Work Status and Its Determinants Among Patients with Ankylosing Spondylitis. A Systematic Literature Review

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ABSTRACT. ***Objective.*** To evaluate work status and its determinants among patients with ankylosing spondylitis (AS).

Methods. A systematic literature review of original studies published after 1980 in which work status in AS was an outcome. Medline was searched and references of retrieved reports were checked for additional studies.

Results. Sixteen full articles and 2 abstracts were identified, describing work status in 14 patient groups. Employment ranged from 34 to 96% after 45 and 5 years disease duration, respectively, and work disability from 3 to 50% after 18 and 45 years disease duration, respectively. Days of sick leave varied from 12 to 46 days per patient per year among those who had a paid job. Determinants of work status were reported in 9 studies. Age, education, and physical function were shown to be associated with work disability, while peripheral joint disease was associated with sick leave.

Conclusion. Results on work status show considerable variability due to heterogeneity of patient populations studied, but also because of large variation in choices and definitions of endpoints. The absence of data referring to a reference population and failure to adjust results for age and sex are striking. Although standardization in analyzing and reporting data on work status is badly needed, it is clear that work disability and sick leave in AS are substantial. (J Rheumatol 2001;28:1056–62)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS EMPLOYMENT WORK
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In the broader concept of patient outcome, work status is important not only because it contributes to quality of life of the individual patient but also because of its economic consequences. The costs attributable to loss of productivity (indirect costs of disease) are the major component of the total costs of musculoskeletal diseases[1]. Insight into the magnitude and determinants of impaired work status for specific rheumatologic conditions might help to keep patients in the labor force by adequate professional counseling and vocational rehabilitation. Ankylosing spondylitis (AS) affects people, mostly men, at young age[2] and can lead to important functional impairment not only because of spinal disease, but also because of extraspinal manifestations[3]. We reviewed the literature on work status and its determinants in patients with AS.

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MATERIALS AND METHODS

Selection criteria. Original studies in adult patients with AS with work status among the endpoints and published after 1980 in English, French, Dutch, or German were selected. Work status refers to the ability or inability to perform a paid job. Endpoints considered were employment, work disability, early retirement, withdrawal from labor force, unemployment, and sick leave for those having a paid job. The search was limited to publications within the last 20 years since we were interested in present work status and since economic developments over time as well as changes in social security systems might influence labor force participation of patients with AS and the general population differently.

Search strategy. Medline was searched from 1980 up to March 2000. The combination of MESH terms [ankylosing spondylitis or spondylitis or arthritis] and [work or labor or labour or economics or employment or indirect costs or burden of illness or job] as headings and subheadings was used. Additionally, abstracts from the American College of Rheumatology (ACR) Annual Scientific Meeting and the references from the Epidemiology and Health Services Research section of *Current Opinion in Rheumatology* from 1995 to 2000 were hand searched to find data from recent unpublished studies. Finally, references of selected articles were checked.

Data collection and analysis. Data were extracted by one evaluator (AB) and in cases of doubt independently by a second reader (HdV). A self-composed list of items over 6 domains was used (Appendix). These domains were (1) identification of the study, (2) study design, (3) characteristics of the patient group, (4) endpoints related to work, (5) determinants of work status, and (6) appropriateness of defining and reporting work

related endpoints. Whenever possible, we recalculated data on work status for patients of working age in order to improve comparability among studies.

RESULTS

Search and selection of articles. The Medline search provided 1535 citations. Most articles could be eliminated after reading the title or the abstract. For 28 citations the entire article had to be checked. Finally, only 16 articles fulfilled our requirements[4-18]. Two articles[18,19] dealt with the same study. The publication with the more extensive data was included[18]. One additional article[20] was found in the references[10]. Hand search of *Current Opinion in Rheumatology* did not provide additional articles. Hand search of ACR abstract books revealed 2 not yet published abstracts from Mexico dealing with the same population, of which the second reported results after 5 years' followup[21,22]. In total 18 publications were included[4-18,20-22].

Patient groups and endpoints. Table 1 presents characteristics of the selected studies, while Table 2 provides some results of the critical appraisal of the articles. All studies were done in European countries except for 2 Mexican studies[21,22] and one from New Zealand[15]. Four patient groups were followed longitudinally[9,10,18,20,22] and only one was an inception cohort[10,20]. The 18 articles dealt with 14 patient groups. Two groups were again reported after longer followup became available[10,20-22]; another group was analyzed a second time after inclusion of more women to compare work status between male and female patients[16,17]. A fourth group compared first hospital and community samples and later male and female patients after inclusion of more patients[11,12]. The number of patients included varied from 20 to 739[5], mean age from 35[21] to 48 years[5], and mean disease duration from 10[21] to 45 years[18]. However, mean age[14,18,20], age range[5,6,8,11,13,15,21], and mean disease duration[14,16,17] were not always provided and information on disease activity, presence of extraspinal disease, and education level was often insufficient. Most studies reported on several endpoints related to work status. Terminology used to refer to patients without paid employment or having some type of disability varied importantly: work disability[10,20,21], disability pension[5], registered disablement[13], (early) retirement[6,11,12], invalidity rent[14], inability to work[18], withdrawn from work[9,22], and unemployment[5-7,15]. Strikingly, only 4 studies provided sufficient definition of at least one of these endpoints[9,10,21,22]. When reporting further in this article on endpoints, we classified the terms used in the original articles into 3 categories: employed, unemployed, and work disabled comprising: work disability, disability pension, registered disablement, (early) retirement, invalidity rent, inability to work, and withdrawn from work. In Tables 1, 3, and 4 terminology as used in the original articles is respected. Also, reporting endpoints was not uniform. Sick leave, for example, was sometimes presented as proportions of patients experiencing sick leave in the past year[14,21] or during a certain followup period[9,15], and sometimes as the number of days absent at work per year[14,22] or per month[22]. Often, it remained unclear if the particular endpoint was assessed as AS-specific. Data were never adjusted for age or sex and only one study provided reference data on employment in the general population[7]. Nine studies analyzed determinants of work status by univariate or multivariate statistics[5-7,9,12-14,21,22]. Costs associated with loss of productivity were never calculated.

Work status and sick leave. Table 1 also provides the results of the separate studies. For 7 studies it was not possible to recalculate data on work status for patients of working age[6,8,11,13,15,18,21]. Overall, employment ranged from 34 to 96% in patients with 45 and 5 years' disease duration, respectively. Both figures came from the same Finnish cohort[10]. Excluding this study, employment varied from 61% in both a Slovak[14] and a Mexican[21] study to 89% in another Finnish cohort[20]. Mean disease duration in the Mexican group was 10 years in contrast to 3 years in the Finnish cohort. Disease duration in the Slovak group was not provided.

Work disability (reported under various terms) ranged from 3 to 50%. The lower figure came from a Swiss study[5] dealing with a group of patients belonging to the national AS society who had average disease duration of 18 years. The Finnish group reported the higher figure of 50% after 45 years of disease[18].

Overall, the influence of disease duration on work status remains unclear. Three studies provided data on employment[4,15,18] or work disability[4,18] in relation to disease duration. One of these studies showed a clear adverse effect of disease duration on work status[18], while this effect was only minimal in another study[15] and absent in a third study[4]. Examining influence of disease duration on work status across studies, no clear relation could be seen, probably reflecting the differences in patients studied, in endpoints used, and in the year the studies were conducted.

For the 5 studies reporting on unemployment[5-7,13,15], figures ranged from 0.2[5] to 18%[6]. However, clear definition of unemployment was not provided and in 2 studies[6,7] this probably does not refer to those economically having an official unemployment benefit, but to those having no paid job, whatever the reason. Excluding these 2 studies, unemployment ranged from 0.2[5] to 9%[15].

Several studies compared work status in subgroups of patients with AS. Differences in employment between male and female patients were reported in 5 studies. In 2 groups employment was lower among female patients[6,16,17], but this was not confirmed in 3 other groups[11,12,18]. Work disability was lower in female patients in one study[12], but equal between male and female patients in another study[6]. A Norwegian study[12] compared employment between patients from a hospital population and patients from the general population. In the latter group employment was 89%, which

Table 1. Characteristics and findings of studies having work status among the primary outcomes.

Study	Type (number of patients), population	Endpoints* and Results
Lehtinen[18], Finland, 1981	Cohort study (76); hospital sample, retrospectively analyzed, mean disease duration 30 yrs, mean age: NA	Employed: at 5 yrs 96%, at 10 yrs 95%, at 15 yrs 87%, at 25 yrs 65%, at 45 yrs 34% Unable to work: at 5 yrs 4%, at 10 yrs 5%, at 15 yrs 13%, at 25 yrs 30%, at 45 yrs 50% No difference between ` and a
Chamberlain[16], UK, 1981**	Cross sectional study (31, 25 `), hospital sample, mean disease duration: NA, mean age 41 yrs	Employment in ` 84%
Chamberlain[17], UK, 1983**	Cross sectional study (25 `, 25 a), hospital sample, mean disease duration: NA, mean age: ` 39, a 43 yrs	Employment in a 60%
Nissila[20], Finland, 1983***	Inception cohort (84 SpA), community sample, retrospectively assessed, followup at 3 yrs, mean disease duration 3 yrs, mean age: NA	Employed 89%, disability due to AS 9%
McGuigan[15], New Zealand, 1984	Cross sectional study (60), hospital sample, mean disease duration 44 yrs, mean age 24 yrs	Employed 76%, unemployed due to AS 6.6%
Urbanek[14], Slovakia, 1984	Cross sectional study (170), hospital sample, mean disease duration: NA, mean age: NA	Employed 61%, invalid rent 29%, episode sick leave past year due to AS 60%, mean 39.5 days/patient/yr
Gran[11], Norway, 1984†	Cross sectional study (100), ¼ community, ¾ hospital sample, mean disease duration 18 & 14 yrs respectively, mean age 42 & 37 yrs respectively	Employed 69%, COM-AS 89% (` 87%, a 100%), HOS-AS 63% (` 63%, a 65%), retired due to AS 15%
Gran[12], Norway, 1985†	Cross sectional study (126), ⅕ community, ⅘ hospital sample, mean disease duration 14 yrs, mean age: ` 40, a 37 yrs	Employed: ` = a = 69%, permanent retired: ` 23%, a 11%
Wordsworth[13], Oxford, UK, 1986	Cross sectional study (100), hospital sample, mean disease duration 20 yrs, mean age 42 yrs	Employed 84%, unemployed 9%, retired 4% (2% due to AS), registered disabled 18%, cumulative sick leave > 2 mo due to musculoskeletal disease: 32.9%
Kaarela[10], Finland, 1987***	Inception cohort (20 SpA), community sample, retrospectively assessed, followup 6–9 yrs, mean disease duration 8 yrs, mean age 37 yrs	Employed 85%, disability due to AS 15%
Guillemin[9], France, 1990	Cohort study (182: all working at start), hospital sample, retrospectively assessed, followup maximal 10 yrs, mean disease duration 14 yrs, mean age 42 yrs	Cumulative prolonged sick leave (≥ 4 wks) 32%, withdrawal from work 36%
Edmunds[8], UK, 1991	Cross sectional study, ⅓ hospital sample, ⅔ patient society; total 1331 with 1128 primary AS, 121 Ps-AS (age 46 yrs; disease duration 23 yrs) 82 IBD-AS (age 48 yrs; disease duration NA)	120 primary AS vs 121 Ps-AS, employed 68 vs 65% 82 primary AS vs 82 IBD-AS, employed 56 vs 55%
Ringsdal[4], Denmark, 1991	Cross sectional (231; 224 working age), patient society, mean disease duration 22 yrs, age 21 to 90 yrs	Employed 70.9% (52% work full time), disability pension 29.0%
Fellmann[5], Switzerland, 1996	Cross sectional (739; 702 working age), patient society, mean disease duration 18 yrs, mean age 45 yrs	Employed 80% (36% work < 42 h/week), disability pension 3%, unemployed 0.2%
Roussou[7], UK, 1997	Cross sectional study (1044, all `), ⅓ hospital sample, ⅔ patient society, mean disease duration 10 yrs, mean age: NA (< 55 yrs)	Employed 85%, unemployed 15%
Gran[6], Norway, 1997	Cross sectional study (99), hospital sample, mean disease duration 16 yrs, mean age 42 yrs	Employed 62%, (` 71%, a 45%), part-time 10% (` 5%, a 24%), retired: ` = a = 3% (in 96% due to AS), unemployed 28% (` 20%, a 42%)
Ramos-Remus[21], Mexico, 1997‡	Abstract (103), cross sectional study, hospital sample, mean disease duration 10 yrs, mean age 35 yrs	Employed 61.6%, permanent disability 27%, sick leave 67% of those working: mean 45.8 days/patient/yr, duration 69 days/sick patient
Ramos-Remus[22], Mexico, 1998‡	Abstract (103), cohort study, hospital sample, followup 5 yrs, mean disease duration 10 yrs, mean age 35 yrs	Withdrawal from work: 3% per yr, sick leave: mean 1 day/patient/mo

* Terminology from the original articles is used; NA: not assessed, SpA: spondyloarthropathy, IBD-AS: AS associated with inflammatory bowel disease, Ps-AS: AS associated with psoriasis, HOS-AS: hospital sample of patients with AS, COM-AS: population sample of patients with AS.
** Both studies report on nearly the same patient group; the second study comprises more female patients.
† Both studies report on nearly the same patient group; the second study comprises a larger number of patients.
***‡ Both studies report on the same cohort after longer followup.

was 26% higher than in the hospital group. A UK study[8] examined differences in employment among patients with primary AS compared to psoriatic AS and to AS associated with inflammatory bowel disease (IBD). No differences in employment rate were noted between primary and psoriatic AS (68 versus 65%) nor between primary AS and IBD-AS (56 versus 55%). The 12% difference in employment between both groups with primary AS might be explained by the fact that each group of patients with primary AS was matched for age and sex to the psoriatic or IBD group,

Table 2. Critical appraisal of 18 studies on work status in AS.

Domain	Reported in Sufficient Detail Numbers indicate references*	Reported but Insufficiently Numbers indicate references*
AS diagnosis ascertained	4–13	
	15–17	
	20–22	
Calendar year of study	4	
	9	
	22	
Age range of patients	5	7 (< 55 yrs)
	4	13 (only working age)
	11	20 (only working age)
	14	
	16	
Extraspinal manifestations		
IBD	6 ("IBD excluded")	
	11 ("IBD excluded")	
	12 ("IBD excluded")	
	13 (8%)	
Peripheral arthritis	4 (40%)	5 (62% ever pain in peripheral joints)
	8 (27%)	
	9 (72%)	
	12 (29%)	
	14 (23%)	
	20 (30%)	
Endpoint defined		
Work disability	9	
	10	
	21–22	
Endpoint AS-specific		
Work disability	6 (96% due to AS)	4
	10 (some due to other diseases)	
	11 (because of AS)	
Unemployment	15 (44% due to AS)	
Sick leave	14 (due to AS)	
	13 (AS or associated disease)	
Adjusted for age and sex	None	
Reference data provided		
Employment	7 (90–93%)	14
Unemployment	6 (3%)	
	13 (8%)	
Sick leave	21 (8.8 days/yr)	

*References not described did not report on a particular domain. IBD: inflammatory bowel disease.

respectively. For example, in the group comparing primary and psoriatic AS 78% were male in contrast to 49% in the group comparing primary AS and AS associated with IBD.

Sick leave was substantial in all studies[9,13,14,21,22], ranging from 12[22] to 46 days per working patient per year[21]. In a French study 32% of patients had experienced sick leave of more than 4 weeks duration after 5 years of disease[9]. In a study from the UK, 33% of patients had been on sick leave longer than 2 months after 20 years of disease[13].

Table 3 presents results of work status across several countries. It is clear that even for studies within the same country results vary importantly. For example, employment ranges from 56 to 86% among the 5 UK studies[7,8,13,16,17].

Determinants of work status. Nine articles used univariate or multivariate statistical methods to explore determinants of work status[5-7,9,12-14,21,22]. Only 2 studies were prospective[9,22]. Different dependent variables were studied (Table 4). We classified independent variables into 4 domains: sociodemographic characteristics, disease characteristics, job characteristics, and psychological characteristics. Only one study stated which variables were used in the statistical model[9]. In no study were variables of each domain included. Two studies used a multivariate analysis[9,22].

Table 4 summarizes determinants of work status for several countries. Overall, employment or work disability were associated with age[6,12,21,22], education[6,14,21], job characteristics[9], physical functioning[7,21], disease duration[21], disease activity[7], pain and depression[7], spinal fusion[6], acute

Table 3. Work status* summarized per country.

Country	Employed	Not Employed	Withdrawn from Work	Sick Leave
Denmark[4]	71%	Disability pension: 29%		
Finland[10,18,20]	85%[10] to 96%[18]	Unable to work: 4%[18] Disability: 15%[10]		
France[9]			Cumulative 36% after 20 yrs 3% per year[22]	32% episode of sick leave ≥ 4 weeks over 5 yrs
Mexico[21,22]	61%[21]	Work disability 27%[21]		67% of those working at least one day sick past yr 1 day per mo[22] to 45.8 days per yr[21]
New Zealand[15]	76%	Unemployed due to AS: 6.6%		
Norway[6,11,12]	62%[6] to 89%[11]	Retired due to AS: 3%[6] to 15%[11] Unemployed: 28%[6]		
Slovakia[14]	61%	Invalid rent: 29%		60% of those working at least one day sick past yr 39.5 days/patient/yr
Switzerland[5]	80%	Disability pension: 3% Unemployed: 0.2%		
UK[6,7,13,16,17]	56%[8] to 85%[7]	Unemployed: 9%[13] to 15%[7] Retired: 4% (2% due to AS)[13] Registered disabled: 18%[13]		65% had ever episode of sick leave ≤ 2 mo[13] 32% had ever episode of sick leave > 2 mo[13]

*Terminology from the original articles is used.

Table 4. Determinants of work status per country.

Country	Determinants of Being Employed	Determinants of Not Being Employed*	Determinants of Withdrawal from Work*	Determinants of Sick Leave*
France[8]			Withdrawal: exposure to cold (RR 2.01); job counseling (RR 0.57); prolonged standing (RR 1.34); non-sedentary work (RR 0.35) (univariate); job counseling (RR 0.38) and prolonged standing (RR 3.26) (multivariate)	Cumulative probability of prolonged sick leave (> 4 weeks) at 5 years: > 2 peripheral joints (RR 3.9); exposure to cold (RR 1.92); exposure to humidity (RR 1.5); carrying loads (RR 1.23) (univariate); > 2 joints (RR 1.9) and carrying loads (RR 1.92) (multivariate)
Mexico[21,22]		Work disability: older age, lower education; longer disease duration; worse functioning, delay diagnosis; increased occiput-wall distance; decreased axial movement[21]	Withdrawal: age but not disease duration (univariate); age (multivariate)[22]	Sick leave: disease activity and function[22]
Norway[6,11]	Employment: gender; education; uveitis; fused spine; comorbidity but NOT peripheral arthritis; hip replacement; spinal x-ray changes and psychologic functioning[6]	Age at retirement: sex[6] Retired: not sex[11]		
Slovakia[14]		No work: education		
Switzerland[5]				"Problems at work": pain; hip involvement; shorter official education and diagnosis after start of first job but NOT involvement of knee or shoulder
UK[7,13]		Unemployment in 50 employed vs 50 unemployed (matched for age and disease duration): ASAQ; DAI; AIMS impact, physical functioning, pain and depression scale but NOT AIMS anxiety and social functioning[7]		> 2 months time off work: psoriasis and peripheral joint disease but NOT disease duration; age and IBD[13]

*Terminology from the original articles is used. AIMS: Arthritis Impact Measurement Scale, ASAQ: Ankylosing Spondylitis Assessment Questionnaire, DAI: Disease Activity Index, RR: relative risk, IBD: inflammatory bowel disease.

replacement[6], psychosocial functioning[6,7], and anxiety[7]. An association between sex and work status was seen in one study[6], but not in another[12]. Sick leave and problems at work were associated with education[5], job characteristics such as carrying heavy loads and exposure to cold[9], peripheral joint disease[9,13], hip involvement[5], psoriasis[13], disease activity[22], and physical functioning[22], but not with age[13], disease duration[13], IBD[22], and involvement of knee or shoulder joints[5].

DISCUSSION

Employment in AS ranged from 34 to 96%, with half the studies reporting employment below 70%[6,8,11,12,14,17,18,21]. Work disability varied from 3 to 50%, with half the studies reporting work disability in more than 20% of patients[4,6,12,14,18,21], compared to around 10% in the general population of most European countries[23].

The striking variation in employment and work disability can be attributed at least partly to heterogeneity of patient populations, differences in definitions of endpoints related to work status, and differences in employment rates among countries. Clear definitions of endpoints in the context of the social security system are essential to assess the possible influence of different systems on work status and to improve generalizability of data on work status across countries. Sex, age, and education level, but also disease characteristics such as disease duration, physical function, and presence of extraspinal disease, might influence work status. Surprisingly, these data were often lacking. The relative contribution of these variables can only be reliably assessed by collecting unbiased data in prospective studies and analyzing these data multivariately. Disease duration, for example, had an effect increasing the risk of work disability in one study providing data for groups of patients with different disease duration[18], while this could not be seen in 2 other studies[4,15]. In a multivariate analysis in which age was included[22] it was shown that age but not disease duration had an effect on work status. Therefore, it seems that age is a stronger determinant of work status than disease duration. The influence of sex on work status is still controversial[6,11,12,16-18]. Since work status differs as well in the general population among men and women, the lower employment rate in female patients with AS reported in some studies[6,16,17] might possibly reflect such population differences. Clearly, firm conclusions on this subject cannot be drawn yet. Interestingly, neither peripheral arthritis[6,8,9] nor IBD[8] as comorbidity increased work disability. Notably, patients from community samples fared better than patients from hospital samples, despite older age and longer disease duration[11]. This has important implications for generalizability of findings on work status among patients with AS.

Limitations also apply to the interpretation of data on sick leave in those with a paid job. Findings varied from 12 to 46 days per patient per year[21,22]. It is important to define whether sick leave is assessed in an AS-specific way and whether the findings apply to those with a paid job or to all patients included in the sample. In contrast to findings for work disability, sick leave was associated with hip involvement and peripheral joint disease[5,9,13]. Availability of treatment for peripheral arthritis, such as more effective drugs and especially hip replacement therapy, could possibly be related to sick leave but can prevent permanent work disability.

In the literature, data were not adjusted for age and sex and reference data on work status were usually lacking. Such data of course are often useful to interpret results meaningfully. For example, in a study among 658 Dutch patients with AS we showed the employment rate fell from 62.9 to 54.2% after adjusting for age and sex. In comparison to the general Dutch population this would mean a reduction of only 2.3% for unadjusted data, but 11.0% after adjustment (unpublished findings).

Despite the limitations in methodology in some reports we examined, this review shows that work disability and sick leave in AS are substantial. Reliability of data on work status in AS would be improved if a large multinational inception cohort was followed for many years to regularly collect demographic, socioeconomic, and disease variables. As long as such large prospective databases are not available, the minimal requirements for studies on work status should be precise characterization of the patients with respect to age, social class, disease duration, and presence of comorbidity or extraspinal disease, and should include clear definitions of work related endpoints (including whether assessment was disease-specific). Data must be adjusted for age and sex, whereas reference data will be helpful in interpreting the relevance of the findings.

APPENDIX

Items of data extraction applied to the articles selected after literature search.

1. Identification of the study: Country where the study was done, year the study was done, year the study was published, aim of the study.

2. Study design: Prevalence or incidence based study, cross sectional or cohort (duration of followup), Prospective or retrospective study design.

3. Characteristics of the patient group: Sample size and response rate, community selected or hospital selected group, validation of diagnosis, proportion of males and females, age: mean and range (proportion in working age), education level, professional class (how assessed?), disease duration diagnosis (since diagnosis or symptoms), extraspinal and extraarticular disease included (proportions), comorbidity.

4. Endpoints: choice of endpoint: Employment — full-time versus part-time separately, men and women separately; Work disability pension (or related endpoint) — full versus partial separately, men and women separately; (Early) retirement, men and women separately; Withdrawal from work (after onset of disease); Sick leave — proportion of patients having sick leave, work days lost (proportion of work days, number days/patient/year, duration of sick leave); endpoint sufficiently defined, How was endpoint assessed: self-report (questionnaire/interview), register; Endpoint disease-specific or nonspecific?

5. Determinants of work status: Dependent variable(s); Independent variable(s): sociodemographic characteristics, disease characteristics, job characteristics, psychological well being; How was strength of relationship

assessed — prospective or retrospective data, univariate or multivariate analyses.

6. Appropriateness of defining and reporting work related endpoints: Definition of the endpoints present? (short description of the social security system); Endpoint assessed as disease-specific or nonspecific; Results presented for patients in working age category or total age range; Data adjusted for age and sex; Data referring to general population or other patient groups (including source of these data); Indirect costs calculated (by which method).

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