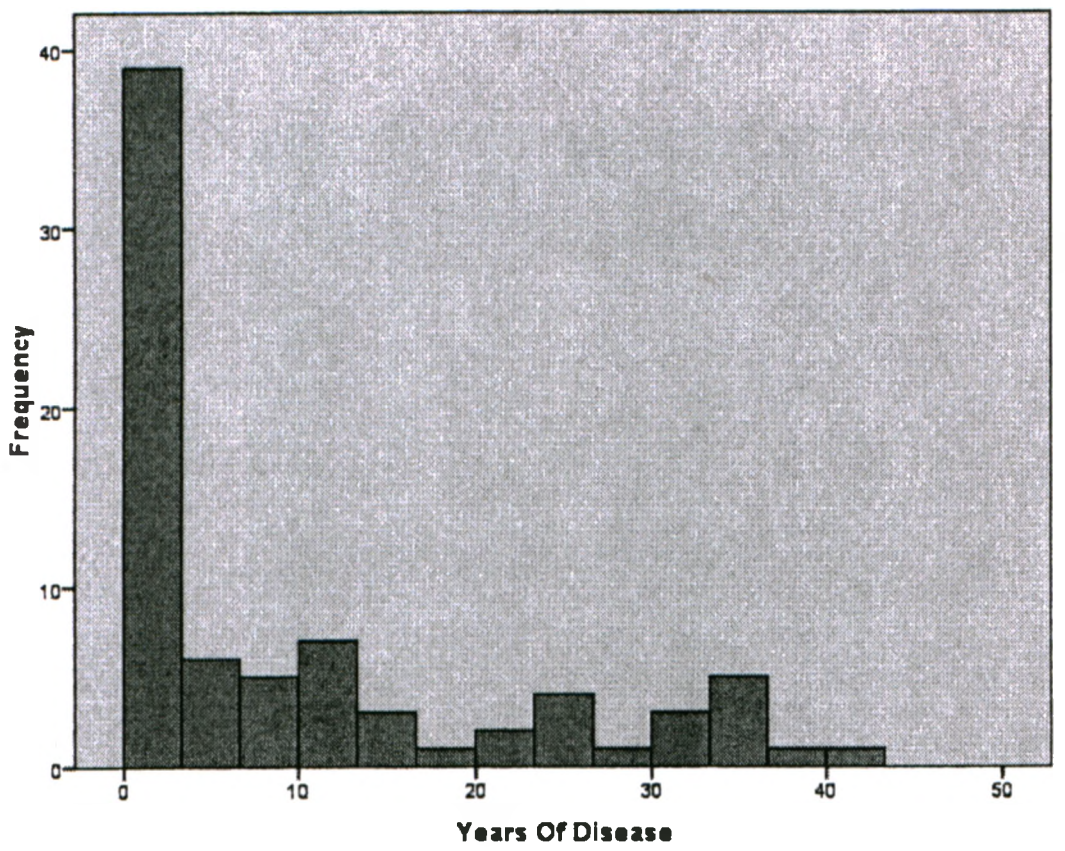


Figure 9: Frequency distribution of the years of disease activity of the study respondents.

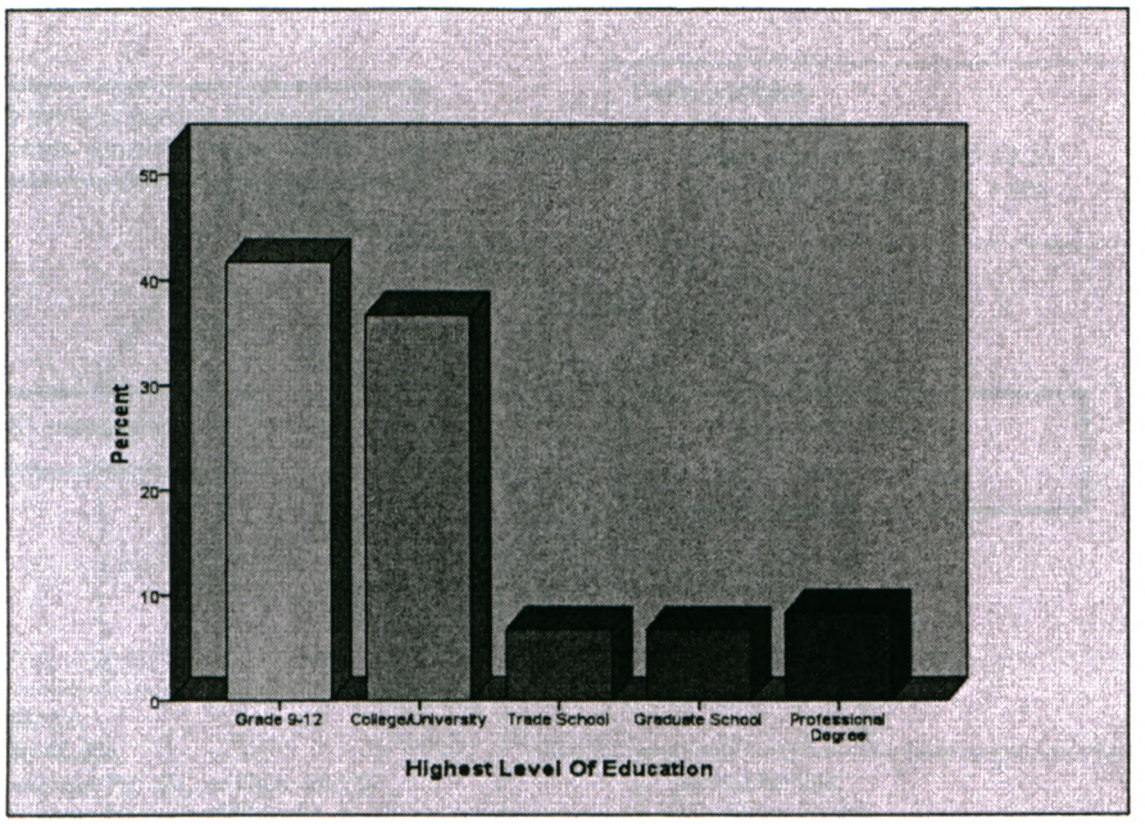


Figure 10: Reported education level of study respondents.

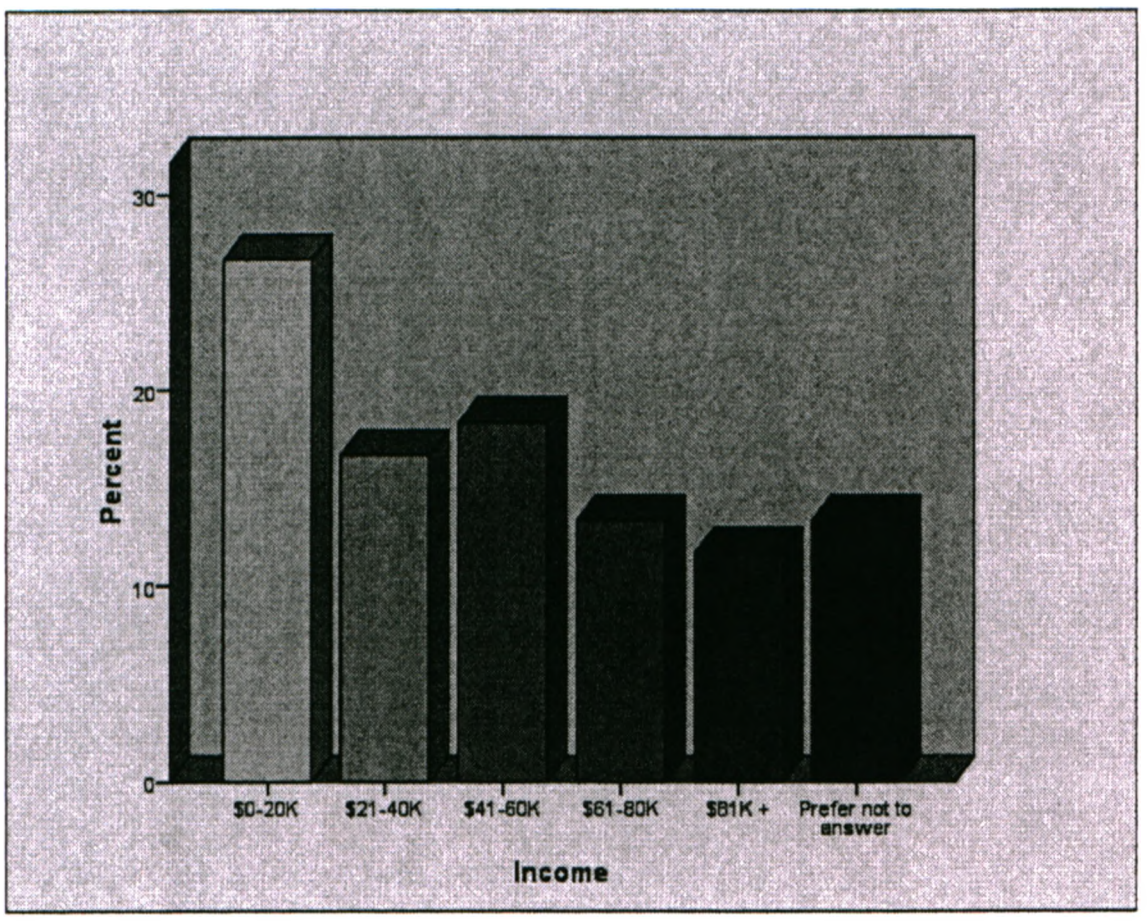


Figure 11: Reported income level of study respondents.

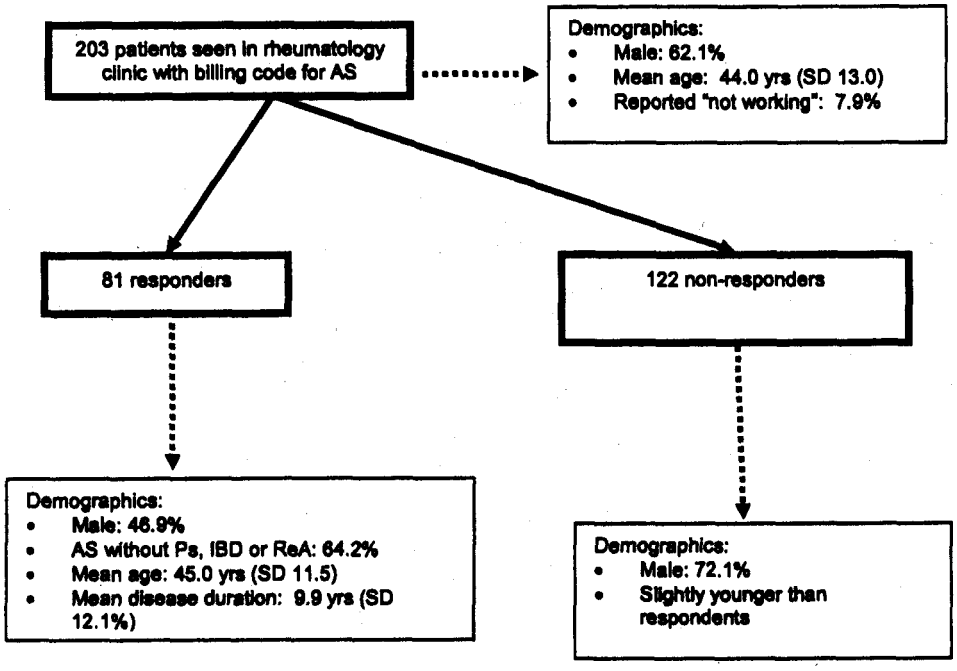


Figure 12: Study design with details regarding demographic features of responders and non-responders.

4.1.2 Current Employment Status

Subjects reported most often working full-time in a paid position outside of the home (49.4%). The next most frequent employment statuses was not working (18.5%), part-time paid outside of the home (12.3%) and unpaid work at home (7.4%). 15 patients (18.5%) were work disabled. A summary of all of the work status responses is reported in Figure 13. The mean number of hours worked per week was 29.2 (SD 20.1). None of the respondents were retired. All of those who reported not working were work disabled. A histogram of the hours worked per week by the survey respondents can be found in Figure 14.

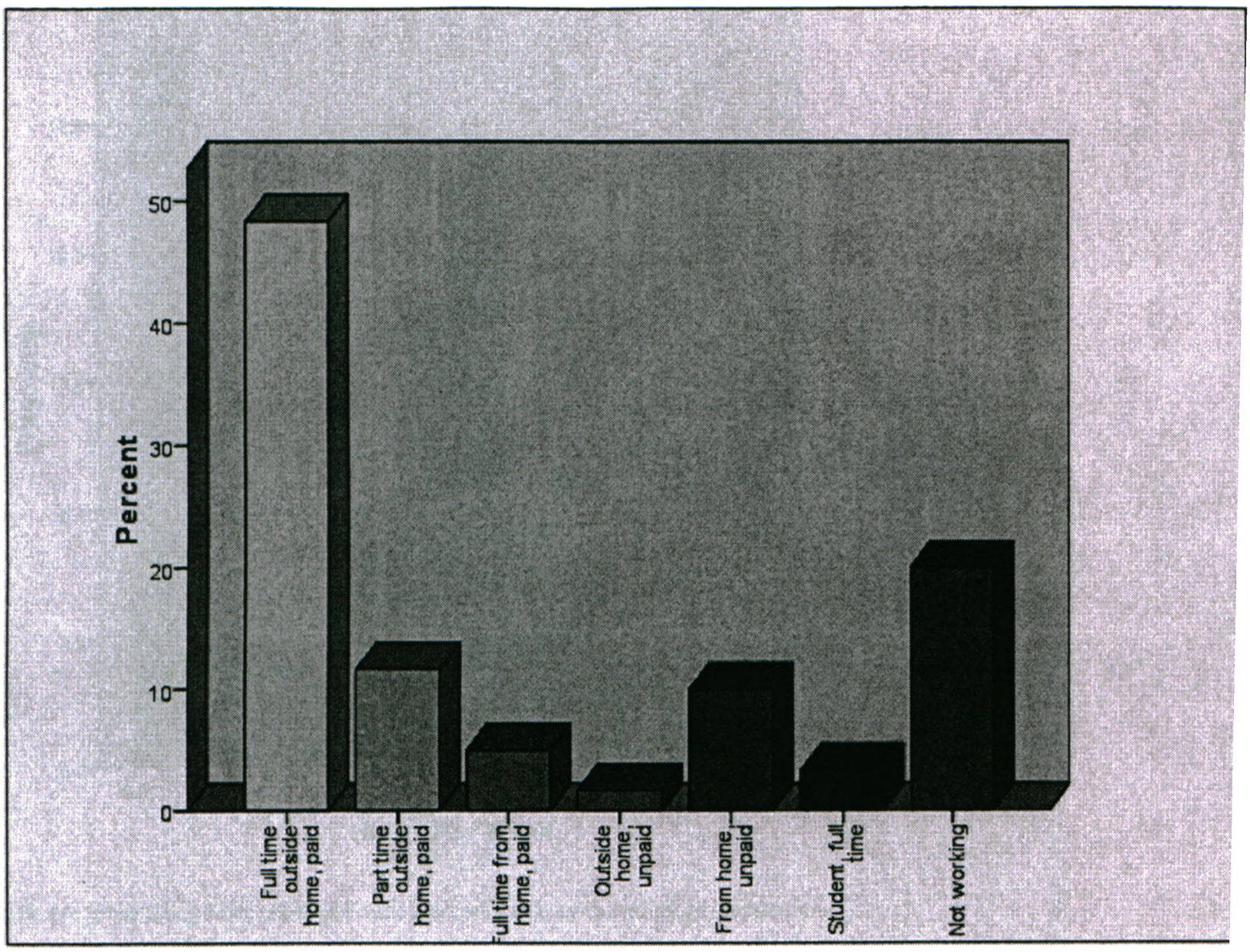


Figure 13: Employment status of study respondents.

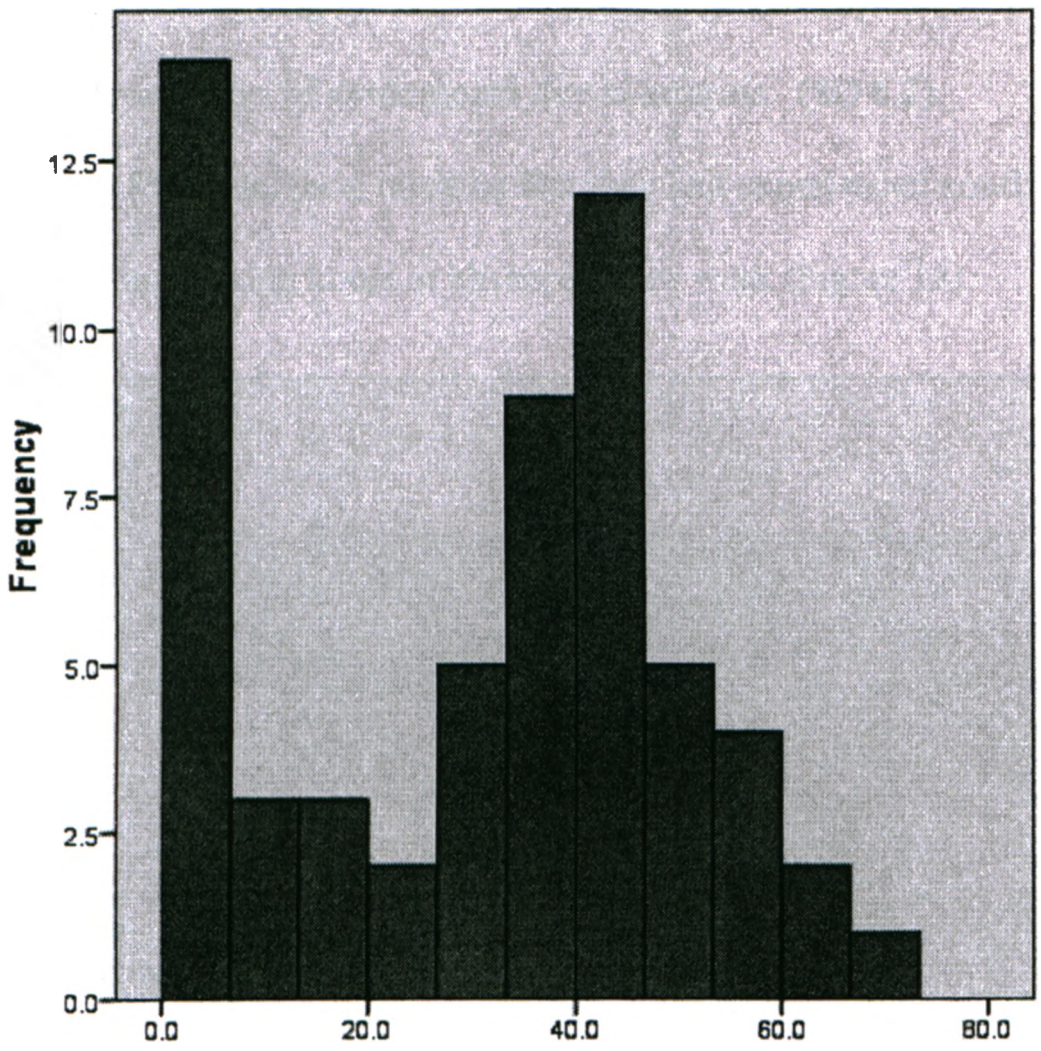


Figure 14: Frequency histogram of hours worked/week by the study respondents.

4.1.3. Alterations In Work Habits Due To Arthritis

Patients were asked specifically whether they had been forced to make changes to their work schedule as a result of their arthritis. A high percentage of subjects (39.5%) indicated that they had decreased the number of hours they worked per week, specifically due to effects of their arthritic symptoms (Figure 15). On average, those working had to have some reduction of their work hours 3.7 days per work week (SD 8.1). Figure 16 demonstrates the frequencies of responses for decreased work hours in greater detail. Many subjects also reported taking entire days

off due to arthritis (Figure 17). The mean number of days off work per month was 2.5 days complete days of work/month due to arthritis. (SD 6.2).

14.8% of subjects reported that they had experienced conflict at work due to decreases in working hours or absences from work (Figure 18).

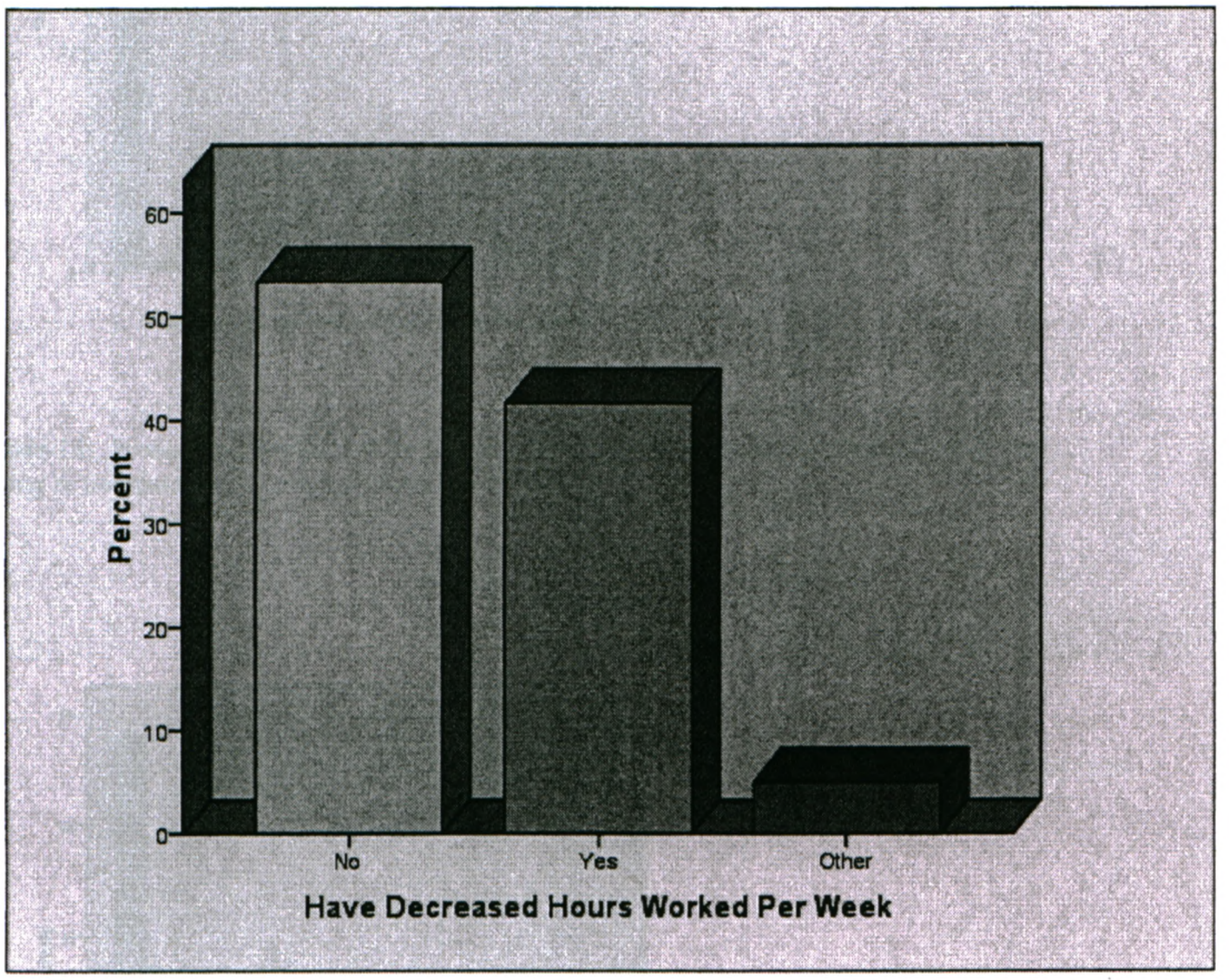


Figure 15: Proportion of respondents who reported decreasing the number of hours they work/week due to arthritis.

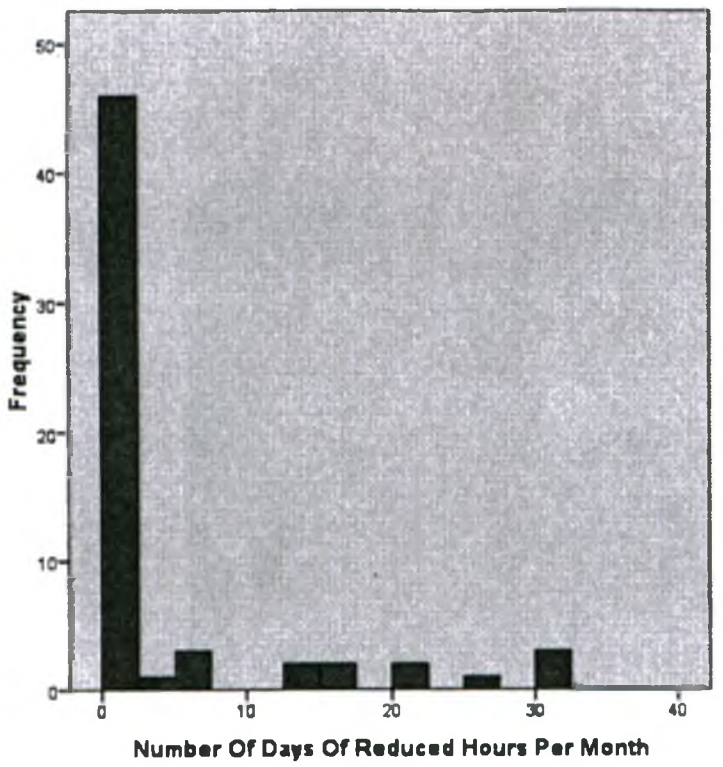


Figure 16: Frequency distribution for the number of days/month that respondents described having to decrease their work hours due to arthritis.

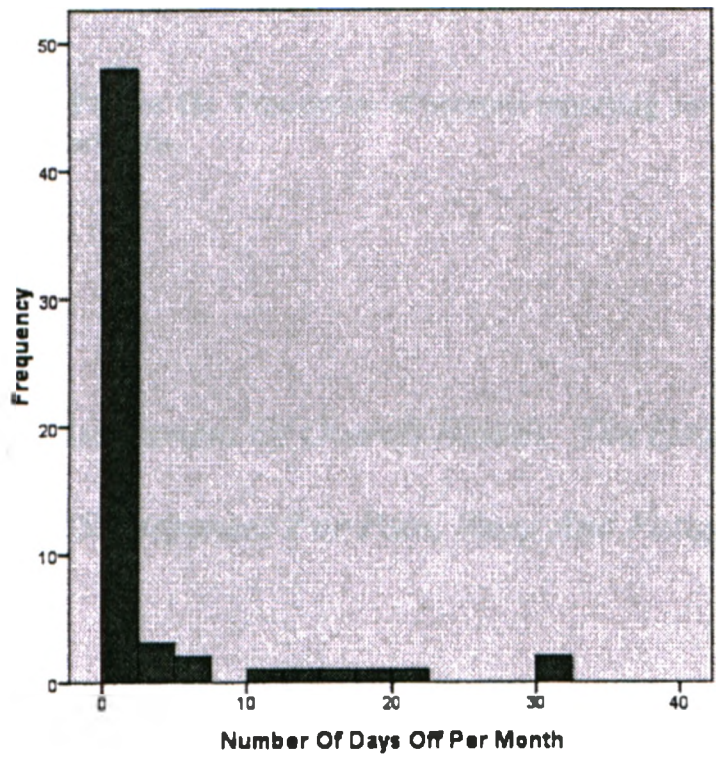


Figure 17: Frequency distribution of number of complete days off/month due to arthritis.

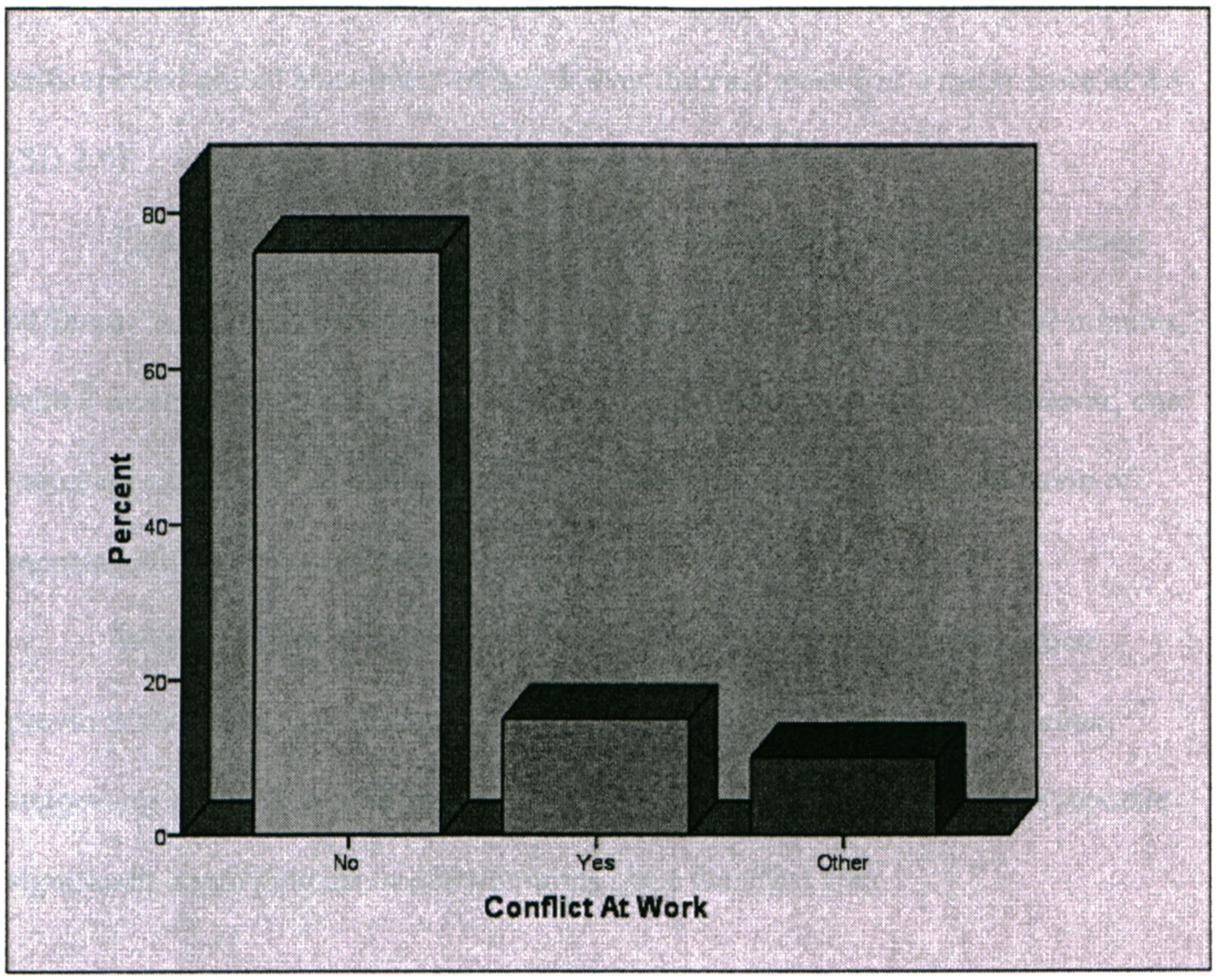


Figure 18: Proportion of patients reporting conflict at work due to absences secondary to arthritis.

4.1.4. Assessment Of Overall Health: The Health Assessment Questionnaire (HAQ) And VAS Responses For Pain, Sleep And Fatigue

HAQ scores were compiled for all subjects, and are summarized in Figure 19. The mean HAQ of the study population was 0.90 (SD 0.61).

Results of respondents' VAS scoring of overall pain, sleep disturbance and fatigue are summarized in Figures 20-23. The mean rating for pain over the past

week was 4.9 (SD 2.8), fatigue 5.6 (SD 3.0) and poor sleep 5.2 (SD 3.3). Subjects' self-reported global assessment of health over the past week had a mean score of 4.4 (SD 2.6).

Figure 24 illustrates the results of the patient-reported minutes of morning stiffness. As shown, there was a wide range of results, between 0 and 1440 minutes, with a mean result of 107.7 minutes (SD 271.7) of morning stiffness. However, one value appeared to be an outlier. Both the median and mode value for duration of morning stiffness was 60 minutes.

When asked to compare health status at the current time to that at their previous visit with their rheumatologist, 55.6% reported that they felt the same, suggesting stable disease activity over time (Figure 24). Smaller numbers reported significant improvements or deteriorations since their last visit.

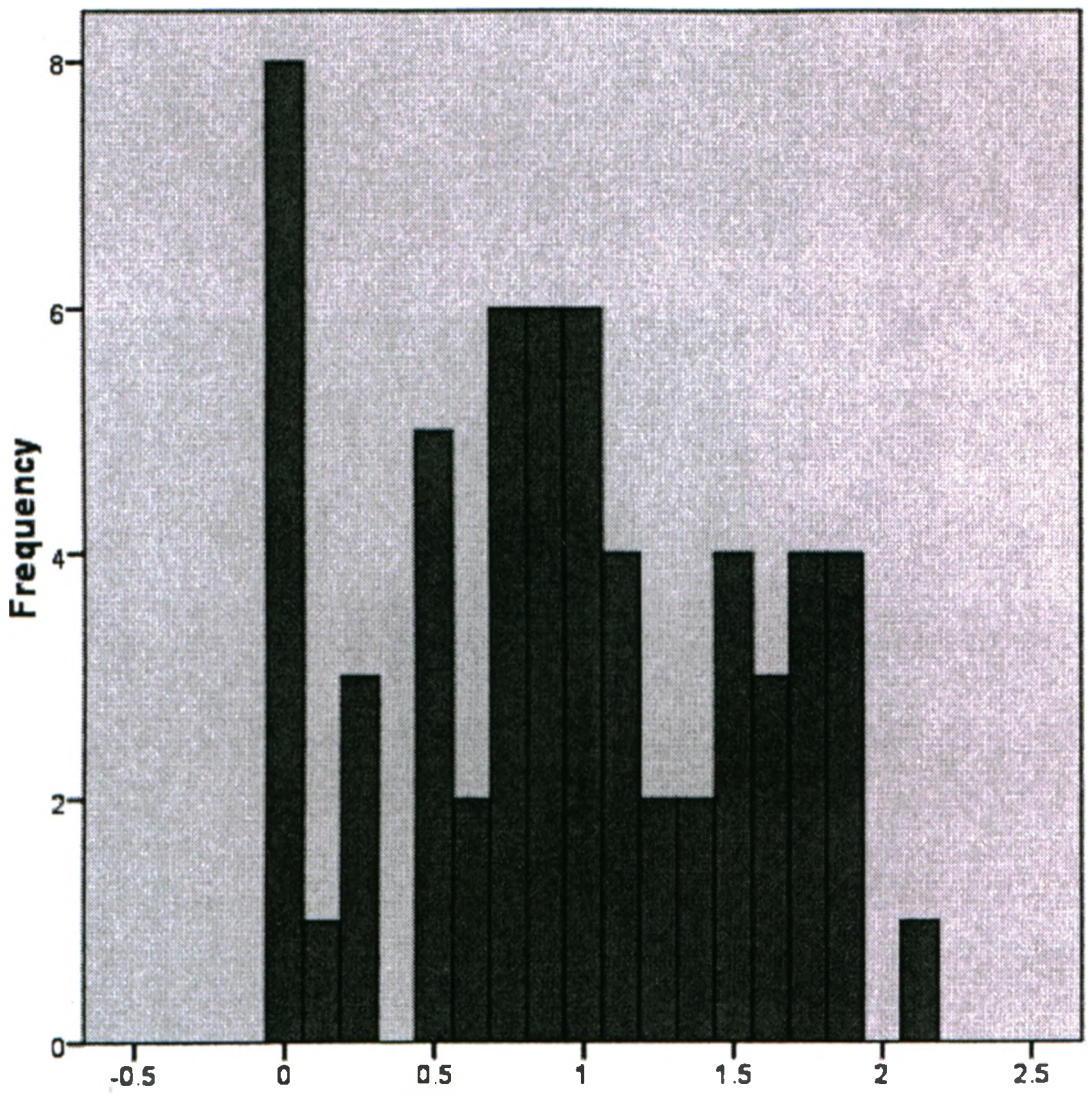


Figure 19: Frequency distribution of results for the HAQ.

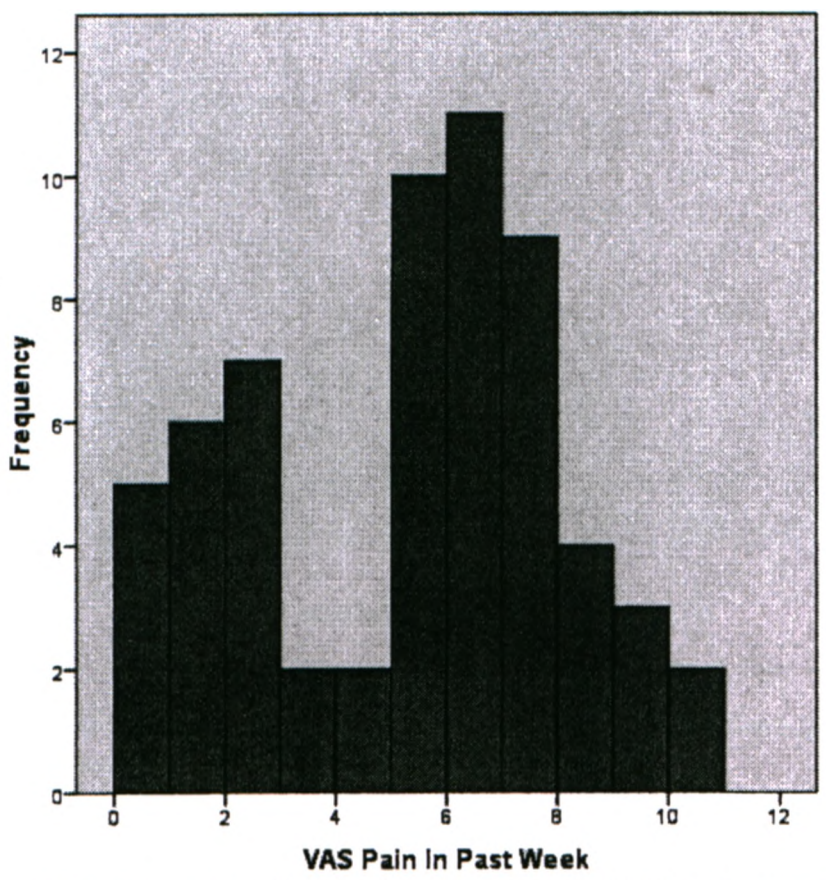


Figure 20: Frequency distribution of results for VAS pain over the last week.

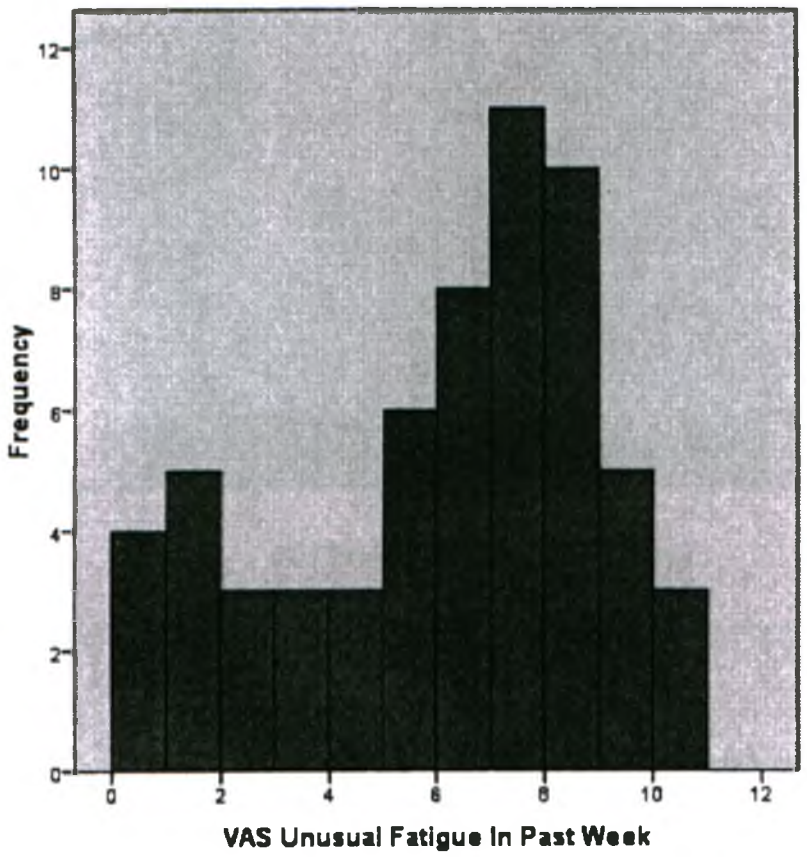


Figure 21: Frequency distribution of results for VAS fatigue over the last week.

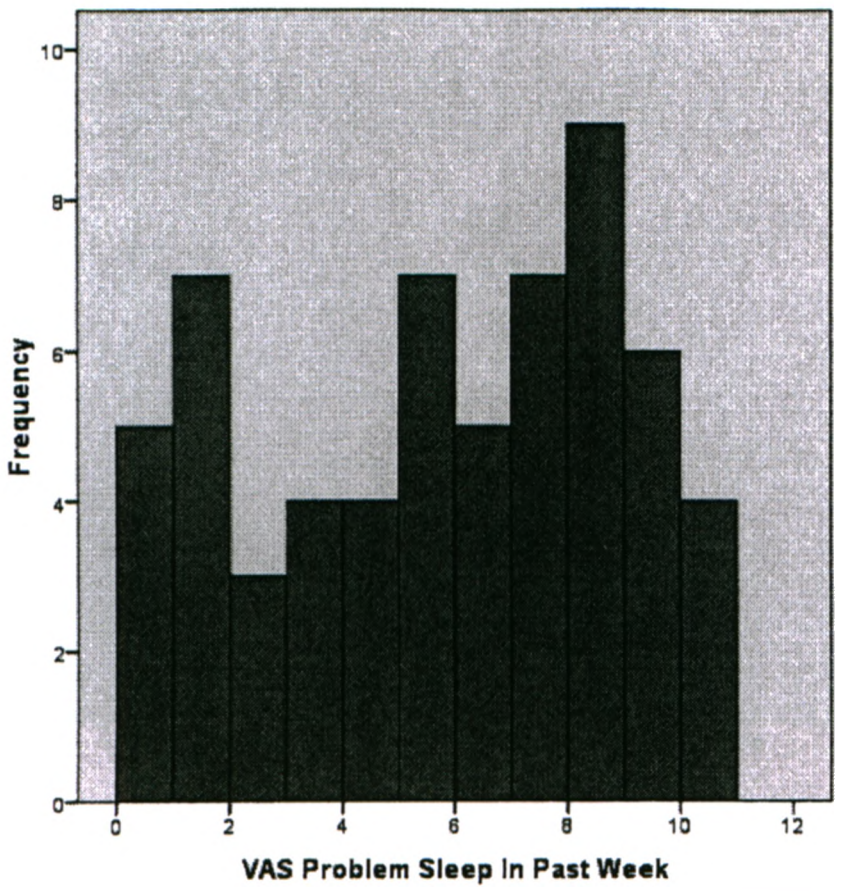


Figure 22: Frequency distribution of results for VAS sleep disturbance over the last week.

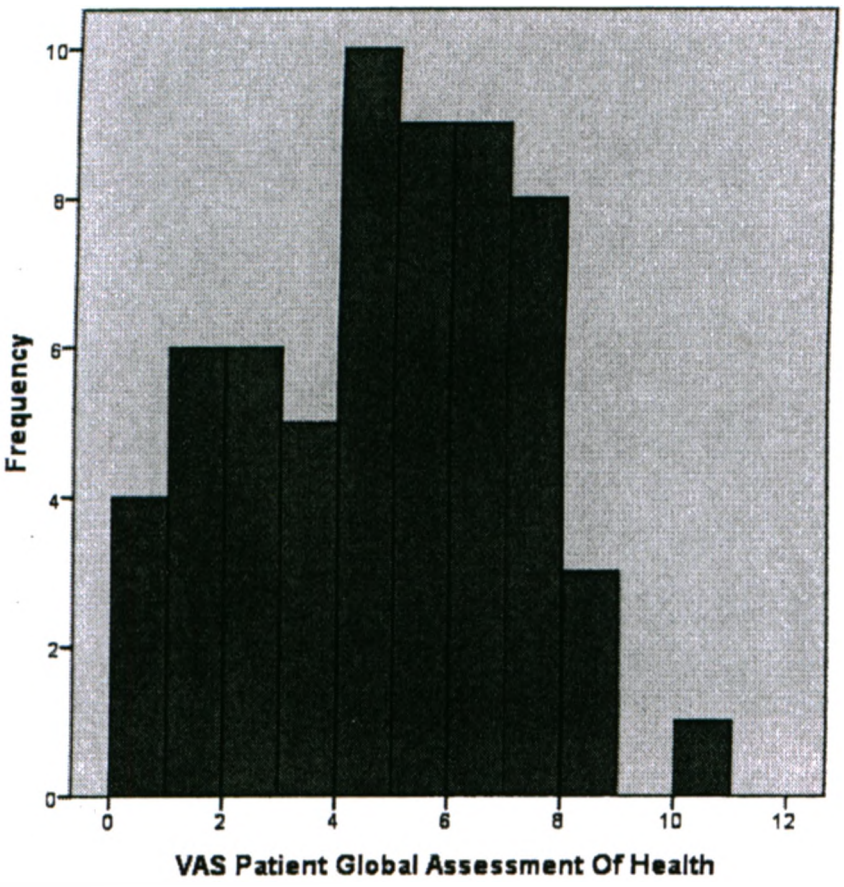


Figure 23: Frequency distribution of results for VAS patient global assessment of health over the last week.

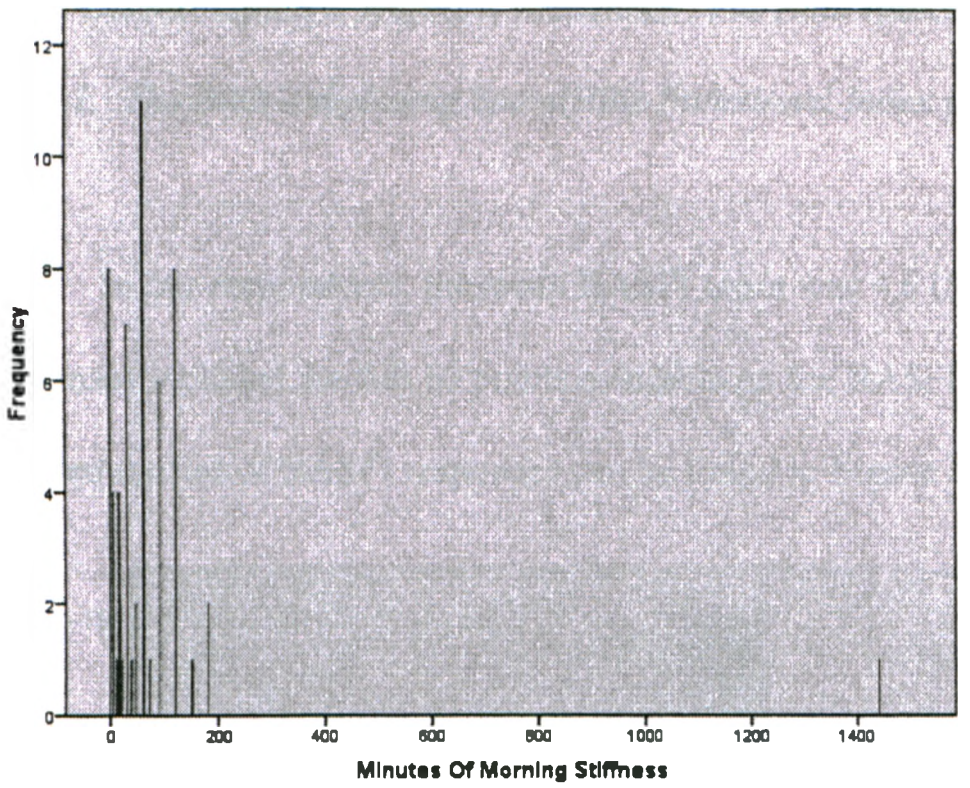


Figure 24: Frequency distribution of results for duration of morning stiffness over the last week.

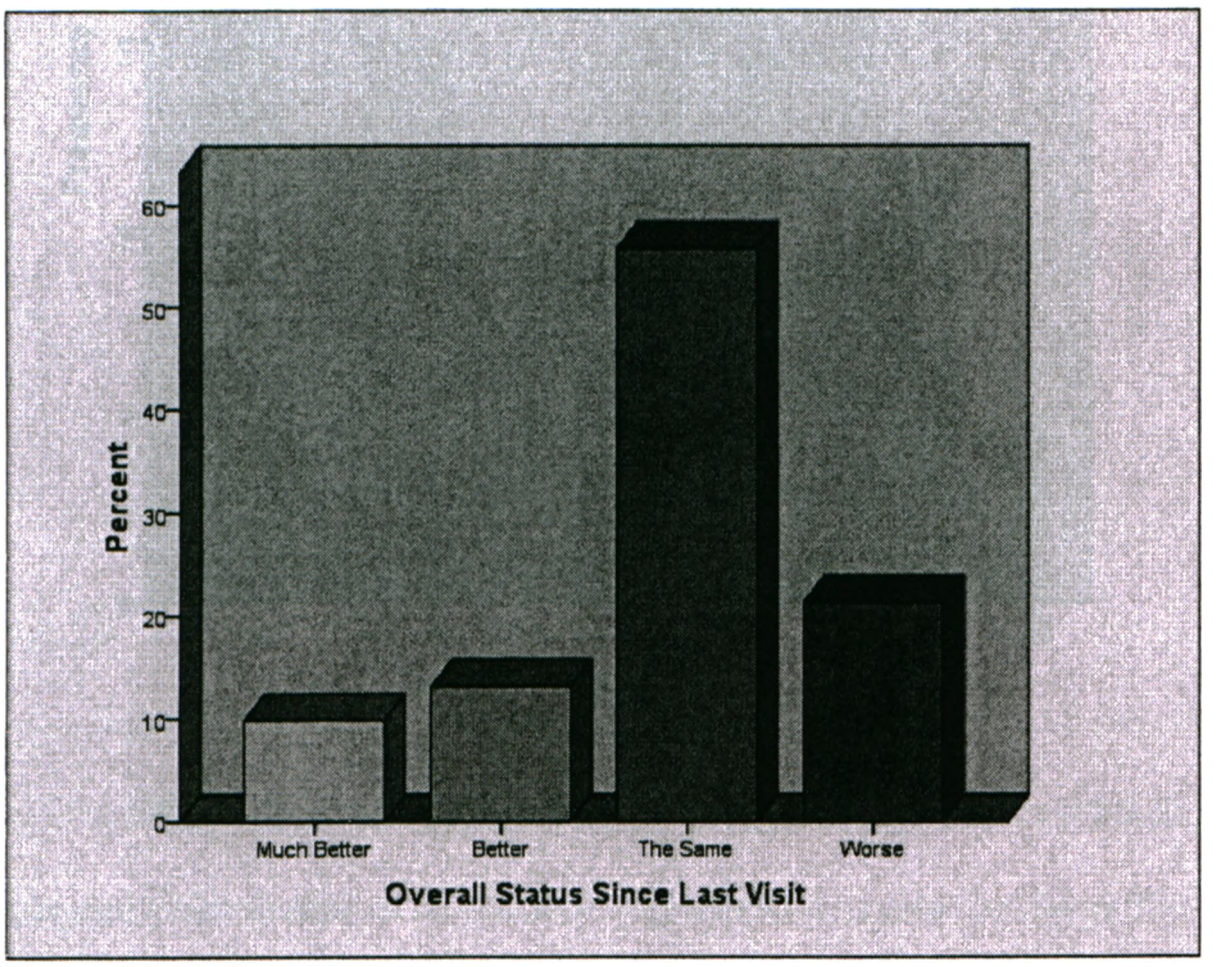


Figure 25: Patient reported overall status since last visit.

4.1.5. Disease-Specific Outcome Measures: The Bath Indices

4.1.5.1. The Bath Ankylosing Spondylitis Functional Index (BASFI)

In our respondents, the mean BASFI score was 4.6 (SD 2.8). The range of responses included the full 10 points available on the BASFI scale. A histogram of the frequencies of BASFI responses can be found in Figure 26.

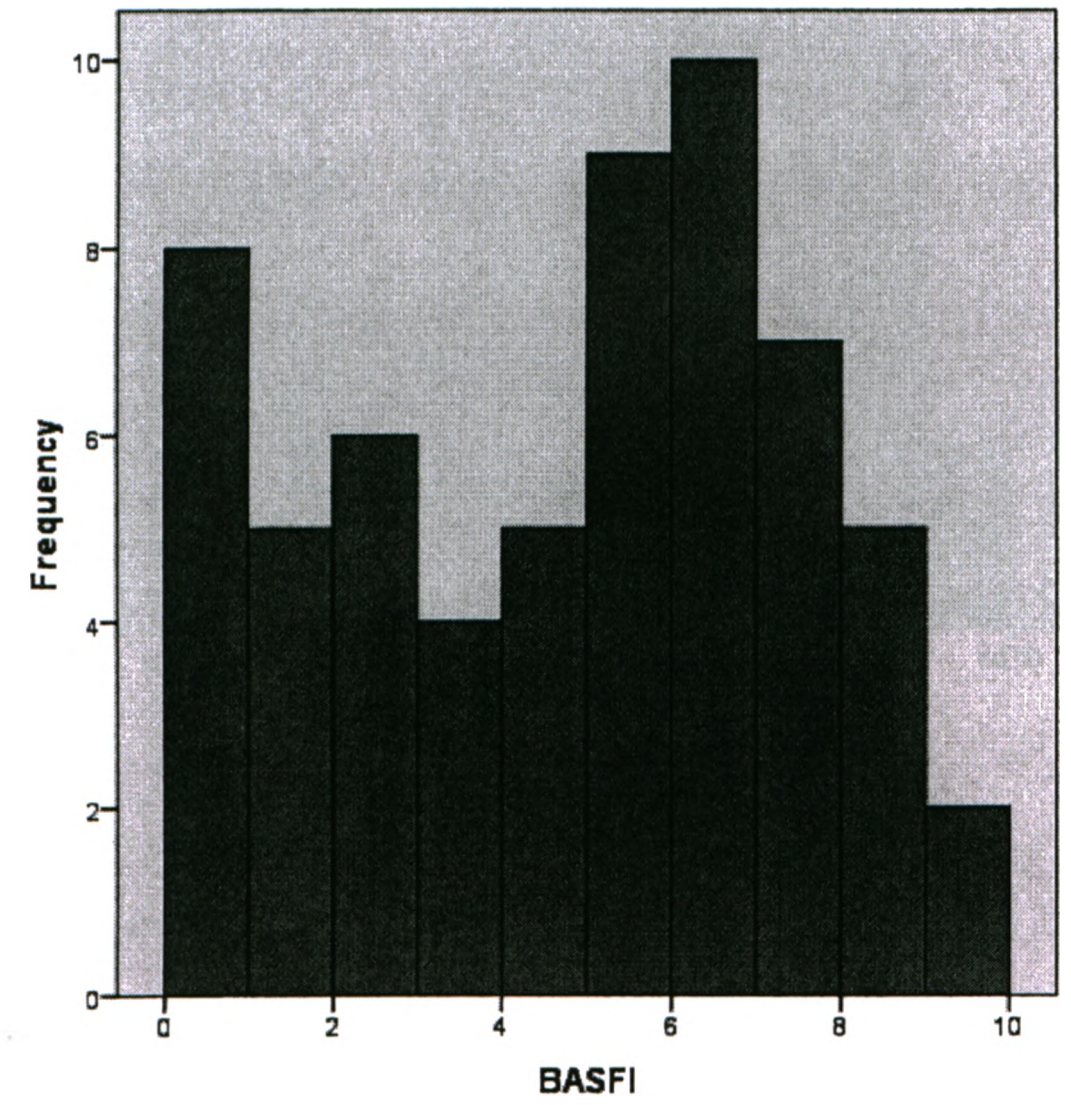


Figure 26: Frequency distribution of BASFI scores.

4.1.5.2. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Subjects in our population had a mean BASDAI score of 5.2 (SD 2.5). A frequency distribution of the reported BASDAI results can be found in Figure 27.

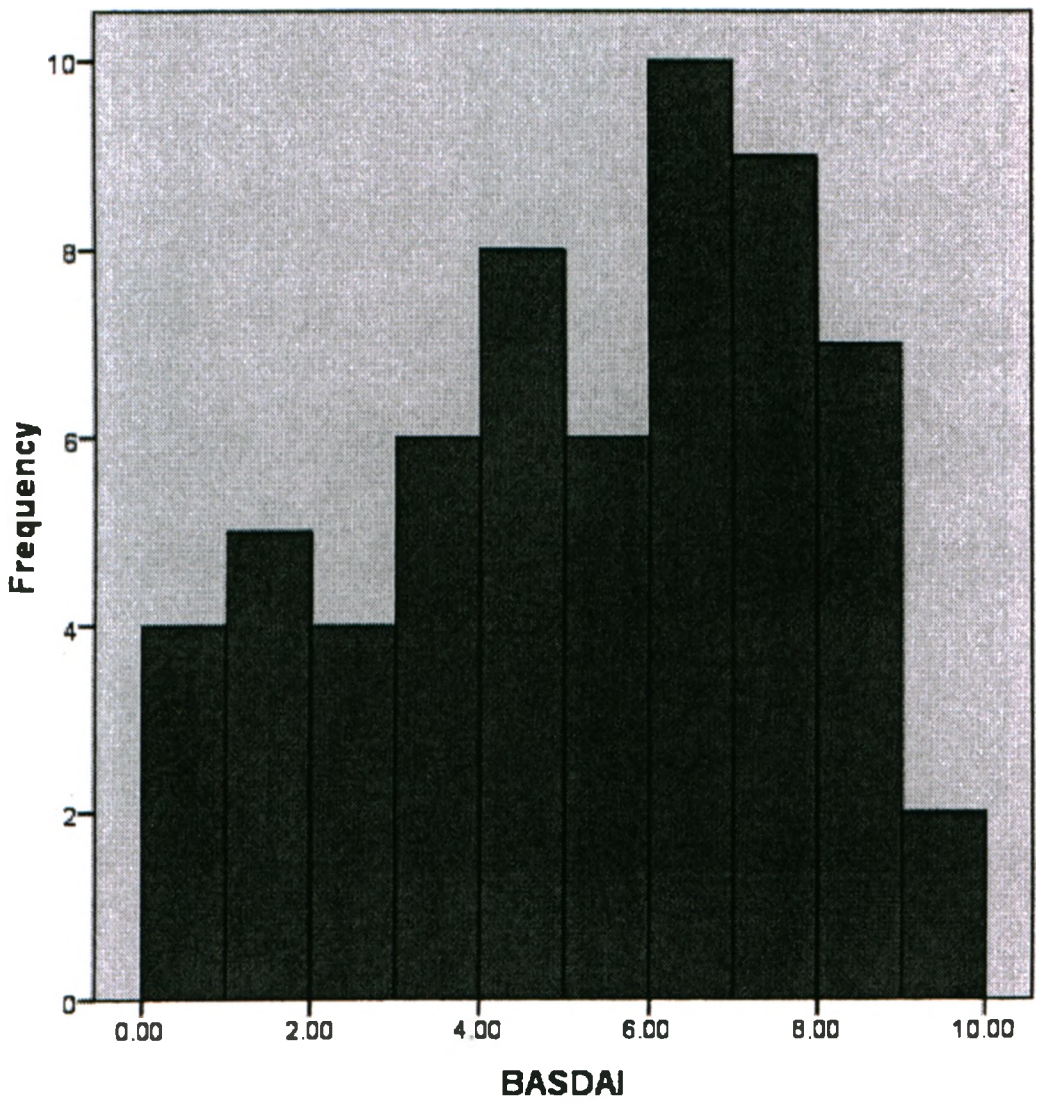


Figure 27: Frequency distribution of BASDAI scores.

4.1.5.3. The Bath Ankylosing Spondylitis Global Score (BAS-G)

The mean BAS-G score of our study population was 5.0 (SD 2.6). A frequency distribution of all BAS-G responses is illustrated in Figure 28.

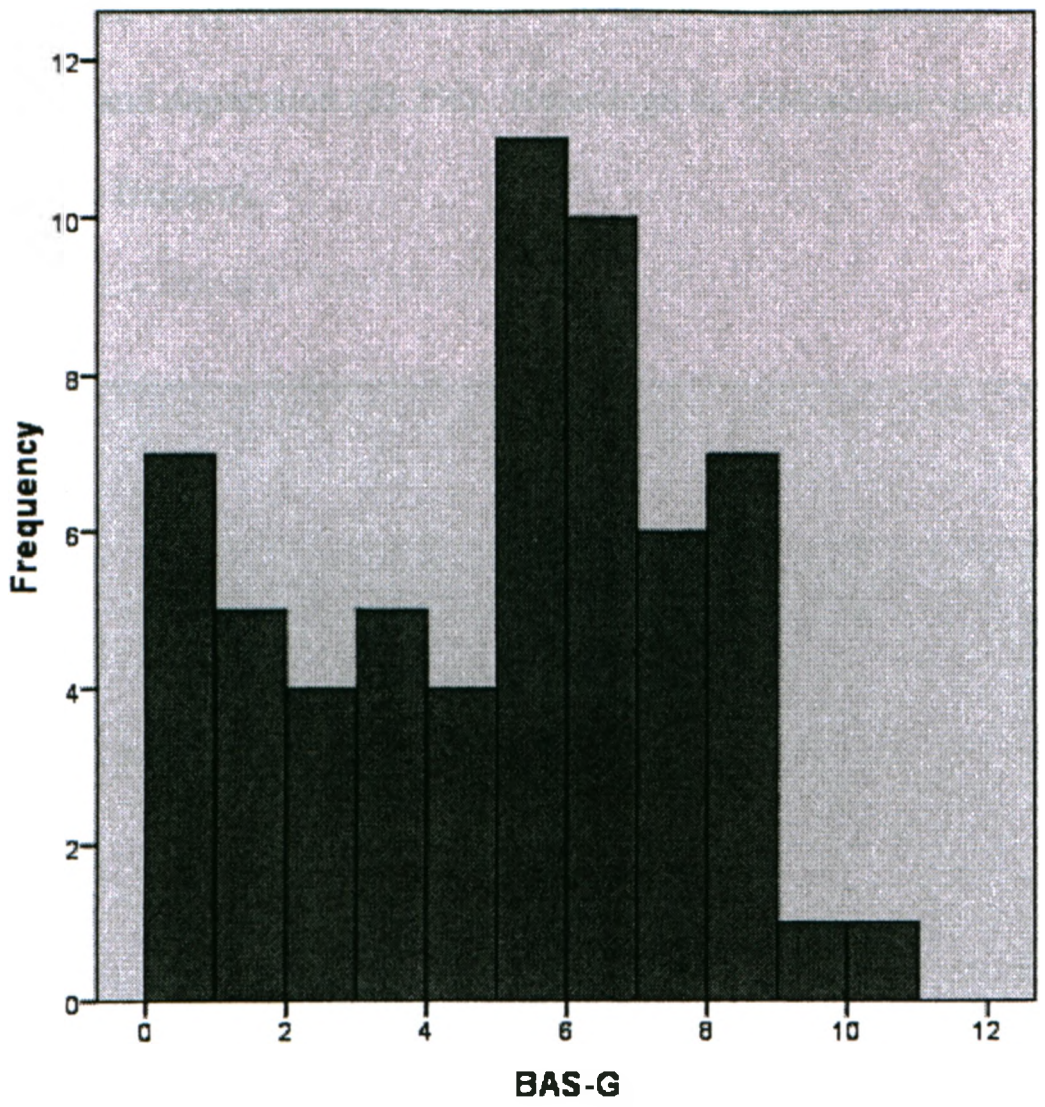


Figure 28: Frequency distribution of BAS-G scores.

4.1.6. Assessment Of Comorbidities: The Functional Comorbidity Index (FCI)

Figure 29 demonstrates the comorbidities found in our studied population. By far, the most common comorbidity indicated was arthritis (69.0%). This is actually an interesting finding, since technically the response to this question should have been 100%, given that AS is a form of arthritis. Some subjects may have misinterpreted the question as applying to only other forms of arthritis, or arthritis of the peripheral joints. Other frequently reported comorbid conditions included: degenerative disc

disease (32.1%), obesity with BMI > 30 (25.9%), upper gastrointestinal (GI) disease (23.5%) and depression (22.2%). Neurological, cardiac and vascular comorbidities were less frequent.

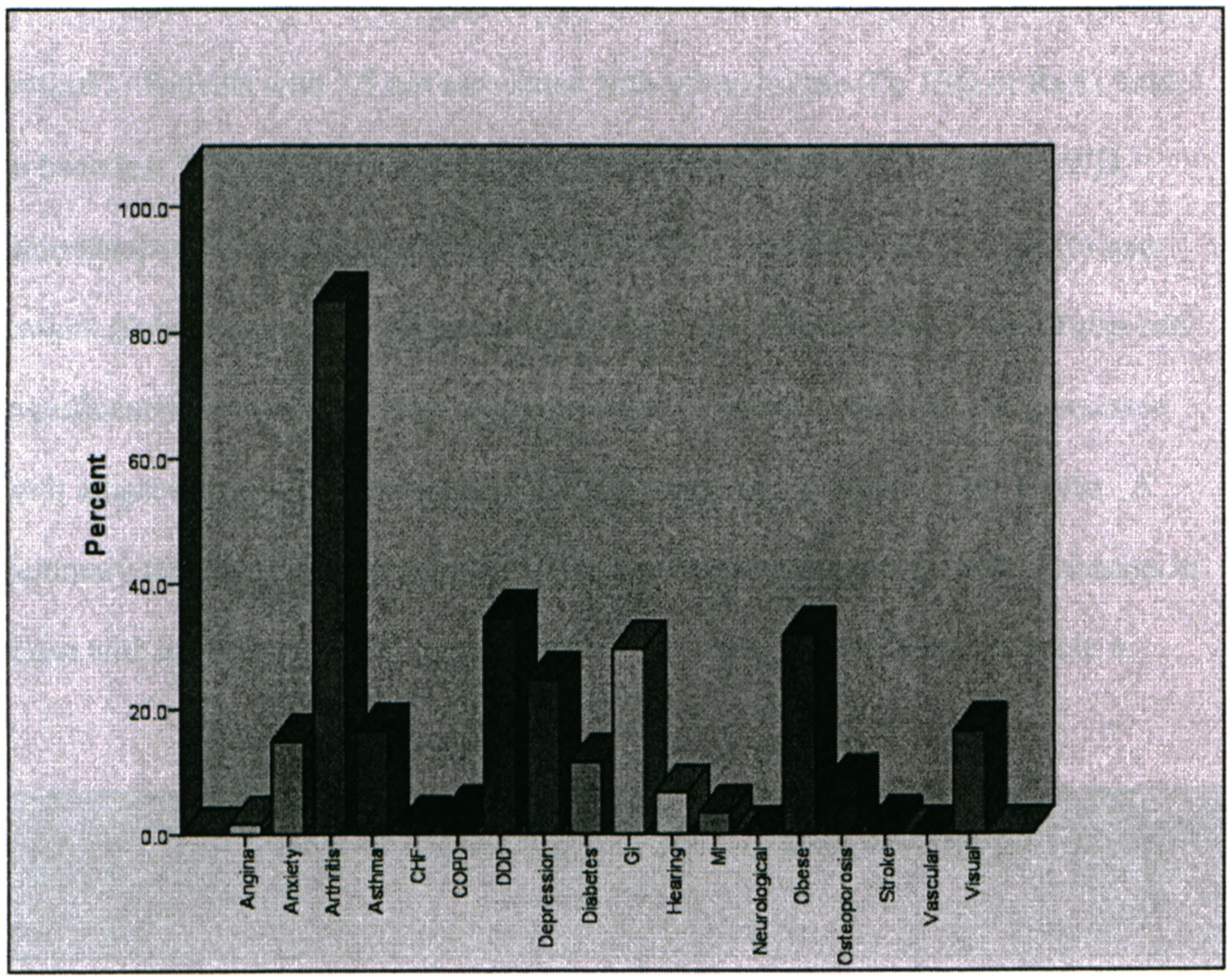


Figure 29: Comorbidities found in study population, as assessed by the Functional Comorbidity Index (FCI).

4.2. Work Disability

WD was defined as unable to work at all, attend school, volunteer, or do unpaid work at home (i.e. homemaking). In our respondents, 18.5% were WD by this classification.

4.2.1. Associations With Work Disability

Those with WD were significantly older than non-WD (52.9 vs 43.1 years, $p<0.05$). Patients with AS not associated with other disease (Ps, IBD or ReA) tended to have less WD than those with other systemic manifestations ($p<0.001$). WD individuals also had higher scores on BASFI (6.8 vs 4.1), BAS-G (6.5 vs 4.6) and patient global assessment of poor health (5.8 vs 4.0). Spondylitis with WD also had significantly more comorbidity than non-WD (2.3 vs 4.0). WD was not associated with longer duration of disease, higher HAQ scores or higher BASDAI scores. A summary the comparison of clinical characteristics and clinical outcome measures in those with and without WD, using independent t-tests, may be found in Table 4.

Characteristic	Mean In All Respondents (SD) (n=81)	Mean In Not WD Group (SD) (n=63)	Mean In WD Group (SD) (n=15)	p-value Not WD vs. WD
Age	**45.0 yrs (11.5)**	**43.1 yrs (11.3)**	**52.9 yrs (9.1)**	**<0.05**
% Male	46.9	52.1	77.8	0.154
Disease Duration	9.9 yrs (12.1)	10.0 yrs (12.0)	9.3 yrs (12.6)	0.85
HAQ Score	0.90 (0.61)	0.78 (0.56)	1.38 (0.59)	0.89
VAS Pain Score	4.9 (2.8)	4.7 (2.8)	6.0 (2.2)	0.053
VAS Fatigue Score	5.6 (3.0)	5.4 (3.0)	6.6 (2.4)	0.155
VAS Problem Sleep Score	5.2 (3.3)	4.9 (3.3)	6.2 (3.0)	0.188
Duration of Morning Stiffness	107.7 min (271.7)	97.6 min (251.9)	68.0 min (49.7)	0.654
BASDAI Score	5.2 (2.5)	5.0 (2.5)	6.2 (2.2)	0.342
BASFI Score	**4.6 (2.8)**	**4.1 (2.6)**	**6.8 (2.4)**	**<0.05**
BAS-G Score	**5.0 (2.6)**	**4.6 (2.5)**	**6.5 (2.5)**	**<0.05**
Number Of Comorbidities		**2.3 (1.8)**	**4.0 (3.3)**	**<0.05**

Table 4: *Comparison of clinical characteristics and clinical outcome measures in those with and without WD.*

4.2.2. Logistic Regression: Work Disability As A Binary Outcome

Univariate binary (binomial) logistic regression was carried out for the dichotomous dependent variable work disabled (yes/no). Of the demographic factors, age and number of comorbid medical conditions were significantly associated with work disability (OR 1.10 [95% CI: 1.03, 1.18] and 1.35 [95% CI: 1.05, 1.73], respectively). Higher scores on WLQ time management, mental-interpersonal skills, and output were all significantly associated with WD (Table 5). Additionally, higher scores on HAQ, VAS patient global assessment, BASFI and BAS-G scores were significantly associated with WD (Table 5).

Multivariable logistic regression did not yield any final models in which the independent variables were included. In each case, the final models were reduced to the original univariate models.

WORK DISABILITY

Variable	Exp(B)	95% CI for Exp(B) (lower, upper)	Significance
Age (years)	1.104	1.029, 1.184	0.006
Gender (male)	3.220	0.606, 17.112	0.170
Years of disease activity	0.995	0.949,1.044	0.851
WLQ Time Management Score	1.038	1.001, 1.077	0.042
WLQ Physical Score	1.026	0.995, 1.058	0.098
WLQ Mental Interpersonal Skills Score	1.061	1.014, 1.111	0.011
WLQ Output Score	1.106	0.998, 1.225	0.055
Loss in health-related work productivity (%)	1.415	1.023, 1.958	0.036
HAQ Score	6.561	2.027, 21.243	0.002
VAS Pain Score	1.216	0.968, 1.528	0.093
VAS Fatigue Score	1.168	0.941, 1.449	0.158
VAS Sleep Score	1.132	0.941, 1.362	0.189
VAS Patient Global Assessment	1.366	1.059, 1.761	0.016
Duration of am stiffness (minutes)	0.999	0.996, 1.003	0.662
BASFI Score	1.610	1.189, 2.180	0.002
BASDAI Score	1.255	0.972, 1.621	0.082
BAS-G Score	1.431	1.077, 1.901	0.013
Number of comorbidities	1.349	1.054, 1.727	0.017

Table 5: Results of univariate binary logistic regression. In each case, the dependent is work disabled (yes/no). Each variable is run separately.

4.2.3. Other Measures Of WD

In those who were still working, 39.5% of respondents had decreased the number of hours they worked per week due to their arthritis, with an average 3.7 days/week (SD 8.1) of reduced work hours. Additionally, respondents reported

missing an average of 2.5 complete days (SD 6.2) of work/month due to arthritis. 14.8% described conflict at work due to lack of productivity or absences. These results are summarized in Table 6.

Characteristic (n=66)	Result
Number Of Hours Worked/Week	29.2 hrs (SD 20.1)
Decreased Number Of Hours Worked/Week	39.5%
Mean Days/Month Of Reduced Work Hours	3.7 days (SD 8.1)
Mean Days Off/Month	2.5 days (SD 6.2)
Conflict At Work	14.8%

Table 6: Summary of work restrictions reported in those still working.

4.3. WLQ Productivity Loss Score And Scale Scores

WLQ scores were calculated using the confidential technical report which accompanies the WLQ guide (29). The mean loss in health related work productivity was 8.3% (SD 6.6) (Figure 30). Individual scale scores were also computed for the four domains that comprise the WLQ: Time Management Scale (TMS), Physical Demands Scale (PDS), Mental-Interpersonal Demands Scale (MIDS) and Output Demands Scale (ODS). The individual scale scores indicate the percentage of time in the preceding two weeks that the subject was limited in performing that component of their job (29). Subjects reported a mean 37.3% limitation in TMS, 38.3% limitation in PDS, 23.0% limitation in MIDS and 33.1% limitation in ODS. SDs were large, at 31.5, 28.5, 18.1 and 25.0 respectively. Figures 31-34 illustrate the distribution of responses for the WLQ scale scores.

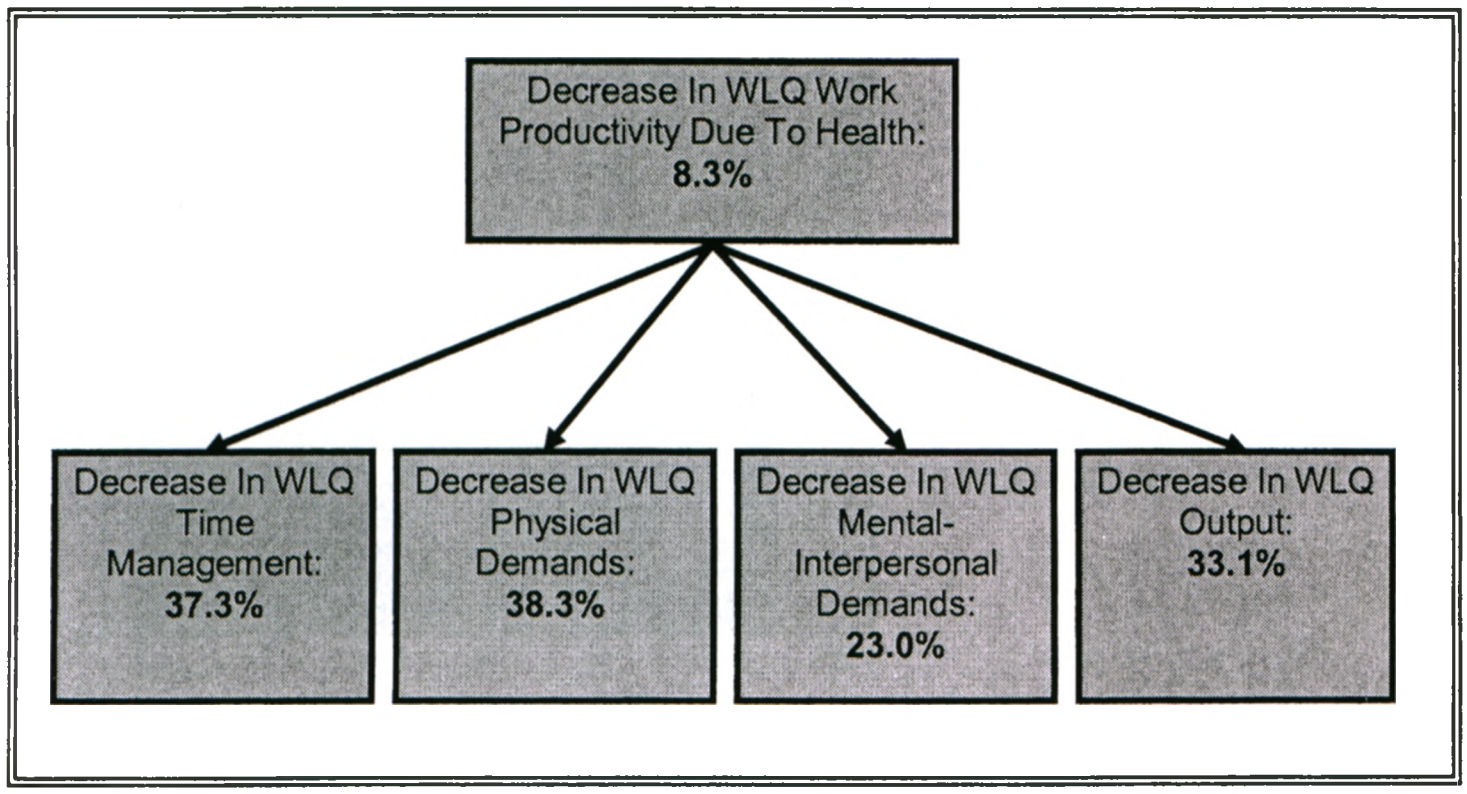


Figure 30: Summary of results of WLQ work productivity analysis.

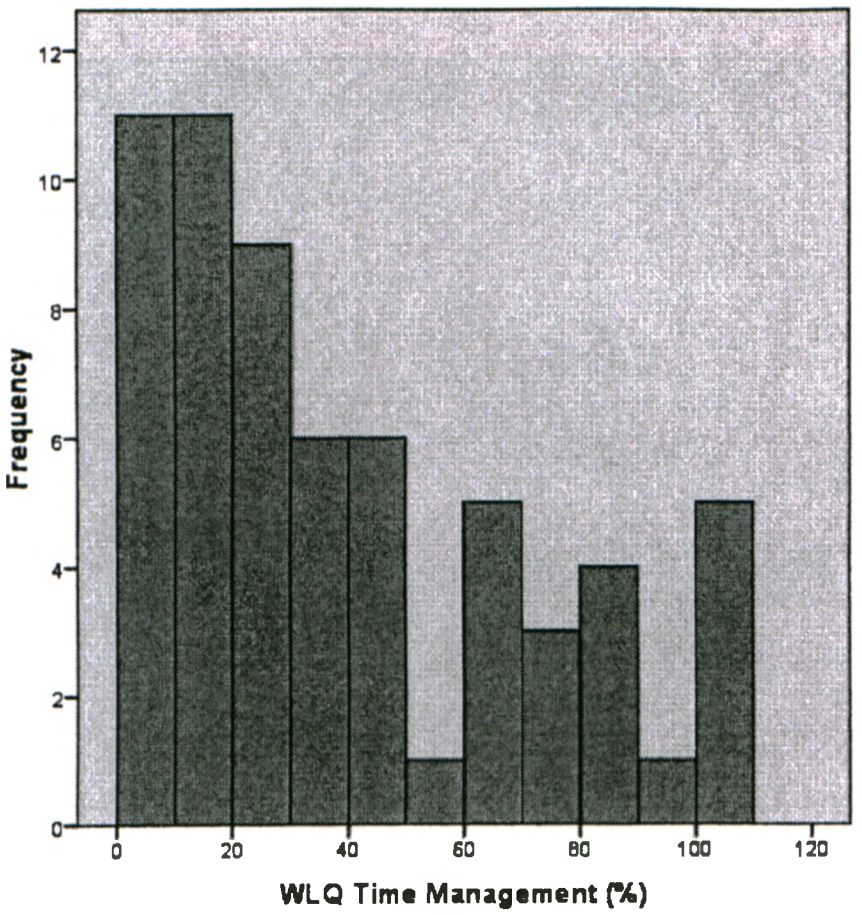


Figure 31: Histogram demonstrating distribution of reported losses in WLQ Time Management.

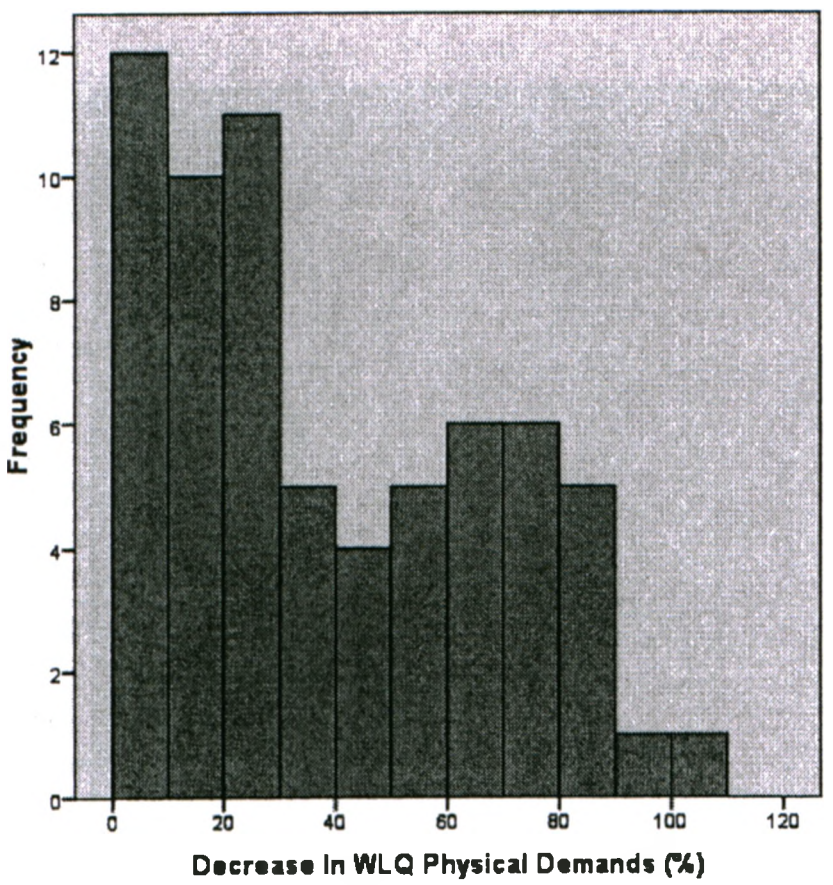


Figure 32: Histogram demonstrating distribution of reported losses in WLQ Physical Demands.

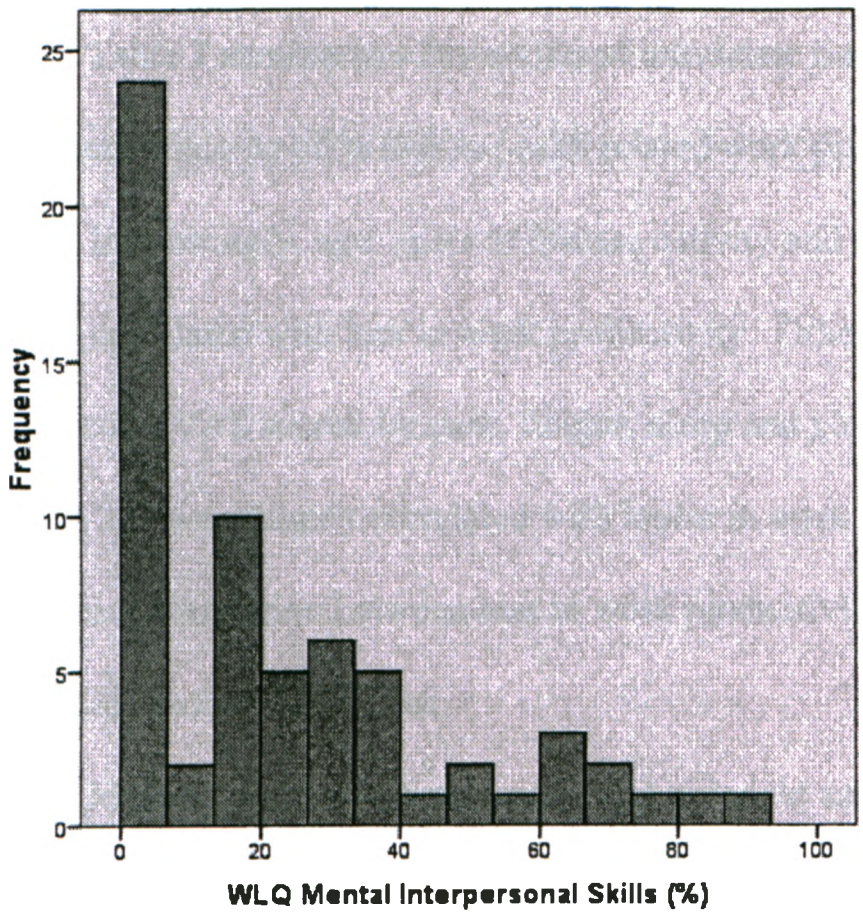


Figure 33: Histogram demonstrating distribution of reported losses in WLQ Mental Interpersonal Skills.

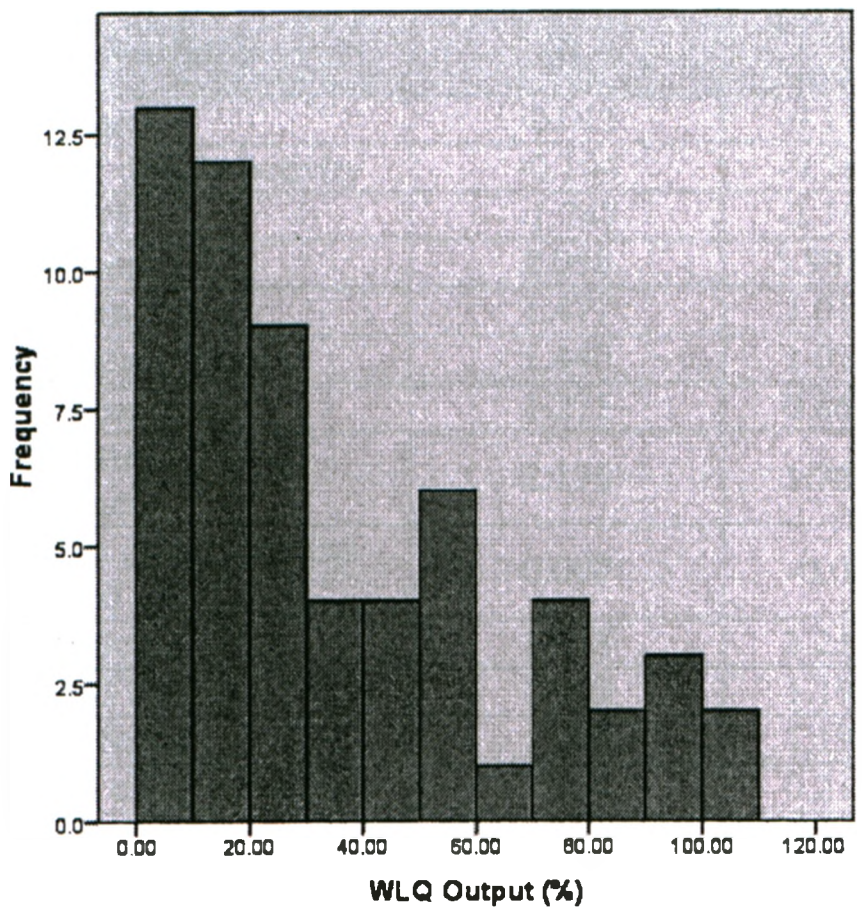


Figure 34: Histogram demonstrating distribution of reported losses in WLQ Output.

4.3.1. Linear Regression: Loss In Health-Related Work Productivity (%)

Table 7 summarizes the results of univariate linear regression for the dependent outcome of % loss in health related work productivity as measured by the WLQ. Interestingly, age, years of disease activity and duration of morning stiffness did not correlated with loss in work productivity. Other outcome measures, such as HAQ score, VAS scores for pain, fatigue, sleep and global health, BASFI, BASDAI and BAS-G were highly correlated with losses in work productivity. There was also a significant correlation between loss in work productivity and an increasing number of comorbid medical conditions.

Multinomial logistic regression did not yield any final models in which the independent variables were included. All multinomial logistic regression models reduced to the original model.

LOSS IN HEALTH-RELATED WORK PRODUCTIVITY (%)

Variable	B	95% CI for B (lower, upper)	Significance
Age (years)	-0.013	-0.177, 0.150	0.871
Years of disease activity	-0.104	-0.260, 0.052	0.186
Income ($)	-1.747	-2.764,-0.730	0.001
HAQ Score	8.058	5.995, 10.120	0.000
VAS Pain Score	1.477	1.017, 1.937	0.000
VAS Fatigue Score	1.440	1.015, 1.865	0.000
VAS Sleep Score	1.275	0.866, 1.684	0.000
VAS Patient Global Assessment	2.136	1.764, 2.509	0.000
Duration of am stiffness (minutes)	0.007	-0.002, 0.17	0.115
BASFI Score	1.698	1.211, 2.186	0.000
BASDAI Score	1.779	1.193, 2.196	0.000
BAS-G Score	1.695	1.193, 2.196	0.000
Number of comorbidities	1.177	0.212, 2.141	0.018

Table 7: Results of univariate linear regression. In each case, the dependent is loss in health-related work productivity (%). Each variable is run separately.

4.3.2. Summary Of Correlations With WLQ Productivity Loss

Table 8 summarizes correlations with WLQ productivity loss.

Factor	Pearson r	p-value	Spearman's rho	p-value
Age	-0.02	0.87	-0.05	0.71
Disease Duration	-0.18	0.19	-0.18	0.19
HAQ	0.72	<0.001	0.70	<0.001
VAS Pain	0.65	<0.001	0.65	<0.001
VAS Fatigue	0.67	<0.001	0.71	<0.001
VAS Problem Sleep	0.64	<0.001	0.64	<0.001
VAS Overall Health	0.84	<0.001	0.82	<0.001
Morning Stiffness	0.21	0.115	0.52	<0.001
BASFI	0.68	<0.001	0.65	<0.001
BASDAI	0.69	<0.001	0.69	<0.001
BAS-G	0.67	<0.001	0.66	<0.001
Number Of Comorbidities	0.31	0.02	0.34	0.01

Table 8: Correlation of clinical characteristics and clinical outcome measures with WLQ work productivity loss.

4.3.2.1. Association Of Demographic Characteristics With WLQ Productivity Loss

There was no significant association between type of AS (dichotomized into AS vs. AS with other systemic disease) and WLQ productivity loss (χ^2 =23.4, p=0.175). Gender was also not associated with productivity loss (χ^2 =7.17, p=0.989), nor was level of education (χ^2 =60.0, p=0.299).

Age and years of disease activity did not correlate with loss of productivity, with r of –0.02 and –0.18 respectively (p=0.87 and p=0.19) (Figures 33-34). Changing to a non-parametric correlation measure, Spearman's rho, did not alter these results.

Income level was significantly associated with loss of productivity (χ^2 =70.0, p=0.01), with lower incomes reporting greater work productivity losses.

4.3.2.2. The Health Assessment Questionnaire (HAQ), Visual Analogue Scale (VAS) Measures, And Morning Stiffness

HAQ scores were highly correlated with WLQ productivity loss, with Pearson's r of 0.72 (p<0.001) (Figure 34). In addition, VAS scores on scales of pain, fatigue, problem sleep and overall well-being were highly correlated with losses in productivity (Figures 35-39). The Pearson correlation coefficient for the association between VAS pain and productivity loss scores was 0.65 (p<0.001). VAS unusual fatigue in the past week had an r of 0.67 (p<0.001) and problem sleep was also highly correlated with an r of 0.64 (p<0.001). Patient global assessment, determined by VAS scores, was also highly correlated with productivity loss (r=0.84, p<0.001).

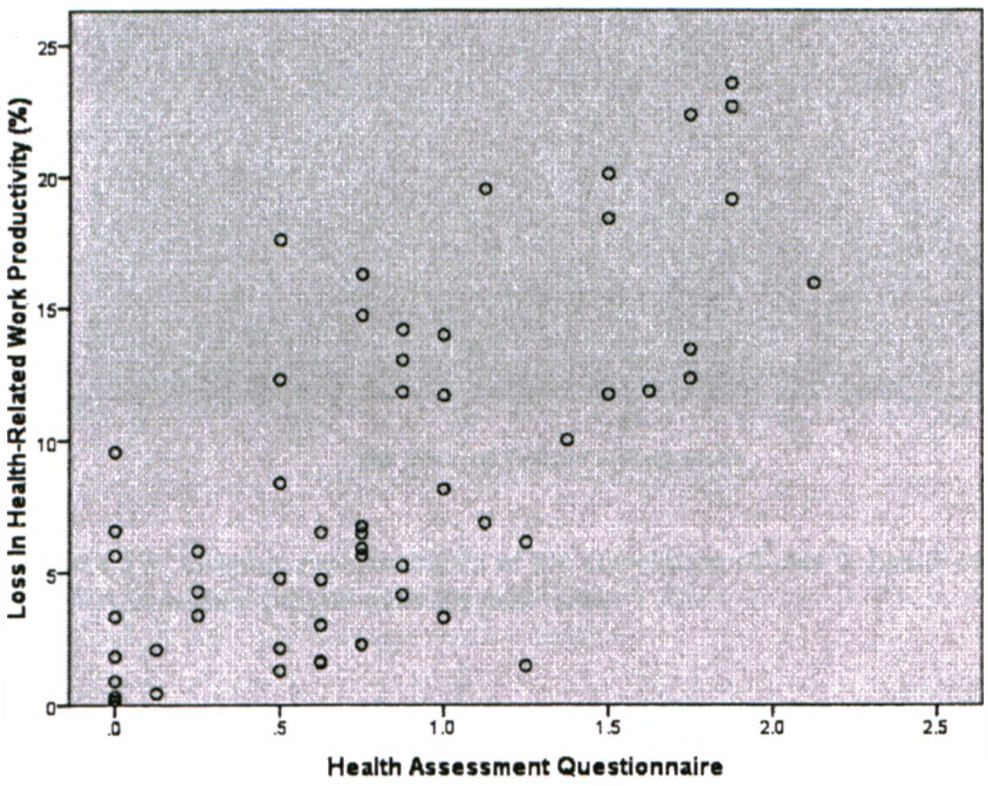
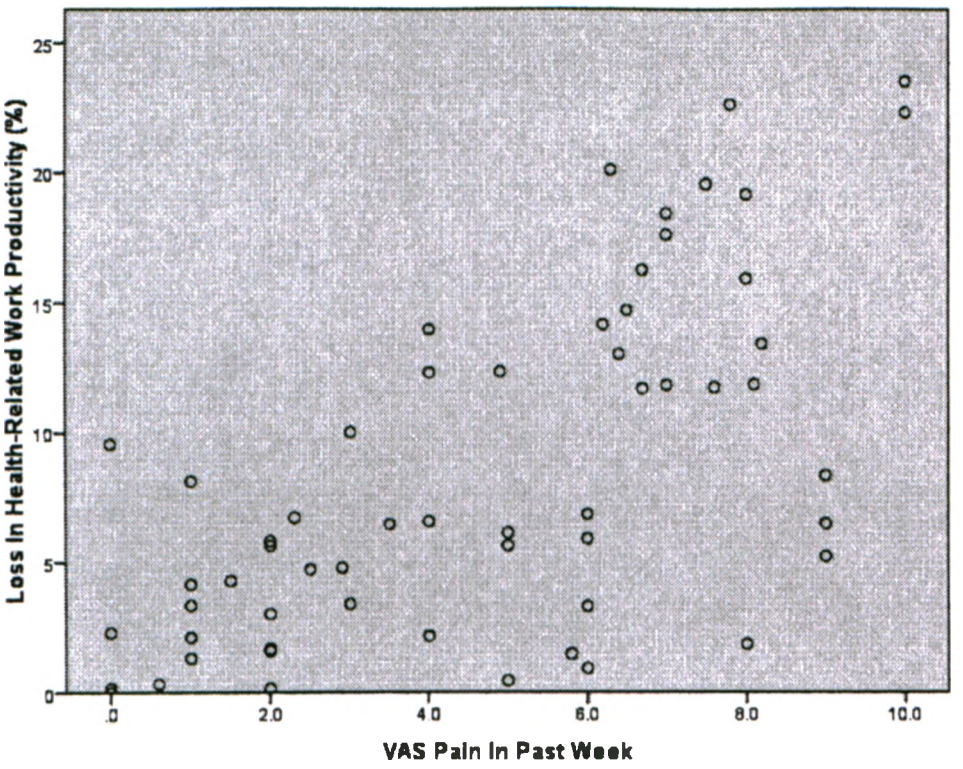
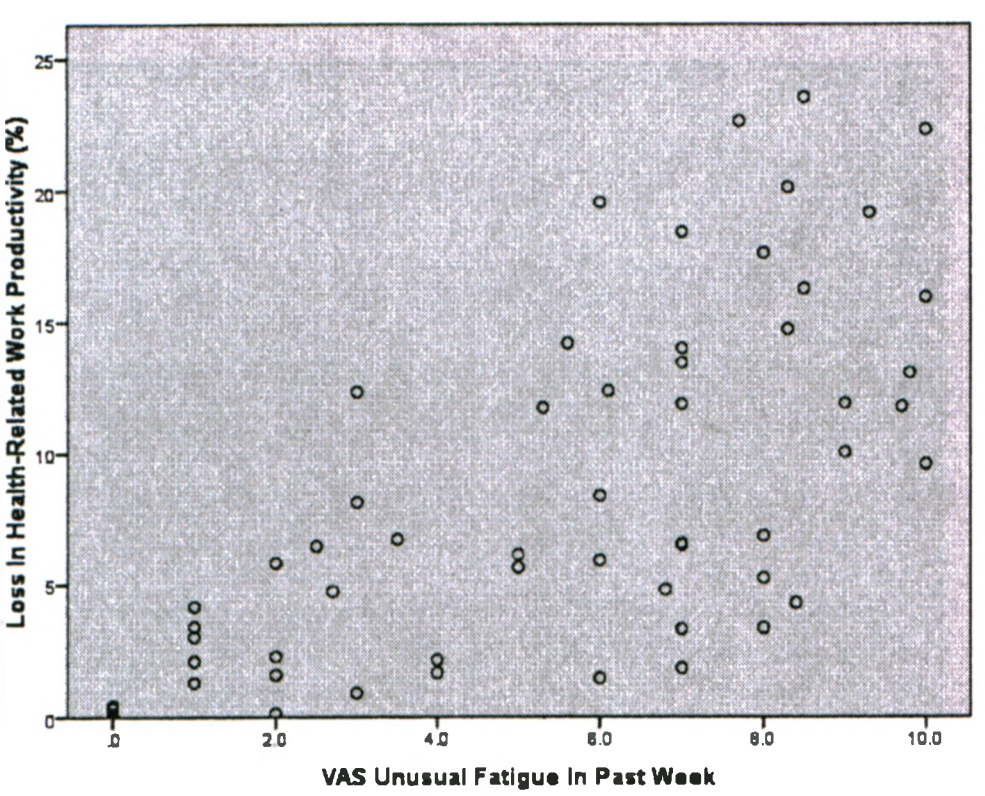


Figure 35: Graphic representation of the correlation of loss in health-related work productivity and responses to the HAQ.



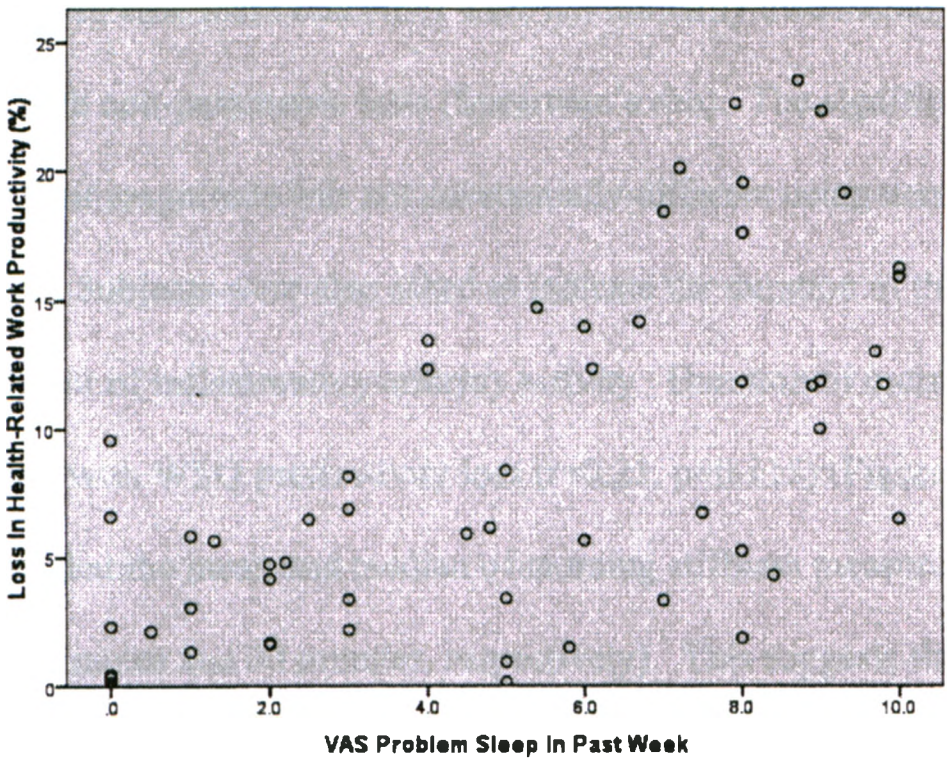
Pearson r = 0.65
Spearman's rho = 0.65

Figure 36: Graphic representation of the correlation of loss in health-related work productivity and VAS pain over the past week.



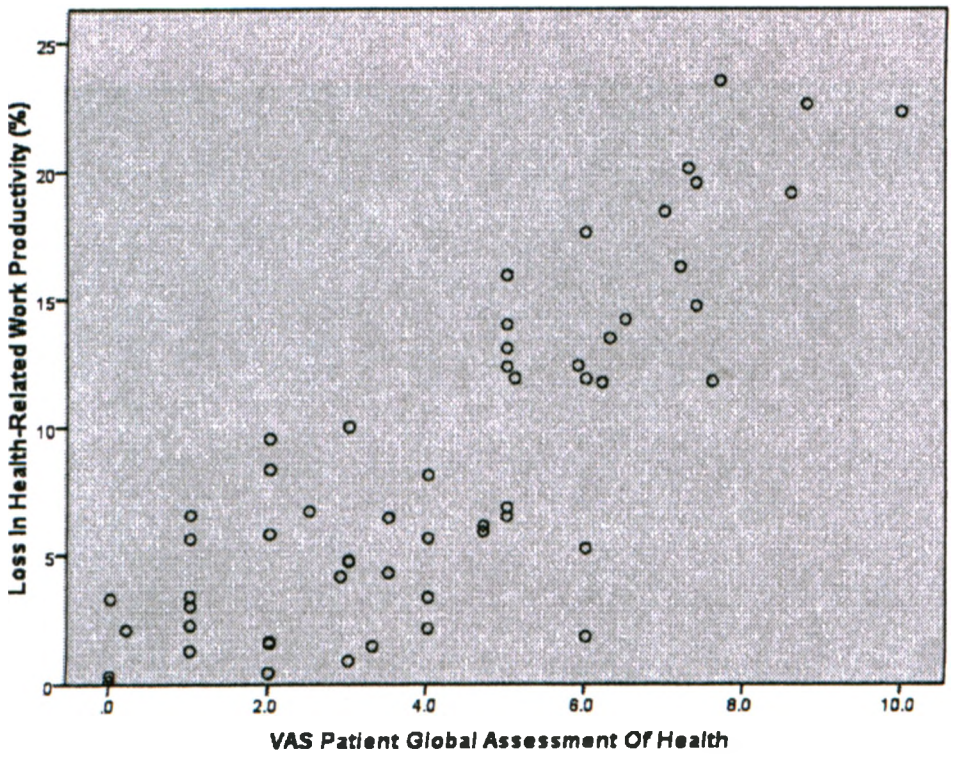
Pearson r = 0.67
Spearman's rho = 0.71

Figure 37: Graphic representation of the correlation of loss in health-related work productivity and VAS unusual fatigue over the past week.



Pearson r = 0.64
Spearman's rho = 0.64

Figure 38: Graphic representation of the correlation of loss in health-related work productivity and responses to VAS problem sleep in the past week.



Pearson r = 0.84
Spearman's rho = 0.82

Figure 39: Graphic representation of the correlation of loss in health-related work productivity and VAS patient global assessment of health.

In case these outcomes were not normally distributed, correlations were also run with non-parametric tests (Spearman's rho). The significance of the correlations and their magnitude was not substantially different using non-parametric measures.

Subjects were also asked to indicate the duration of their morning stiffness, an indicator of inflammatory arthritis activity. Duration of morning stiffness correlated poorly with WLQ productivity loss ($r=0.21$, $p=0.115$) (Figure 40). However, it was noted that the mean and median of morning stiffness measures were quite different (108 minutes and 60 minutes, respectively). This suggests that morning stiffness was not normally distributed. When non-parametric measures were used, there was a significant correlation between duration of morning stiffness and WLQ productivity loss scores (Spearman's $rho=0.52$, $p<0.001$).

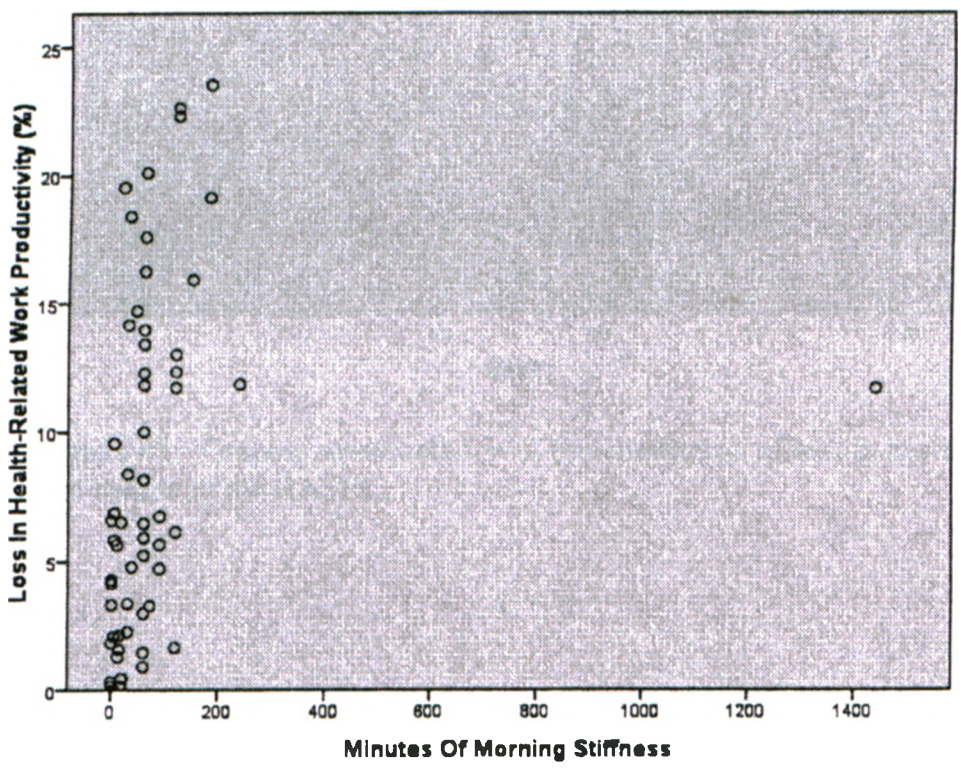
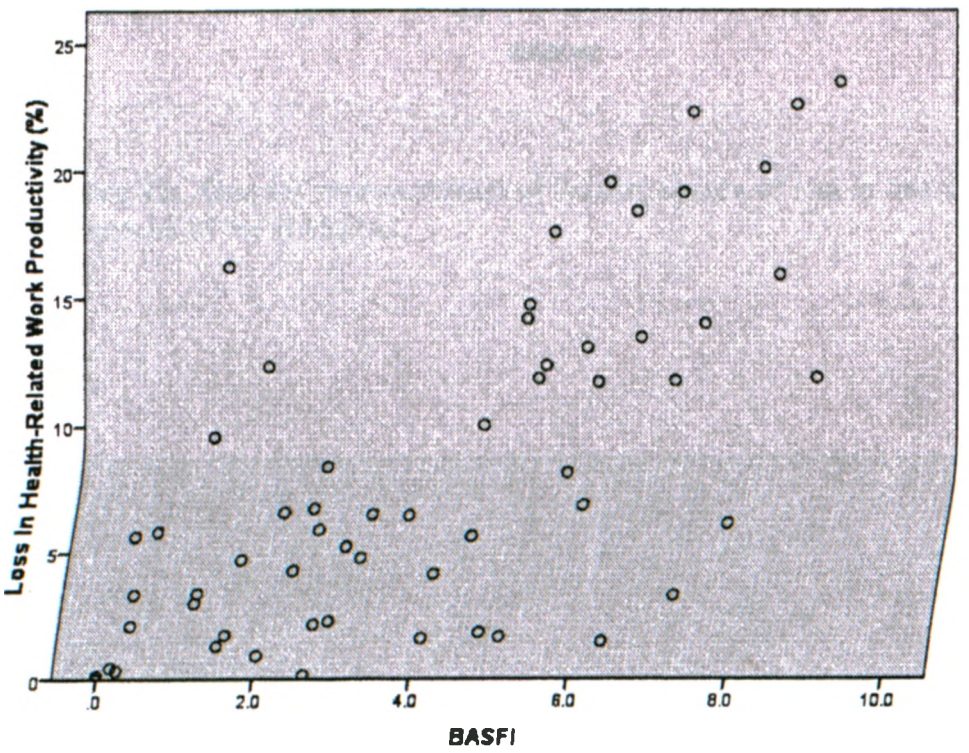


Figure 40: Graphic representation of the correlation of loss in health-related work productivity and minutes of morning stiffness.

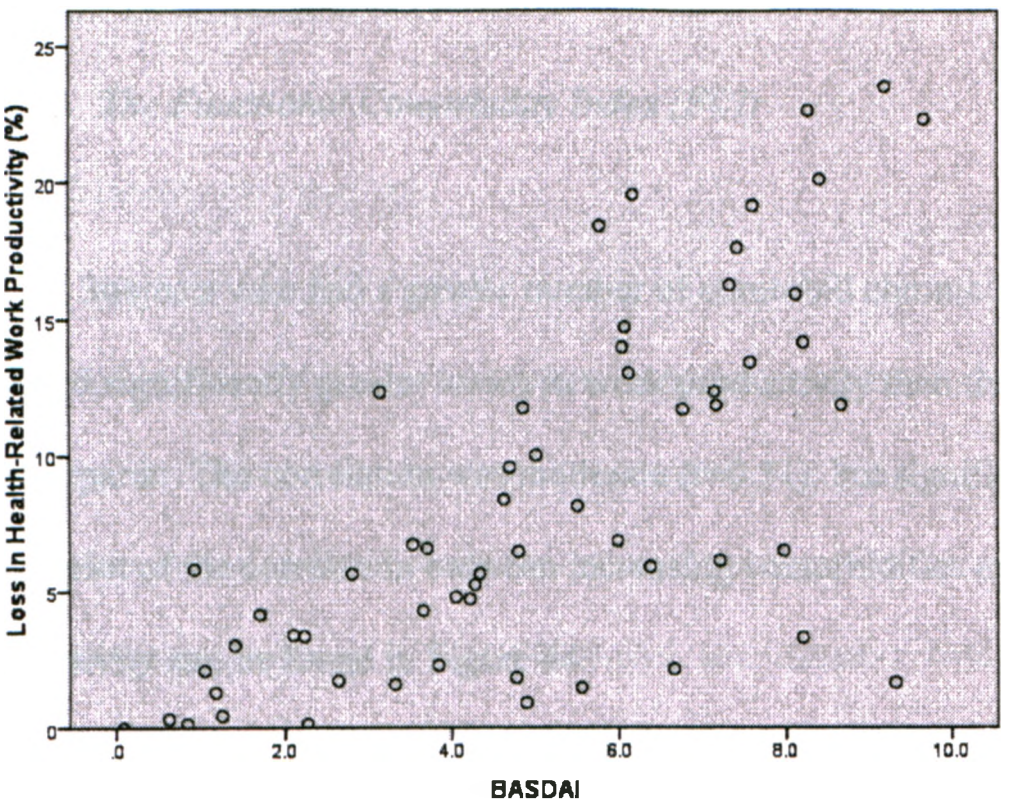
4.3.2.3. The Bath Indices

Losses in WLQ productivity were highly correlated with all Bath Indices (Figures 41-43). The correlation with BASFI was r=0.68 (p<0.001), BASDAI r=0.69 (p<0.001) and BAS-G r=0.67 (p<0.001). For each of the Bath outcome measures, there were no substantial differences if non-parametric correlations (Spearman's rho) were used rather than parametric measures.



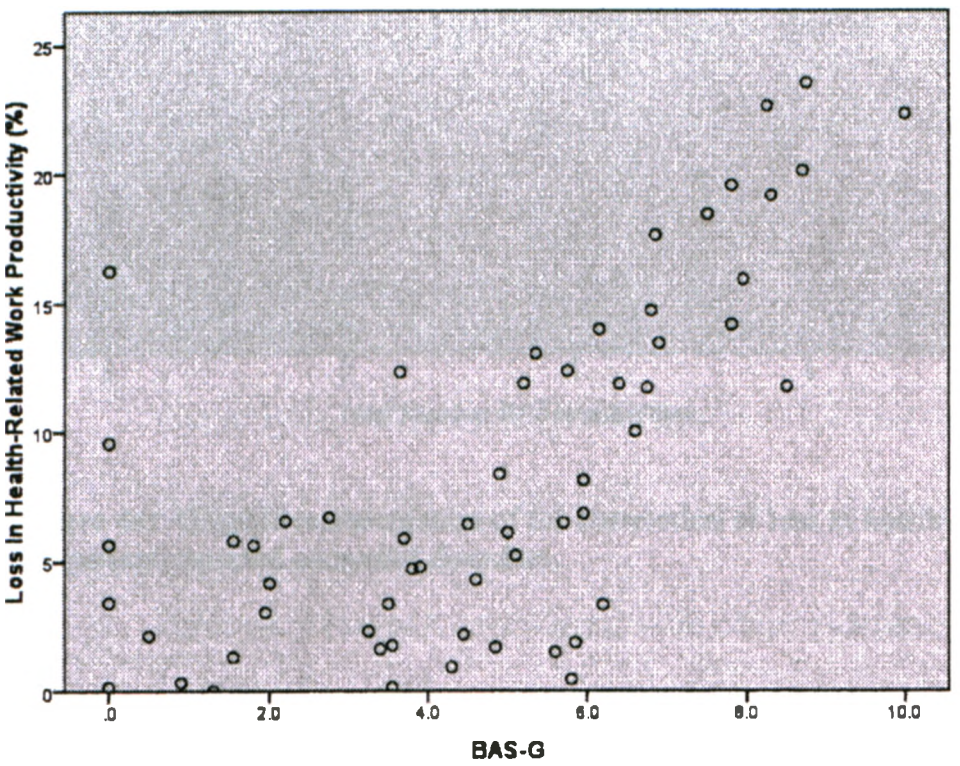
Pearson r = 0.68
Spearman's rho = 0.65

Figure 41: Graphic representation of the correlation of loss in health-related work productivity and results of the BASFI.



Pearson r = 0.69
Spearman's rho = 0.69

Figure 42: Graphic representation of the correlation of loss in health-related work productivity and results of the BASDAI.



Pearson r = 0.67
Spearman's rho = 0.66

Figure 43: Graphic representation of the correlation of loss in health-related work productivity and results of the BAS-G.

4.3.2.4. The Functional Comorbidity Index (FCI)

Subjects who had a greater number of comorbid chronic health conditions reported significantly greater losses in work productivity than their healthier counterparts. The correlation was moderate (r=0.31), but significant (p=0.02). A scatterplot of the correlation between increasing comorbidities and loss in work productivity can be found in Figure 44.

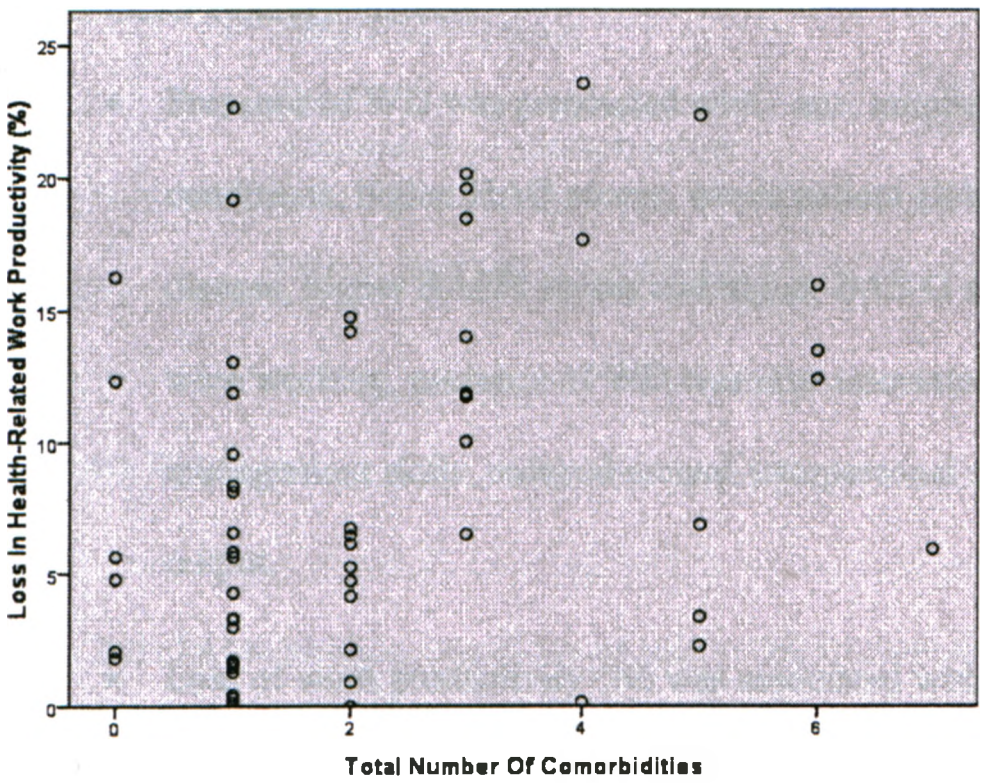


Figure 44: Graphic representation of the correlation of loss in health-related work productivity and patient-reported comorbid disorders.

Chapter 5: Discussion

5.1. Summary Of Findings

In our study, 18.5% were work disabled, which is consistent with previous studies, and very similar to the reported rates in other Canadian populations. Our findings also indicate that a substantial proportion (8.3%) of working subjects with seronegative SpA suffer from losses in work productivity due to health. The cause of this decreased productivity is multifactorial, and includes issues with time management, physical function, mental-interpersonal skills and reduced output.

Other findings include:

- Presence of WD was associated with: age, number of comorbid conditions, higher HAQ scores, worse patient global assessment of disease, higher BASFI scores and higher BAS-G scores. In those who were working, presence of WD was also associated with a decrease in time management skills, reduced mental-interpersonal skills, and reduced output.
- Loss of work productivity (%) was associated with higher HAQ scores, worse pain, fatigue and global health VAS scores, higher scores on BASDAI, BASFI and BAS-G, as well as number of comorbid disorders.
- Patients with SpA associated with other systemic disease, such as Ps, IBD and ReA, had higher levels of WD but did not differ from those with AS in terms of work productivity.

Table 9 summarizes associations with WD and loss in work productivity.

Associations With WD	Associations With Loss Of Work Productivity
• Older age • More comorbid diseases • Higher BASFI scores • Higher BAS-G scores • Worse WLQ time management • Worse WLQ mental-interpersonal skills • Higher HAQ score • Higher VAS patient global assessment of disease scores	• More comorbid diseases • Higher BASFI scores • Higher BAS-G scores • Higher BASDAI scores • Higher HAQ scores • Higher VAS pain scores • Higher VAS fatigue scores • Higher VAS sleep scores • Higher VAS patient global assessment of disease scores

Table 9: Summary of associations with WD and loss of work productivity.

5.2. Study Weaknesses

All clinical studies, regardless of how carefully they are planned and conducted, will have inevitable weakness. Acknowledging these weaknesses allows the investigators and those who interpret the data for application to a clinical population to use the results appropriately.

The main limitations were the poor response rate, the small sample size and uncertainty regarding the generalizability of our single site study to other SpA patients.

5.3. Sources of Research Bias

All clinical studies are subject to selection, measurement and intervention bias, and unfortunately this study is no exception. The following section will briefly outline each potential source of research bias and its potential effect on our results.

5.3.1. Selection Biases

Since this study did not assess every patient with AS in Southwestern Ontario, it could be subject to sampling error (51). Every effort was made to capture all patients seen in London rheumatology clinics, but certainly 100% of the AS population was not included.

Not all patients with AS attend specialty clinics. This would mean that some patients with AS did not have the chance to participate in our study, potentially contributing to coverage error (51). Additionally, the surveys were distributed on the basis of OHIP billing data, and it is quite possible that some of the subjects received a package in error due to miscoding on the part of the attending physician. This would also increase coverage error (51). It is possible that some coverage error occurred due to poor literacy, or because the subject did not read English.

We did attempt to reduce coverage error by performing a detailed chart review of all patients with a 720 billing code, thus obtaining employment information on survey non-responders.

This study involved a self-administered mail questionnaire, and response rate was mediocre at best. Thus, respondents would be subject to volunteer bias, in that those who are more motivated about health concerns would be more likely to volunteer to participate. These motivated individuals may be more likely to comply

with treatment or aggressively manage their disease. Our study also suffered from a significant nonrespondent bias. In our study, the response rate of 40% is consistent with that seen in other studies. Participants were telephoned to remind them to complete their surveys in an attempt to improve response rates. Additionally, subjects were reminded to respond to the survey during clinic visits. Patients with a new diagnosis of AS or those who were seen in clinic for the first assessment were also given survey packages in person.

Despite these meaures, it is clear that the respondents and non-respondents differed demographically. Responders were 46.9% male, versus non-responders at 72.1% male. AS is classically defined as a disease with a male predominance, with an approximately 2:1 male:female ratio (1). Traditionally, males have been thought to have more severe SpA than females, so this significant gender bias in our results may impact generalizability to other populations.

5.3.2. Measurement Biases

Measurement biases occur when there are errors in data collection. Instrument bias occurs when survey questions are ambiguously worded, inappropriately weighted or the responses are uninterpretable (51). Risk of ambiguous wording was minimized through the use of highly validated and commonly used survey tools. In regards to interpretation of subject responses, a standardized approach was used, as described in Section 3.7 above.

Insensitive measure bias occurs when the measurement tools used in assessment are not sensitive enough to discriminate between health states of interest.

In our case, we used highly validated and reliable measures which have had testing of their discriminative properties. This would hopefully minimize the risk of insensitive measure bias.

Since patients were aware that we were assessing WD, it is possible that they responded to our surveys such it tended to support higher levels of disability, leading to expectation or attention bias.

Parts of the surveys asked subjects to recall events that had occurred over a period of weeks (i.e., one month in the case of the WLQ). This leads to potential recall bias. Patients may forget the severity of their symptoms at earlier periods. We hope that the relatively small time frame used would minimize recall bias while allowing us to fully assess disease activity, which may fluctuate over time.

5.3.3. Intervention Biases

Our study did not involve any intervention, and thus is not suspect to intervention bias.

5.3.4. Use Of An Available Patient Cohort

The largest weakness in this study of WD in AS is that it is a study of an "available patient group"(52). The study is a cross-sectional survey of all patients seen in a London, Ontario, rheumatology clinic, but only asks patients about their WD at a single point in time. Because of this, it can only describe WD at the time that the respondents filled out their questionnaires, and does not describe WD in AS over the

course of this disease. In order to derive this information, a true cohort would be needed: patients who were entered into a database on the date of their diagnosis and had multiple measurements of WD over time. Additionally, the use of an available patient cohort means that each respondent was assessed at a different time in his or her own individual disease course. Certainly some patients with longstanding disease may be markedly different than those with early disease. We tried to account for this by asking patients to indicate their current age and the age of diagnosis, which were then included as confounders in our statistical analysis. We did use all spondyloarthritis patients seen over 1 year by 6 rheumatologists, which may counterbalance this drawback.

Though the use of an available patient cohort is less than ideal, it is realistically difficult to assemble true cohorts in AS patients. Since AS in generally a slowly progressive disease, a true cohort would require the accumulation of hundreds of patients at the time of diagnosis that were then followed prospectively for years. The assemblage of such a large, prospective, cohort is a future goal for our research group.

5.3.5. Use Of Billing Codes For The Determination Of Ankylosing Spondylitis

The sampling frame for this survey-based study was determined through the use of OHIP billing codes; specifically, all patients who had been coded "720, Ankylosing Spondylitis". However, the use of billing codes, though convenient, is subject to a degree of error. At times, a rheumatologist may suspect AS at the first appointment, but later information may cause the diagnosis to change. In this case,

the first visit may have been coded as AS incorrectly. These individuals would be captured in our sampling strategy and could potentially respond to the survey inappropriately.

To try and minimize the effect of incorrect or inappropriate coding, all subjects were asked to self-report their known arthritic conditions. In some cases, the subject indicated that they did not have AS and likely had received the survey in error. The data from these individuals was not included in our analysis.

It is possible that some patients with SpA were coded under code "721, psoriatic arthritis" if they also had prominent peripheral symptoms in addition to axial symptoms.

5.4. Study Strengths

This is the first study to directly assess losses in work productivity in seronegative SpA, and as such, adds substantial knowledge regarding practical prognostic outcomes for patients. Presenteeism is increasingly important to both employers and employees, and our study shows that work limitations were high in this group. This is also the first study to demonstrate that SpA associated with other systemic disease has higher rates of WD than those with AS alone. We hypothesize that those with other systemic manifestations are likely prone to flares of their non-arthritic condition which contributes to their work disability status. Interestingly, those who are able to work are just as productive as those with AS alone.

The WLQ is a well-established tool for the assessment of losses in work productivity, and its use in other rheumatic diseases allows for a crude comparison to

other conditions. It is one of few WD assessment tools that can actually measure the on-the-job impact of chronic medical conditions, such as inflammatory arthritis (27, 28). The design of the WLQ allows it to address areas of uncertainty found on other employment measurement tools, specifically losses in productivity (27, 28).

5.4.1. Comparison Of Results With Those For WD In Other Rheumatic Diseases

It is difficult to compare WD across rheumatic disease as most studies use dissimilar methodologies, sampling methods and even definitions of WD. One study examined a longitudinal cohort of >5000 subjects with rheumatologist-diagnosed RA (38). In this study, employment was any paid work or unpaid work if in the context of a family-owned business (38). WD was defined as work cessation prior to the age of 65, with confirmation that the cessation was due to arthritis or pain (38). In this study, the prevalence of work cessation due to RA increased with disease duration, from 22.9% (<3 years) to 51.1% (>25 years) (38). The incidence of arthritis-attributed work cessation was between 4.8-6.7%, depending on the year studied (38). WD had varying degrees of permanence, with some patients able to return to work after an absence (38). The results found in this study of RA show comparable rates of disability as our current study in AS.

The WLQ has been used in the assessment of work limitations in patients with RA (31). In this cross-sectional study, WLQ scales were linked to observed productivity so that individual scores could be interpreted as decreased productivity in comparison to healthy controls. The results revealed highly skewed WLQ scores for patients with RA (31). Almost one quarter of respondents indicated that they had no work limitations, and less than 1% indicated high levels of work limitations (scores >

30) (31). Overall, those with RA had a 4.9% decreased work productivity in comparison to controls (31). Interestingly, the decrease in WLQ work productivity due to health was substantially higher in our SpA population, at 8.3%. This is an intriguing finding as RA is classically considered to be a more severe and disabling condition than RA. Of course, due to different methodologies and patient populations, the RA study cannot be directly compared to our current study's results. It may be possible that patients with RA were more likely to be completely disabled and thus only those with mild or moderate disease may have been able to respond to the WLQ.

5.5. Clinical Significance

Half of the studies included in a recent international meta-analysis of WD in AS reported WD in greater than 20% of the studied AS patients (4).A Canadian cohort was recently studied using patients largely from Alberta and Ontario (5). In this mailed survey, 20% of patients reported that they had retired from their jobs due to AS (5) Other alterations in work patterns included a reduction in working time (9.5% of patients) or change in work (8.4% of patients) (5). Surprisingly, sick leave use was only marginally higher than that of the general population (8 days/year vs. 7.5 days/year) (5). In our study, 18.5% were work disabled, which is consistent with previous studies, and very similar to the reported rates in other Canadian populations.

Our findings also indicate that a substantial proportion (8.3%) of working subjects with seronegative spondyloarthritis suffer from losses in work productivity due to health. The cause of this decreased productivity is multifactorial, and includes

issues with time management, physical function, mental-interpersonal skills and reduced output.

Treating seronegative disease aggressively can be daunting due to the high costs of medications, such as anti-TNF drugs. However, our finding show that WD in this population is not small, and WD has a high impact on costs. Resource utilization and costs of AS have been recently studied in a Canadian cohort (5). Mean annual costs of AS, per patient, were estimated at $9 008 (Canadian dollars), with indirect costs representing 38% (5). Half of the direct costs were attributed to patients' out of pocket expenses, such as over the counter medication and informal care (5). Notably, the study found that the costs of AS were not normally distributed. A small number of patients with high levels of functional impairment disease increased costs substantially (5). Functional impairment was a stronger driver of costs than disease activity (5). The difference in cost from the lowest level of functional impairment to the highest was $ 25 000 (5). Increasing age was also associated with increasing costs, but sex was not (5). We found that the most severely affected patients were the most likely to be work disabled, which is as expected.

Chapter 6: Conclusions

In our study, 18.5% were work disabled, which is consistent with previous studies, and very similar to the reported rates in other Canadian populations. Our findings also indicate that a substantial proportion (8.3%) of working subjects with seronegative SpA suffer from losses in work productivity due to health. The cause of this decreased productivity is multifactorial, and includes issues with time management, physical function, mental-interpersonal skills and reduced output.

Other findings include:

- Presence of WD was associated with: age, number of comorbid conditions, higher HAQ scores, worse patient global assessment of disease, higher BASFI scores and higher BAS-G scores. In those who were working, presence of WD was also associated with a decrease in time management skills, reduced mental-interpersonal skills, and reduced output.
- Loss of work productivity (%) was associated with higher HAQ scores, worse pain, fatigue and global health VAS scores, higher scores on BASDAI, BASFI and BAS-G, as well as number of comorbid disorders.
- Patients with SpA associated with other systemic disease, such as Ps, IBD and ReA, had higher levels of WD but did not differ from those with AS in terms of work productivity.

This is the first study to directly assess losses in work productivity in seronegative SpA. The WLQ is a well-established tool for the assessment of losses in work productivity, and its use in other rheumatic diseases allows for a crude comparison to other conditions. Presenteeism is increasingly important to both employers and employees, and our study shows that work limitations were high in this group. This is also the first study to demonstrate that SpA associated with other systemic disease has higher rates of WD than those with AS alone. We hypothesize that those with other systemic manifestations are likely prone to flares of their non-arthritic condition which contributes to their work disability status. Interestingly, those who are able to work are just as productive as those with AS alone.

Aggressive treatment of SpA can be achieved by using expensive biologic medication, but due to their cost, use of such drugs are often limited by the government. Our findings show that WD in this population is not small, and WD has a high impact on costs both to patients and society. We have also shown that presenteeism also contributes to the "hidden" economic costs of SpA. These results may be used to advocate on behalf of our patients for improved access to care.

Future work will concentrate on verifying these results in a larger population, as well an assessment of the effect of drugs on WD.

We conclude that in our SpA population, WD occurred in 18.5%. Subjects with systemic disease associated with SpA (Ps, IBD, ReA) had higher rates of WD than those with AS alone. Of those who were working, 8.3% suffered losses in work productivity due to their arthritis. These findings suggest that SpA has a high burden of disease in our population.

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APPENDICES

APPENDICES

APPENDIX A: THE HEALTH ASSESSMENT QUESTIONNAIRE

St JOSEPH's HEALTH CARE LONDON

Affix Label Here

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)

Please try to answer each question, even if you do not think it is related to you at this time. There are no right or wrong answers. Please answer exactly as you think or feel. Thank-you.

Please check (✓) the ONE best answer for your abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE to DO
DRESSING & GROOMING				
Dress yourself, including tying shoelaces and buttons? ..	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Stand up from an armless chair?	☐	☐	☐	☐
Get in and out of bed?.....	☐	☐	☐	☐
EATING				
Cut your meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐
HYGIENE				
Wash and dry your entire body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Reach and get a 5-lb object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
Bend down and pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Open car doors?	☐	☐	☐	☐
Open jars which have been previously opened?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming, yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

Dressing: ☐ Devices used for dressing (button hook, zipper puller, etc)
Eating: ☐ Built-up or special utensils
Walking: ☐ Cane ☐ Walker ☐ Crutches ☐ Wheel Chair ☐ Special chair
Hygiene: ☐ Raised toilet seat ☐ Bathtub seat ☐ Bathtub bar
Reach: ☐ Long-handled appliances for reach ☐ Long-handled appliances in bathroom
Grip: ☐ Jar opener
Other: _____

Please check any categories for which you need HELP FROM ANOTHER PERSON

☐ Dressing and Grooming ☐ Arising ☐ Eating ☐ Walking
☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

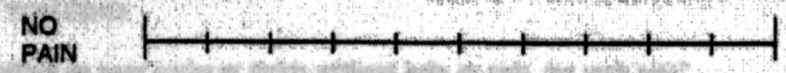
1=0.125	2=0.25	3=0.375	4=0.5	5=0.625	6=0.75	7=0.875	8=1.0
9=1.125	10=1.25	11=1.375	12=1.5	13=1.625	14=1.75	15=1.875	16=2.0
17=2.125	18=2.25	19=2.375	20=2.5	21=2.625	22=2.75	23=2.875	24=3.0

PLEASE TURN OVER

74863

VISUAL ANALOGUE SCALES

1. **How much PAIN have you had because of your illness in the PAST WEEK? Please indicate on the scale below how severe your pain has been:**



3. **How much of a problem has UNUSUAL FATIGUE or tiredness been for you OVER THE PAST WEEK? Place a mark on the line below**

4. **How much of a problem has SLEEPING been for you OVER THE PAST WEEK? Place a mark on the line below**

5. **Considering all the ways in which illness and health conditions may affect you at this time, please make a mark on the line below to show how you are doing:**

6. **When you get up in the MORNING do you feel STIFF?** ❑ YES ❑ NO
   If you answer NO please go to item number 7.
   If you answer YES, please write the number of minutes: _____, OR number of hours:_____
   until you are as limber as you will be for the day?

7. **How would you describe your OVERALL STATUS since your last visit? Please check only one:**

❑ MUCH BETTER(1) ❑ BETTER(2) ❑THE SAME(3) ❑WORSE(4) ❑MUCH WORSE(5)

APPENDIX B: THE BATH ANKLOSING SPONDYLITIS FUNCTIONAL INDEX (BASFI)

The Bath Ankylosing Spondylitis Functional Index (BASFI)

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the *next month*

HOW DO YOU FIND: **score out of 10**

1 **Putting on your socks or tights without help or aids (eg sock aid)?**

EASY ——————————————— **IMPOSSIBLE**

2 **Bending forward from the waist to pick up a pen from the floor without an aid?**

EASY ——————————————— **IMPOSSIBLE**

3 **Reaching up to a high shelf without help or aids (eg Helping Hand)?**

EASY ——————————————— **IMPOSSIBLE**

4 **Getting out of an arm-less dining chair without using your hands or any help?**

EASY ——————————————— **IMPOSSIBLE**

5 **Getting up off the floor - without help - from lying on your back?**

EASY ——————————————— **IMPOSSIBLE**

6 **Standing unsupported for ten minutes without discomfort?**

EASY ——————————————— **IMPOSSIBLE**

7 **Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)?**

EASY ——————————————— **IMPOSSIBLE**

8 **Looking over your shoulder without turning your body?**

EASY ——————————————— **IMPOSSIBLE**

9 **Doing physically demanding activities (eg physio exercises, gardening, sport)?**

EASY ——————————————— **IMPOSSIBLE**

10 **Doing a full day's activities at home or at work?**

EASY ——————————————— **IMPOSSIBLE**

TOTAL OUT OF 100	
TOTAL / 10 (BASFI SCORE)	

APPENDIX C: THE BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX (BASDAI)

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the past week

SCORE/10

1 **How would you describe the overall level of fatigue/tiredness you have experienced?**

NONE ——————————————— VERY SEVERE

2 **How would you describe the overall level of AS neck, back or hip pain you have had?**

NONE ——————————————— VERY SEVERE

3 **How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?**

NONE ——————————————— VERY SEVERE

4 **How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?**

NONE ——————————————— VERY SEVERE

5 **How would you describe the overall level of discomfort you have had from the time you wake up?**

NONE ——————————————— VERY SEVERE

6 **How long does your morning stiffness last from the time you wake up?**

0 ½ 1 1½ 2 or more hours

MEAN OF 5 & 6	
TOTAL OF 1 TO 4 ADDED TO MEAN OF 5 & 6 (TOTAL OUT OF 30)	
TOTAL / 5 (BASDAI SCORE)	

APPENDIX D: THE BATH ANKYLOSING SPONDYLITIS PATIENT GLOBAL SCORE (BAS-G)

The Bath Ankylosing Spondylitis Global Score (BAS-G)

TOTAL / 10

How have you been over the last week?

VERY GOOD _____ VERY BAD

How have you been over the last six months?

VERY GOOD _____ VERY BAD

TOTAL OUT OF 20

TOTAL / 2 (BAS-G SCORE)

APPENDIX E: THE FUNCTIONAL COMORBIDITY INDEX (FCI)

Functional Comorbidity Index

Have you ever been diagnosed with any of the following medical conditions? Please select one.

1. Arthritis	Yes ☐	No ☐
2. Osteoporosis.....	Yes ☐	No ☐
3. Asthma.....	Yes ☐	No ☐
4. Chronic obstructive pulmonary disease (COPD), acquired respiratory distress syndrome (ARDS), or emphysema.....	Yes ☐	No ☐
5. Angina	Yes ☐	No ☐
6. Congestive heart failure (or heart disease).....	Yes ☐	No ☐
7. Heart attack (myocardial infarct)	Yes ☐	No ☐
8. Neurological disease (such as multiple sclerosis or Parkinson's).....	Yes ☐	No ☐
9. Stroke or TIA	Yes ☐	No ☐
10. Peripheral vascular disease	Yes ☐	No ☐
11. Diabetes types I and II	Yes ☐	No ☐
12. Upper gastrointestinal disease (ulcer, hernia, reflux).....	Yes ☐	No ☐
13. Depression.....	Yes ☐	No ☐
14. Anxiety or panic disorders.....	Yes ☐	No ☐
15. Visual impairment (such as cataracts, glaucoma, macular degeneration).....	Yes ☐	No ☐
16. Hearing impairment (very hard of hearing, even with hearing aids).....	Yes ☐	No ☐
17. Degenerative disc disease (back disease, spinal stenosis or severe chronic back pain).....	Yes ☐	No ☐

18. What is your height? _____ cm or inches (circle unit of measurement)

What is your weight? _____ kg or pounds (circle unit of measurement)

APPENDIX F: THE WORK LIMITATIONS QUESTIONNAIRE (WLQ)

Work Limitations Questionnaire
(Canadian English version of the WLQ)

Work Limitations Questionnaire©

Instructions

Health problems can make it difficult for working people to perform certain parts of their jobs. We are interested in learning about how your health may have affected you at work during the past 2 weeks.

(1) The questions will ask you to think about your physical health or emotional problems. These refer to any ongoing or permanent medical conditions you may have and the effects of any treatments you are receiving for these conditions. Emotional problems may include feeling depressed or anxious.

(2) The questions are multiple-choice. Indicate your answer by putting a checkmark in the appropriate box.

For example:

How satisfied are you with each of the following:

(Checkmark one box on each line for a. and b.)

	Not at All Satisfied	Moderately Satisfied	Very Satisfied
a. Your local schools.	☐1	☐2	☑3
b. Your local police department. . .	☐1	☑2	☐3

These checkmarks tell us you are very satisfied with your local schools and moderately satisfied with your local police department.

OPTIONAL PAGE

(3) Before you begin answering any questions, we would like you to write some information on the calendar.

- Find today's date. Checkmark that box.
- Count back 2 weeks and checkmark that box too.

The questions relate to this 2-week period. Feel free to checkmark other important dates such as birthdays, family events, or work deadlines. Please use the calendar to help you answer correctly.

Insert calendar here.

These questions ask you to assess the amount of time you had difficulty handling certain parts of your job. Please read every question. Then choose a response.

- Checkmark the "Does not apply to my job" box only if the question describes something that is <u>not</u> part of your job.
- If you have more than one job, report on your <u>main</u> job only.

1. In the <u>past 2 weeks</u>, how much of the time did your physical health or emotional problems make it difficult for you to do the following:

(Checkmark one box on each line for a. through e.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a little bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
work the required number of hours	☐1	☐2	☐3	☐4	☐5	☐6
get going easily at the beginning of the workday	☐1	☐2	☐3	☐4	☐5	☐6
begin your job activities as soon as you arrive at work	☐1	☐2	☐3	☐4	☐5	☐6
do your work without stopping more than usual to take breaks or rests	☐1	☐2	☐3	☐4	☐5	☐6
stick to a routine or schedule	☐1	☐2	☐3	☐4	☐5	☐6

PLEASE READ CAREFULLY

These questions ask you to assess the amount of time you were <u>able</u> to handle certain parts of your job without difficulty.

2. a. In the <u>past 2 weeks</u>, how much of the time were you **able** to walk or move around different work locations (for example: go to meetings), without difficulty caused by physical health or emotional problems?

(Checkmark one box.)

- All of the time (100%) ☐1
- Most of the time ☐2
- Some of the time (about 50%) ☐3
- A little bit of the time ☐4
- None of the time (0%) ☐5
- Does not apply to my job ☐6

b. In the <u>past 2 weeks</u>, how much of the time were you **able** to lift, carry, or move objects at work weighing <u>more than 10 lbs./5 kilos</u>, without difficulty caused by physical health or emotional problems?

(Checkmark one box.)

- All of the time (100%) ☐1
- Most of the time ☐2
- Some of the time (about 50%) ☐3
- A little bit of the time ☐4
- None of the time (0%) ☐5
- Does not apply to my job ☐6

c. In the past 2 weeks, how much of the time were you **able** to sit, stand, or stay in one position for longer than 15 minutes while working, without difficulty caused by physical health or emotional problems?

(Checkmark one box.)

All of the time (100%)	☐ 1
Most of the time	☐ 2
Some of the time (about 50%)	☐ 3
A little bit of the time	☐ 4
None of the time (0%)	☐ 5
Does not apply to my job	☐ 6

d. In the past 2 weeks, how much of the time were you **able** to repeat the same motions over and over while working, without difficulty caused by physical health or emotional problems?

(Checkmark one box.)

All of the time (100%)	☐ 1
Most of the time	☐ 2
Some of the time (about 50%)	☐ 3
A little bit of the time	☐ 4
None of the time (0%)	☐ 5
Does not apply to my job	☐ 6

e. In the <u>past 2 weeks</u>, how much of the time were you **able** to bend, twist, or reach while working, without difficulty caused by physical health or emotional problems?

(Checkmark one box.)

All of the time (100%)	☐1
Most of the time	☐2
Some of the time (about 50%)	☐3
A little bit of the time	☐4
None of the time (0%)	☐5
Does not apply to my job	☐6

f. In the <u>past 2 weeks</u>, how much of the time were you **able** to use hand-held tools or equipment (for example: a phone, pen, keyboard, computer mouse, drill, cutting scissors, or sander), without difficulty caused by physical health or emotional problems?

(Checkmark one box.)

All of the time (100%)	☐1
Most of the time	☐2
Some of the time (about 50%)	☐3
A little bit of the time	☐4
None of the time (0%)	☐5
Does not apply to my job	☐6

PLEASE READ CAREFULLY

These questions ask about difficulties you may have had at work.

3. In the <u>past 2 weeks</u>, how much of the time did your physical health or emotional problems make it difficult for you to do the following:

(Checkmark one box on each line for a. through f.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult a** little bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. pay attention to your work	☐1	☐2	☐3	☐4	☐5	☐6
b. think clearly when working	☐1	☐2	☐3	☐4	☐5	☐6
c. do your work carefully	☐1	☐2	☐3	☐4	☐5	☐6
d. concentrate on your work	☐1	☐2	☐3	☐4	☐5	☐6
e. work without losing your train of thought	☐1	☐2	☐3	☐4	☐5	☐6
f. easily read or use your eyes when working	☐1	☐2	☐3	☐4	☐5	☐6

The next questions ask about difficulties in relation to the people you came into contact with while working. These may include employers, supervisors, coworkers, clients, customers, or the public.

4. In the <u>past 2 weeks</u>, how much of the time did your physical health or emotional problems make it difficult for you to do the following:

(Checkmark one box on each line for a. through c.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a little bit of the time	**Difficult** none of the time (0%)	**Does not apply to my job**
a. speak with people in-person, in meetings or on the phone	☐1	☐2	☐3	☐4	☐5	☐6
b. control your temper around people when working	☐1	☐2	☐3	☐4	☐5	☐6
c. help other people to get work done	☐1	☐2	☐3	☐4	☐5	☐6

These questions ask about how things went at work overall.

5. In the <u>past 2 weeks</u>, how much of the time did your physical health or emotional problems make it difficult for you to do the following:

(Checkmark one box on each line for a. through e.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a little bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. handle the workload	☐1	☐2	☐3	☐4	☐5	☐6
b. work at the expected speed	☐1	☐2	☐3	☐4	☐5	☐6
c. finish your work by the expected deadline	☐1	☐2	☐3	☐4	☐5	☐6
d. do your work without making mistakes	☐1	☐2	☐3	☐4	☐5	☐6
e. feel you've done what you are capable of doing	☐1	☐2	☐3	☐4	☐5	☐6

APPENDIXG: RESEARCH ETHICS BOARD APPROVAL AND LETTER OF INFORMATION

LAWSON HEALTH RESEARCH INSTITUTE

CLINICAL RESEARCH IMPACT COMMITTEE

RESEARCH OFFICE REVIEW NO.: R-07-498

PROJECT TITLE: Assessment of Work Disability in Ankylosing Spondylitis

PRINCIPAL INVESTIGATOR: Dr. S Rohekar

DATE OF REVIEW BY CRIC: March 3, 2008

Health Sciences REB#: 13860E

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, Room C210, Nurses Residence, South Street Campus.

Dr. Sherry Rohekar, BSc, MD, FRCPC
Rheumatology, St. Joseph's Hospital
Monsignor Roney Building
268 Grosvenor St., London ON N6A 4V2
519-646-6242 Fax 519-646-6348

Study:
Assessment Of Work Disability In Ankylosing Spondylitis

Patient Letter Of Information And Consent Form

You are being invited to voluntarily participate in this study because you have been diagnosed with ankylosing spondylitis (AS), a form of arthritis.

Before you decide to participate in this study, please take as much time as you need to read the following information carefully. Ask if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

Arthritis can affect activities of daily living, including the ability to work or to work efficiently. To date, there have not been any studies that have evaluated work disability in those with AS. However, we feel that measuring how work is affected by arthritis is a very important outcome.

We would like you to answer a series of questionnaires that will help us evaluate how AS affects your ability to work. Some of the questionnaires will also look at how active your AS is and other medical conditions that may also be impacting your ability to work.

Do I have to take part in this study?

It is completely up to you to decide whether or not to take part in this study. If you decide to take part, we would appreciate it if you complete the attached questionnaires and return them to us using the preaddressed envelope we have included. By returning the questionnaires, you will give us your consent to participate. You are free to leave the study at any time and you do not need to give a reason. This will not affect the type of care you will receive from your doctor. Participation in this study is voluntary.

What will happen if I take part in this study?

If you decide to take part in this study, please complete the attached questionnaires. Use the included preaddressed, stamped envelope to return them. The questionnaires should take about 20 minutes to complete.

You are eligible to participate in this study if:

- You have read this information sheet and have had a chance to ask questions.
- You are 18 years of age or older.
- Taking part in the study is completely your own decision and you know that you are free to stop taking part at any time. You know that you do not have to give a reason if you do not want to take part. You know that your medical care or legal rights will not be affected if you do not take part.
- You agree to complete and return the attached questionnaires.
- You can participate regardless of your current employment status.

What are the possible benefits of taking part in this study?

Although there is no immediate direct benefit to you by participating in the study, the information collected and knowledge gained will allow us to understand how AS affects lives in general. This may be used in future research designed to benefit patients with AS.

What are the possible risks of taking part in this study?

There are no serious risks involved in taking part in this study. You will only be asked to answer questions about your AS.

Will my taking part in this study be kept confidential?

All information obtained about you during this study will be treated confidentially. This information will be coded such that you will be given a study code number. Your name and personal identifiers will be kept separate from your study file, which will be identified only with your study code number. Only Dr. Sherry Rohekar, the Principal Investigator, and her research staff can perform decoding. Access to your identifying information will be restricted and supervised by Dr. Sherry Rohekar. No information that discloses your identity will be allowed to leave this institution.

Data in your study file will be entered in a computer without personal identifiers. Access to this computer is restricted to Dr. Rohekar and her research staff. All records will be kept in a locked, secured area and only Dr. Rohekar and her research staff will have access to these records. No information revealing any personal information such as your name, address or telephone number will be used in this study.

You will not be identified as an individual on any reports or publications that may result from this study.

Representatives of the University of Western Ontario Health Sciences Research Ethics Board may require access to your study-related records or may follow up with you to monitor the conduct of the study.

The results of this study may be published or communicated in other ways, but you will not be identified as a study participant in any reports or publications.

If you agree, we may contact you for future studies.

In the event that you withdraw or are withdrawn from the study, all information collected up to that point for the purpose of this study may be used in order to preserve the scientific integrity of the study. The data will be used to report the number of people who withdrew, and their reasons why.

Will there be compensation for participating in this study?

You will not be paid to take part in the study. However, the researchers will cover all postage costs.

Voluntary Participation/Withdrawal:

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions, or withdraw from the study at any time with no effect on your future care. You indicate your voluntary agreement to participate by completing and returning this questionnaire.

Contact for further information:
If you should have questions or concerns about this study, please contact:

Dr. Sherry Rohekar at (519) 646-6242.

If you have any questions abut your rights as a research participant or the conduct of the study, you may contact:

Dr. David Hill at (519) 667-6649 (Scientific Director, Lawson Health Research Institute), the neutral person for research at St. Joseph's Health Care London.

You may keep this letter of information for your records.

Thank you for your time and consideration.

Sincerely,

Dr. Sherry Rohekar, BSc, MD, FRCPC
Principal Investigator

Please return this portion with the questionnaires:

Please check the appropriate boxes for each question:

I agree to participate in this study.	Yes	No
I agree to be contacted for future studies.	**Yes ☐**	**No ☐**

Please complete the following:

Name: _____

Date: _____

APPENDIX H: ORIGINAL STUDY QUESTIONNAIRE

Assessment Of Work Disability In Ankylosing Spondylitis

Please answer the following to the best of your ability. Thank you for taking the time to answer our questions.

1. Are you currently working? Please select the statements from the list below that best describe your employment status. You may choose more than one.

- ☐ I currently work outside the home full time, and receive pay.
- ☐ I currently work outside the home part time, and receive pay.
- ☐ I currently work from my home full time, and receive pay.
- ☐ I currently work from my home part time, and receive pay.
- ☐ I currently work outside the home, but do not receive pay (for example, volunteer work).
- ☐ I currently work at home, but do not receive pay (for example, homemaker).
- ☐ I am currently a full time student.
- ☐ I am currently a part time student.
- ☐ I am not currently working.

2. How many hours per week do you work, on average?

_____ hours per week.

3. Have you reduced the number of hours you work per week due to your arthritis? Please select one.

- ☐ No.
- ☐ Yes. → Please specify details: _____
  _____
  _____
  _____

4. In the past 30 days, how many days have you taken the whole day off because of your arthritis?

_____ days.

5. In the past 30 days, how many days have you had to reduce the number of hours that you work because of your arthritis, but did not take the whole day off?

_____ days.

6. Have you ever had conflict at work due to absences or decreased hours caused by your arthritis? Please select one.

☐ No.

☐ Yes. → Please specify details: _____
_____
_____
_____

7. What type of arthritis has your rheumatologist diagnosed you with? Please select one.

☐ Ankylosing spondylitis (AS).

☐ Ankylosing spondylitis associated with inflammatory bowel disease such as Crohn's disease or ulcerative colitis.

☐ Ankylosing spondylitis associated with skin disease such as psoriasis.

☐ Ankylosing spondylitis that developed after an infection (reactive arthritis or Reiter's syndrome).

☐ Other. → Please specify: _____

8. How old are you?

_____ years old.

9. How old were you when you were diagnosed with arthritis by a doctor?

_____ years old.

10. What is the highest level of education that you have completed? Please select one.

- ☐ Any grade that is less than or equal to Grade 8.
- ☐ Any grade from Grade 9 to 12.
- ☐ A college or university degree.
- ☐ A trade school.
- ☐ Graduate school (Master's degree or PhD).
- ☐ Professional degree (for example: law, medicine, dentistry).
- ☐ I would prefer not to answer this question.

11. On average, how much income do you make per year, before taxes? Please select one.

- ☐ $0 to $20 000 per year.
- ☐ $21 000 to $40 000 per year.
- ☐ $41 000 to $ 60 0000 per year.
- ☐ $61 000 to $80 000 per year.
- ☐ $81 000 or greater per year.
- ☐ I would prefer not to answer this question.

Thank you very much for answering our questionnaire. We appreciate your time.

APPENDIX I: DATA EXTRACTION FORM USED FOR CHART REVIEW

Work Disability In Ankylosing Spondylitis (AS)

Data Extraction Form

Patient Name: _____

J Number: _____

Age: _____ years

Gender: ☐ Male
☐ Female

Marital Status: ☐ Single
☐ Married
☐ Common-law
☐ Widowed
☐ Divorced
☐ Separated
☐ Other: _____

Occupation: _____

On disability? ☐ Yes
No

Date Of First Visit To Clinic: _____

APPENDIX J: ORIGINAL PAPER SUBMITTED FOR PUBLICATION

Abstract:

Objective: Ankylosing spondylitis (AS) affects patients during their working years and may contribute to work disability (WD). We determined the prevalence of WD (not working due to illness) and limitations in work productivity in AS using surveys, including the Work Limitations Questionnaire (WLQ).

Methods: 203 patients with AS received a mailed questionnaire asking about work status, the WLQ, HAQ, BASDAI, BASFI, BAS-G and Functional Comorbidity Index. Relationships between WD, WLQ, demograghics and disease activity were assessed through bivariate correlations and independent t-tests.

Results: Response rate was 40%; 18.5% were WD in our assessment. Those with WD were significantly older than non-WD, and had significantly higher scores on BASFI, BAS-G and patient global assessment of health. WD also had significantly more comorbid diseases than non-WD. WD was not associated with longer duration of disease, higher HAQ scores or higher BASDAI scores. Using the WLQ, the average decrease in work productivity attributable to health was 8.3%. Decreases in time management (37.3%), physical demands (28.5%), mental-interpersonal demands (23.0%) and output (33.1%) were noted. Reduced productivity was not associated with demographic factors. Productivity loss for those still working was highly correlated ($r>0.6$) with the HAQ, BASFI, BASDAI, and BAS-G. Subjects with primary AS had less WD than those with secondary AS (related to psoriasis, inflammatory bowel disease or reactive arthritis). WD was associated with older age and greater AS disease activity. Losses in

work productivity were highly correlated with currently used clinical outcome measures such as HAQ, BASFI, BASDAI and BAS-G.

Conclusions: WD occurred in 18.5%, and work productivity was also reduced by 8.3%. WD was associated with older age and greater SpA disease activity. Losses in work productivity were highly correlated with currently used clinical outcome measures such as HAQ, BASFI, BASDAI and BAS-G.

Introduction

Ankylosing spondylitis (AS) is a complex, chronic inflammatory disorder causing disease of the sacroiliac (SI) joints and spine, as well as peripheral joints and extra-articular sites (1). AS is a disease that often affects young adults, classically occurring in the second or third decade of life, with a mean age of onset of 26 years (1). There are several forms of AS, including primary disease (AS alone) and secondary AS associated with other systemic disease, such as psoriasis (Ps), inflammatory bowel disease (IBD) and post-infectious reactive arthritis (ReA) (1). Since AS affects patients during their working years, work disability (WD) is an important disease outcome.

A meta-analysis of European and American studies has shown variable rates of WD in AS, ranging from 3-50% (4). This WD contributes significantly to the cost of care for AS in Canada, about 38% of total annual cost of AS(5). Areas of impact include reduced income, early retirement, and increased sick leave (5). A Canadian cohort was recently studied using patients largely from Alberta and Ontario (5). In this mail-based survey, 20% of patients reported that they had retired from their jobs due to AS (5) Other alterations in work patterns included a reduction in working time (9.5% of patients) or change in work (8.4% of patients) (5). Annual sick leave use was only marginally higher than that of the general population (8 days/year vs. 7.5 days/year) (5). Work limitations, particularly in those still employed, have not been extensively studied.

WD has been defined as the state in which the affected individual has had to leave their job, or forced to work fewer hours (partial WD) (24). More is known about WD rheumatoid arthritis (RA) than in AS (24).

Variable methodologies have been used in WD studies. The easiest employment outcome to measure is days or hours missed from work, but not all WD leads to absenteeism. Recently, the concept of *presenteeism*, or decreased work performance due to health conditions, has emerged in the WD literature (26). Presenteeism includes decreased productivity due to time not spent on task, decreased quality of work, decreased quantity of work and personal factors (26). Several self-reported workplace productivity instruments have been developed, and measure elements of presenteeism (26). One such tool is the Work Limitations Questionnaire (WLQ) (30).

Our study aimed to determine the prevalence of WD in patients with a history of AS. Secondary objectives included assessment of risk factors for WD such as age, gender, education, physically demanding work, comorbid diseases and high disease activity as assessed by commonly used clinical tools. These clinical tools included the Health Assessment Questionnaire (HAQ), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Patient Global Score (BAS-G) and the Functional Comorbidity Index (FCI). We also compared the results of the WLQ to these same demographic risk factors and clinical outcome tools.

The WLQ is a 25-item, self-administered questionnaire that assesses work limitation on 4 scales: time demands, physical demands, mental-interpersonal demands and output demands (27). It measures on-the-job work limitations as well as loss of productivity at work (presenteeism). WLQ scores may be converted into estimates of productivity loss. The WLQ has been highly validated and has been shown to have good reliability. The HAQ is a self-reported measure of disability, which has become one of the dominant functional instruments in the field of arthritis (12). We used the HAQ-DI scored from 0-3 (no functional limitations –

limited in most activities). The BASDAI is the current gold standard for measuring disease activity in AS (15). The BASFI is composed of 10 questions, which assess functional limitation in AS patients (14). It assesses limitations due to functional anatomy and patients' ability to cope in everyday life (14). The BAS-G is a single-item, patient administered global assessment score that reports patients' well-being over a certain period of time (18). The Functional Comorbidity Index (FCI) is an 18-item yes/no questionnaire designed specifically to determine how patients' comorbidities affect their physical functioning (19).

We hypothesized that: a large percentage of patients with AS would be work disabled; risk factors for WD would include disease duration, disease activity and level of education; WD, as assessed by the WLQ, would correlate highly with currently used measures of disease activity, severity and function (HAQ, BASDAI, BASFI and BAS-G). Additionally, we hypothesized that even those who were employed would have decreased work productivity.

Methods

This study was conducted using a convenience sample of all patients who had been diagnosed with AS by a rheumatologist and had attended a rheumatology clinic. The use of a convenience sample was justified as there is little prior research on the prevalence of WD in an AS population, making it difficult to perform a formal sample size calculation.

We modeled various response rates to determine potential margin of error (49). We assumed a population size of 200, confidence level of 95% and response distribution of 50%. Using this technique, a 60% response rate would give a margin of error of 5.67%, a 50% response rate a

margin of error of 6.95% and 40% response rate a margin of error of 8.42%. To obtain a margin of error of 5%, a sample size of 132 respondents (66% response rate) would be needed.

The study population consisted of 203 patients with AS, confirmed by a rheumatologist, who attended a rheumatology clinic at St. Joseph's Health Center in London, Ontario. The sampling frame was obtained by searching OHIP billing codes for a diagnosis of 720 (AS) in all patients seen in the clinic in from March 2007-March 2008. Subjects were excluded if they were under the age of 18. Participants received a study package by mail, containing a letter explaining the study, the WLQ, HAQ, BASDAI, BASFI, BAS-G, FCI, and a 10-cm fatigue visual analogue scale (VAS). To improve response rates, subjects were telephoned to remind them to complete their surveys. New survey sets were sent to those who requested them.

Analysis was performed using SPSS (50). Relationships between WLQ and demographic information, other measures of disease activity, and presence of multiple comorbidities were assessed through $\chi 2$ and bivariate correlation. Two-tailed tests were used with a level of significance of $p<0.05$. Linear regression was used to determine the impact of various independents on the dependent loss in health related work productivity (%). Logistic regression was used to predict dependent variables on the basis of continuous and categorical independents, thus allowing the determination of the percent of variance in the dependent that could be explained by the independents. Binomial logistic regression was used for dichotomous dependents (such as work disabled, yes/no). The enter method was used. Probability for stepwise entry was 0.05, and for removal was 0.10, with 20 maximum iterations.

Results

81 completed questionnaire packages were returned (response rate 40%), reporting a physician diagnosis of AS most frequently (64.2%), followed by spondylitis associated with IBD (21.0%). A smaller number of subjects reported spondylitis associated with psoriatic skin disease or reactive arthritis occurring after a prodromal genitourinary or gastrointestinal infection. There were notable differences between respondents and non-respondents, summarized in Figure 1. Non-responders tended to be younger male subjects (Figure 1).

Demographics of the respondents are shown in Table 1. Almost half were employed outside of the home in a full-time, paid position (49.4%), 18.5% were not working, part-time paid work outside of the home was reported in 12.3%, and 7.4% participated in unpaid work at home. 39.5% of respondents had decreased the number of hours they worked per week due to their arthritis. Subjects also reported having to work reduced hours at work (Table 2). On average, they worked shorter hours 3.7 days of each work week; the exact number of hours of reduced work was not collected. Additionally, respondents who were employed reported missing an average of 2.5 complete days of work/month due to arthritis. 14.8% described conflict at work due to lack of productivity or absences. Bath Indices indicated moderate disease (mean scores: BASFI 4.6, BASDAI 5.2, BAS-G 5.0). The mean HAQ score of the respondents was 0.90.

Those with WD were significantly older than non-WD (52.9 vs 43.1 years, $p<0.05$). Patients with AS not associated with other disease (Ps, IBD or ReA) tended to have less WD than those with other systemic manifestations ($p<0.001$). WD individuals also had higher scores on BASFI (6.8 vs 4.1), BAS-G (6.5 vs 4.6). Spondylitis with WD also had significantly more comorbidity than non-WD (4.0 vs 2.3 comorbid conditions). Though not significant, those with

WD had a trend toward higher HAQ scores. WD was not associated with longer duration of disease or higher BASDAI scores. Table 1 summarizes these associations.

Results of the WLQ in working respondents indicated an overall decrease in work productivity due to health of 8.3%. Of these respondents with decreased work productivity, significant decreases in time management (37.3%), output (33.1%), physical demands (28.5%) and mental-interpersonal demands (23.0%) were noted (Figure 2). Reduced WLQ productivity was highly correlated with traditional measures of disease activity and function, such as HAQ, BASFI, BASDAI and BAS-G (Pearson's $r>0.65$ in each case). Using non-parametric tests (Spearman's rho) did not change the results. Table 3 summarizes these results.

Although AS with other systemic disease had more WD, in those working, there was no significant association between type of AS (dichotomized into AS vs. spondylitis from other disease) and WLQ productivity loss ($p=0.175$). Gender was also not associated with productivity loss ($p=0.989$), nor was level of education ($p=0.299$). Age and years of disease activity did not correlate with loss of productivity. Not surprisingly, income level was associated with WD ($p=0.01$), with lower incomes reporting greater work productivity losses.

Univariate binary (binomial) linear regression was carried out for the dichotomous dependent variable work disabled (yes/no). Of the demographic factors, age and number of comorbid medical conditions were significantly associated with work disability (OR 1.10 [95% CI: 1.03, 1.18] and 1.35 [95% CI: 1.05, 1.73], respectively). Higher scores on WLQ time management, mental-interpersonal skills, and output were all significantly associated with WD (Table 4). Additionally, higher scores on HAQ, VAS patient global assessment, BASFI and BAS-G scores were significantly associated with WD (Table 4). Multinomial logistic regression did not add any extra information to the results yielded by the univariate regressions.

Table 5 summarizes the results of univariate linear regression for the dependent outcome of % loss in health related work productivity as measured by the WLQ. Interestingly, age, years of disease activity and duration of morning stiffness did not correlate with loss in work productivity. Other outcome measures, such as HAQ score, VAS scores for pain, fatigue, sleep and global health, BASFI, BASDAI and BAS-G were highly correlated with losses in work productivity. There was also a significant correlation between loss in work productivity and an increasing number of comorbid medical conditions.

Discussion

In our study, 18.5% were work disabled, which is consistent with previous studies, and very similar to the reported rates in other Canadian populations. Our findings also indicate that a substantial proportion (8.3%) of working subjects with AS suffer from losses in work productivity due to health. The cause of this decreased productivity is multifactorial, and includes issues with time management, physical function, mental-interpersonal skills and reduced output.

The WLQ has been used in the assessment of work limitations in patients with RA(31). In this cross-sectional study, WLQ scales were linked to observed productivity so that individual scores could be interpreted as decreased productivity in comparison to healthy controls. The results revealed highly skewed WLQ scores for patients with RA (31). Almost one quarter of respondents indicated that they had no work limitations, and less than 1% indicated high levels of work limitations (scores > 30) (31). Overall, those with RA had a 4.9% decreased work productivity in comparison to controls (31).

Treating AS aggressively can be daunting due to the high costs of medications, such as anti-TNF drugs. However, our finding show that WD in this population is not small, and WD has a high impact on costs. Resource utilization and costs of AS have been recently studied in a Canadian cohort (5). Mean annual costs of AS, per patient, were estimated at $9 008 (Canadian dollars), with indirect costs representing 38% (5). Half of the direct costs were attributed to patients' out of pocket expenses, such as over the counter medication and informal care (5). Notably, the study found that the costs of AS were not normally distributed. A small number of patients with high levels of functional impairment disease increased costs substantially (5). Functional impairment was a stronger driver of costs than disease activity (5). The difference in cost from the lowest level of functional impairment to the highest was $ 25 000 (5). Increasing age was also associated with increasing costs, but sex was not (5). We found that the most severely affected patients were the most likely to be work disabled, which is as expected.

This is the first study to directly assess losses in work productivity in AS. Other studies have examined outcomes in adults with juvenile AS, but none have looked directly at work disability and productivity (53). The WLQ is a well-established tool for the assessment of losses in work productivity, and its use in other rheumatic diseases allows for a crude comparison to other conditions. Presenteeism is increasingly important to both employers and employees, and our study shows that work limitations were high in this group. This is also the first study to demonstrate that AS associated with other systemic disease has higher rates of WD than those with AS alone. We hypothesize that those with other systemic manifestations are likely prone to flares of their non-arthritic condition which contributes to their work disability status. We also hypothesize that those with psoriasis, IBD or reactive arthritis may suffer from greater peripheral

joint involvement, thus greater impacting work than predominantly axial primary AS. Interestingly, those who are able to work are just as productive as those with AS alone.

Weaknesses of this study include a cross-sectional design and moderate response rate using an "available patient cohort" (52). Our poor response rate did not allow us to meet our target sample size as indicated by our power calculations. Because of this, it can only describe WD at the time that the respondents filled out their questionnaires, and does not describe WD in AS over the course of this disease. We did use all AS patients seen over 1 year by 6 rheumatologists. However, it may be difficult to generalize the results from our sampling frame to other centers.

We also acknowledge that the different groups of AS (AS alone versus that associated with Ps, IBD or reactive) could differ significantly from each other. Ideally, larger numbers would be recruited so that these subgroups of AS can be examined individually and compared with each other.

This study also did not examine the impact of medication use (such as the use of biologic agents) on WD. Greater numbers would again be needed to examine this issue.

Since this study only included patients seen at one large rheumatology clinic and results were reported for those who responded, there could be sampling error (51). Every effort was made to capture all patients seen in London rheumatology clinics, but response rates were low. Additionally, differences existed between responders and non-responders (Figure 1). A thorough chart review was conducted, which showed that non-responders were younger and more likely to be male than those who responded. Traditionally, males have been thought to have more severe AS than females, so this significant gender bias in our results may impact the generalizability to other populations.

The use of billing codes to identify subjects can lead to bias. However, all identified subjects underwent chart review to ensure that their treating rheumatologist had diagnosed AS.

Not all patients with AS attend rheumatology clinics, which could bias results. Those who do not attend the clinics would likely have less severe disease.

Conclusions

We conclude that in our AS population, WD occurred in 18.5%. Subjects with systemic disease associated with AS (Ps, IBD, ReA) had higher rates of WD than those with AS alone. Of those who were working, 8.3% suffered losses in work productivity due to their arthritis. These findings suggest that AS has a high burden of disease in our population.

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Characteristic	Mean In All Respondents (SD) (n=81)	Mean In Not WD Group (SD) (n=63)	Mean In WD Group (SD) (n=15)	p-value Not WD vs. WD
Age	**45.0 yrs (11.5)**	**43.1 yrs (11.3)**	**52.9 yrs (9.1)**	**<0.05**
% Male	46.9	52.1	77.8	0.154
Disease Duration	9.9 yrs (12.1)	10.0 yrs (12.0)	9.3 yrs (12.6)	0.85
HAQ Score	0.90 (0.61)	0.78 (0.56)	1.38 (0.59)	0.89
VAS Pain Score	4.9 (2.8)	4.7 (2.8)	6.0 (2.2)	0.053
VAS Fatigue Score	5.6 (3.0)	5.4 (3.0)	6.6 (2.4)	0.155
VAS Problem Sleep Score	5.2 (3.3)	4.9 (3.3)	6.2 (3.0)	0.188
Duration of Morning Stiffness	107.7 min (271.7)	97.6 min (251.9)	68.0 min (49.7)	0.654
BASDAI Score	5.2 (2.5)	5.0 (2.5)	6.2 (2.2)	0.342
BASFI Score	**4.6 (2.8)**	**4.1 (2.6)**	**6.8 (2.4)**	**<0.05**
BAS-G Score	**5.0 (2.6)**	**4.6 (2.5)**	**6.5 (2.5)**	**<0.05**
Number Of Comorbidities		**2.3 (1.8)**	**4.0 (3.3)**	**<0.05**

Table 1: Comparison of clinical characteristics and clinical outcome measures in those with and without WD.

Characteristic (n=66)	Result
Number Of Hours Worked/Week	29.2 hrs (SD 20.1)
Decreased Number Of Hours Worked/Week	39.5%
Mean Days/Month Of Reduced Work Hours	3.7 days (SD 8.1)
Mean Days Off/Month	2.5 days (SD 6.2)
Conflict At Work	14.8%

Table 2: Summary of work restrictions reported in those still working.

Factor	Pearson r	p-value	Spearman's rho	p-value
Age	-0.02	0.87	-0.05	0.71
Disease Duration	-0.18	0.19	-0.18	0.19
HAQ	0.72	<0.001	0.70	<0.001
VAS Pain	0.65	<0.001	0.65	<0.001
VAS Fatigue	0.67	<0.001	0.71	<0.001
VAS Problem Sleep	0.64	<0.001	0.64	<0.001
VAS Overall Health	0.84	<0.001	0.82	<0.001
Morning Stiffness	0.21	0.115	0.52	<0.001
BASFI	0.68	<0.001	0.65	<0.001
BASDAI	0.69	<0.001	0.69	<0.001
BAS-G	0.67	<0.001	0.66	<0.001
Number Of Comorbidities	0.31	0.02	0.34	0.01

Table 3: Correlation of clinical characteristics and clinical outcome measures with WLQ work productivity loss.

WORK DISABILITY			
Variable	**Exp(B)**	**95% CI for Exp(B) (lower, upper)**	**Significance**
Age (years)	1.104	1.029, 1.184	0.006
Gender (male)	3.220	0.606, 17.112	0.170
Years of disease activity	0.995	0.949,1.044	0.851
WLQ Time Management Score	1.038	1.001, 1.077	0.042
WLQ Physical Score	1.026	0.995, 1.058	0.098
WLQ Mental Interpersonal Skills Score	1.061	1.014, 1.111	0.011
WLQ Output Score	1.106	0.998, 1.225	0.055
Loss in health-related work productivity (%)	1.415	1.023, 1.958	0.036
HAQ Score	6.561	2.027, 21.243	0.002
VAS Pain Score	1.216	0.968, 1.528	0.093
VAS Fatigue Score	1.168	0.941, 1.449	0.158
VAS Sleep Score	1.132	0.941, 1.362	0.189
VAS Patient Global Assessment	1.366	1.059, 1.761	0.016
Duration of am stiffness (minutes)	0.999	0.996, 1.003	0.662
BASFI Score	1.610	1.189, 2.180	0.002
BASDAI Score	1.255	0.972, 1.621	0.082
BAS-G Score	1.431	1.077, 1.901	0.013
Number of comorbidities	1.349	1.054, 1.727	0.017

Table 4: Results of univariate binary logistic regression. In each case, the dependent is work disabled (yes/no). Each variable is run separately.

LOSS IN HEALTH-RELATED WORK PRODUCTIVITY (%)

Variable	B	95% CI for B (lower, upper)	Significance
Age (years)	-0.013	-0.177, 0.150	0.871
Years of disease activity	-0.104	-0.260, 0.052	0.186
Income ($)	-1.747	-2.764,-0.730	0.001
HAQ Score	8.058	5.995, 10.120	0.000
VAS Pain Score	1.477	1.017, 1.937	0.000
VAS Fatigue Score	1.440	1.015, 1.865	0.000
VAS Sleep Score	1.275	0.866, 1.684	0.000
VAS Patient Global Assessment	2.136	1.764, 2.509	0.000
Duration of am stiffness (minutes)	0.007	-0.002, 0.17	0.115
BASFI Score	1.698	1.211, 2.186	0.000
BASDAI Score	1.779	1.193, 2.196	0.000
BAS-G Score	1.695	1.193, 2.196	0.000
Number of comorbidities	1.177	0.212, 2.141	0.018

Table 5: Results of univariate linear regression. In each case, the dependent is loss in health related work productivity (%). Each variable is run separately.

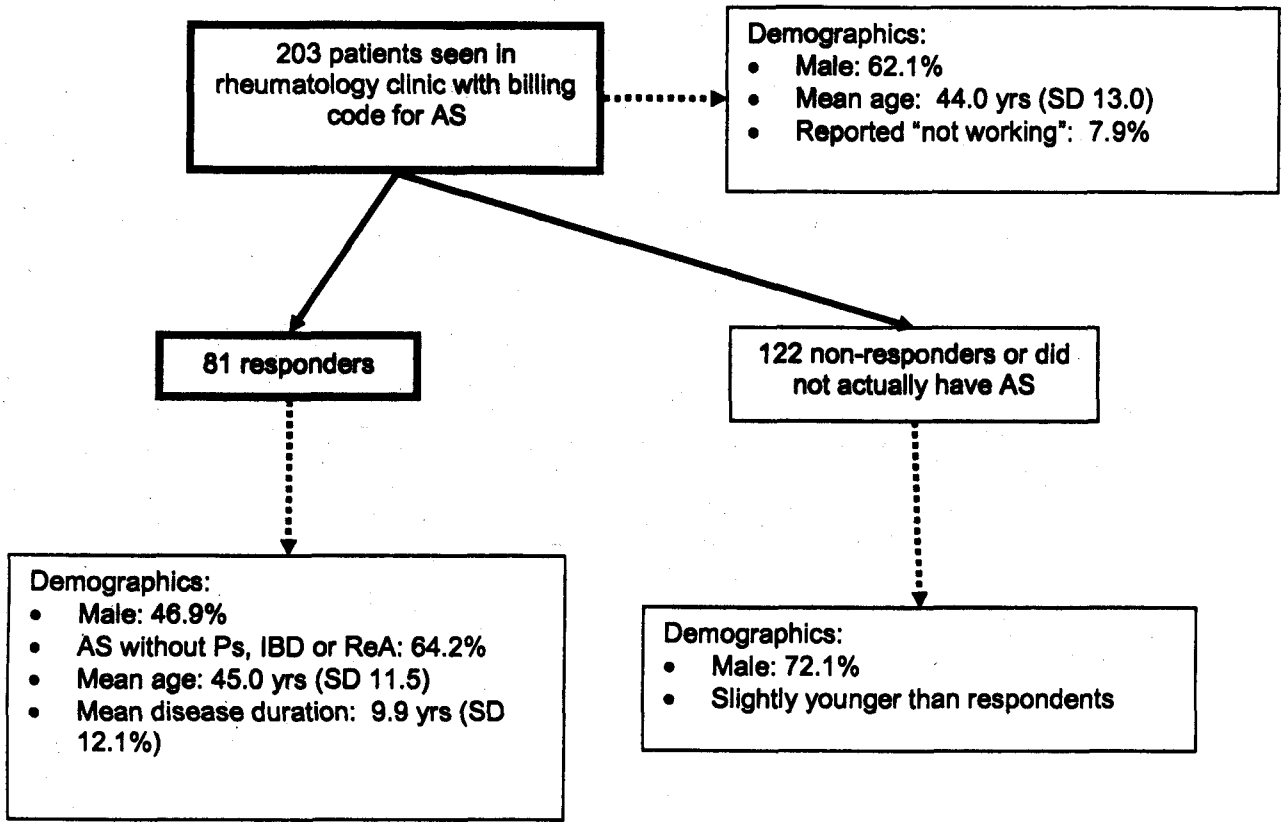

Figure 1: Study design with details regarding demographic features of responders and non-responders.

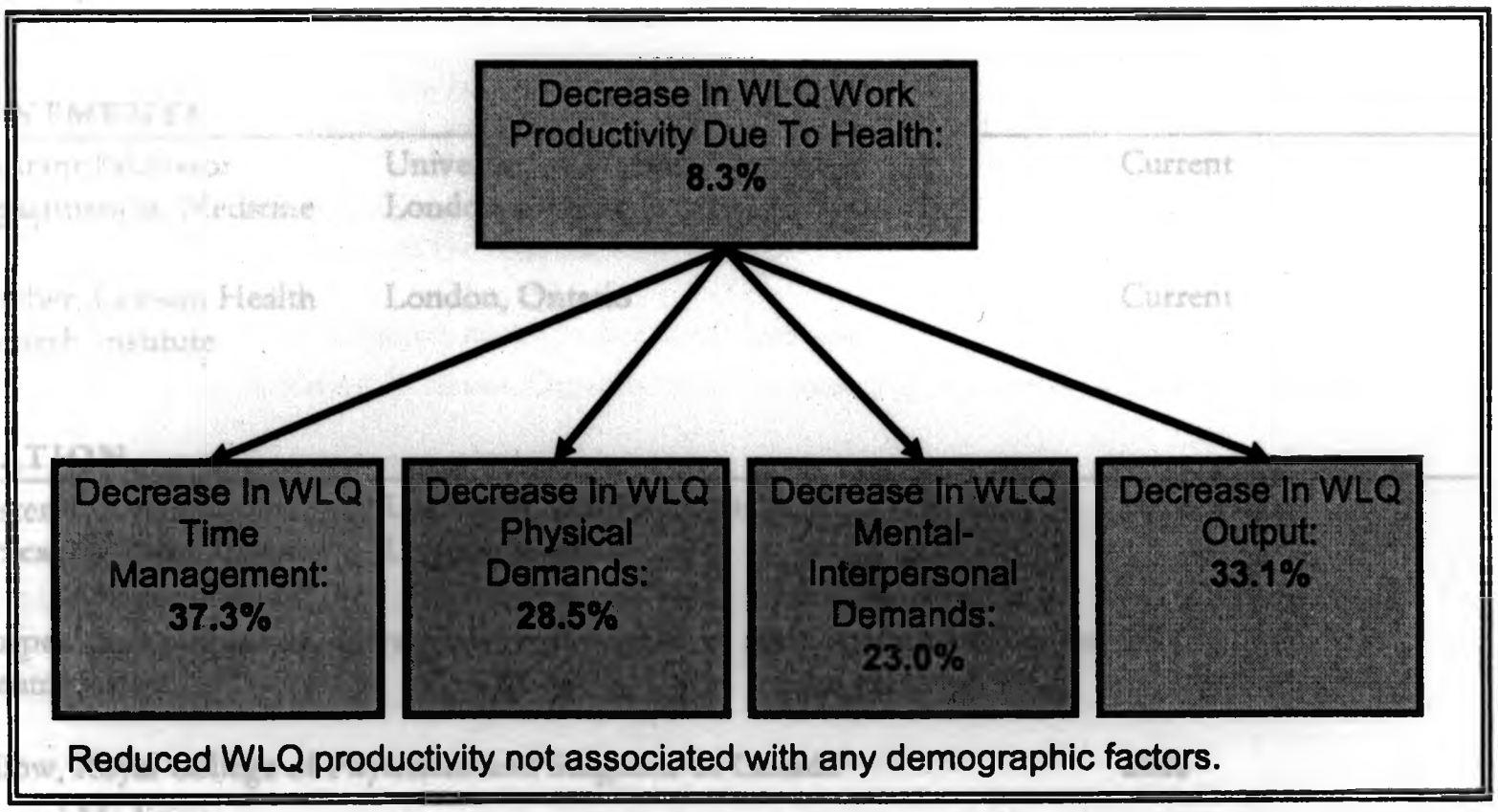

Figure 2: Results of WLQ work productivity analysis.