Comorbidity profiles among adult patients with juvenile idiopathic arthritis: results of a biologic register

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Abstract

Objectives

This study aims to assess the prevalence of comorbidities in adult JIA and the impact of comorbidity on patients' perceived health state.

Methods

Self-reported comorbidity was studied in 344 adult JIA patients who have been included in the biologic register JuMBO. The comorbidity prevalence among the patients was compared to an age- and sex-matched reference group from the population. The correlation of comorbidity with clinical and demographic parameters was analysed by linear or logistic regression models.

Results

Sixty two percent of the JIA patients reported at least one comorbidity. Uveitis was the most common comorbid condition (17.7%), followed by allergic rhinitis (14.5%), migraine (8.7%), and atopic dermatitis (8.7%). The prevalence of cardiovascular disorders was 9.9%, which was not higher than that in the population. However, patients with a systemic onset of JIA (soJIA) had a substantially higher rate of cardiovascular diseases of 40.6% ($p=0.033$). Patients with soJIA also had the highest prevalence (80.0%) and the highest mean number (1.8) of comorbidities. Patients with at least one comorbid condition suffered more often from fatigue and pain, had a lower functional capacity ($p<0.001$, each), and a lower physical and mental health-related quality of life than those without comorbidities ($p<0.001$ and $p=0.017$, respectively). The presence of any comorbidity and the level of disease activity were independent predictors of a lower SF-36 score.

Conclusion

Our results indicate that comorbid conditions have a significant impact on the perceived health state in adult JIA. Among all JIA patients, those with systemic onset carry the highest risk for comorbidities, in particular for cardiovascular disorders.

Key words

juvenile idiopathic arthritis, comorbidity, etanercept, long-term outcome, cardiovascular disease

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Introduction

Juvenile idiopathic arthritis (JIA) comprises a group of heterogeneous disorders of chronic childhood arthritis with unknown aetiology. JIA often takes a chronic course and persists in approximately half of the patients into adulthood (1-3). Several outcome studies have shown that more than a third of the patients have evidence of disability and organ damage in their early adult years. Damage in JIA is mainly articular. Extra-articular damage comprises the following in decreasing order: ocular sequelae with vision loss due to uveitis, growth failure, and muscle atrophy (4-7). In addition to these well-known long-term consequences, the disease may pose patients at risk also for certain comorbidities observed in adult-onset arthritis such as cardiovascular diseases, malignancy, osteoporosis, or infections (8, 9). However, little is known about the comorbidity spectrum in adult JIA.

The established adult JIA biologic register JuMBO (Juvenile arthritis Methotrexate Biologics long-term Observation) (10) was used to assess the prevalence of comorbidity in adult patients with various JIA subgroups. For this purpose, we investigated self-reported comorbidity, because some patients do not regularly see a physician for various reasons. Research has shown that patients can accurately assess their current and past medical conditions, including comorbidities (11-14). In addition to the examination of self-reported comorbidity, we wanted to explore the impact of comorbidity on the JIA patients' perceived health status in early adulthood.

Methods

Participants of this study are part of the ongoing prospective observational cohort study, the adult JIA biologic register JuMBO. Patients with definite JIA, according to the International League of Associations for Rheumatology criteria (15), who had been previously observed in the paediatric biologics register, BiKer (16), and agreed to participate in JuMBO are half-yearly provided with a patient and a physician questionnaire (10).

The patient questionnaire includes the Health Assessment Questionnaire (HAQ) for assessing the functional status and numeric rating scales (NRS, score from 0 [best] to 10 [worst]) for the assessment of fatigue, pain and disease activity (17). Health-related quality of life (HRQoL) is measured via the Medical Outcome Study Short-Form 36 (SF-36) (18). The eight domains of the SF-36 include physical function, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health; each domain is scored from 0 (worst) to 100 (best). Domain scores were normalised and z-transformed into mental component summary (MCS) and physical component summary (PCS) scores. The normative value for the MCS or PCS summary score is 50 with a SD of 10. Additionally, basic sociodemographic data, hospitalisations, educational/vocational situation, and important health problems from the patient's point of view are recorded.

The treating physician is asked to record the following: number of joints with swelling, tenderness or pain on motion, limited range of motion (72 joint count), the erythrocyte sedimentation rate, the C-reactive protein level, morning stiffness, and conventional and/or biologic DMARD therapy, including details of starting and ending therapy, reasons for change of treatment, and concomitant therapies with glucocorticoids or non-steroidal anti-inflammatory drugs. Physicians assess the patient's disease activity on a NRS. Additionally, physicians record known comorbid conditions at inclusion in JuMBO and any adverse or serious adverse events (AEs, SAEs) that occur thereafter. However, physician data were not available for 25% of the patients either because patients' do not regularly visit a rheumatologist or physicians are not willing to participate.

In order to obtain information on comorbidity of all patients, an additional questionnaire was provided to the 411 patients included in JuMBO until 1st January 2011. It inquired about the following lifetime comorbidities: cardiovascular diseases (CVD), pulmonary diseases, gastrointestinal diseases, liver and gallbladder diseases, diseases of the kidneys or the urinary tract, gynaecological dis-

Table I. Baseline characteristics of JUMBO patients.

	n	%
n	344	
Systemic onset of JIA (soJIA)	15	4.4
Persistent oligoarthritis (pers. OA)	28	8.1
Extended oligoarthritis (ext. OA)	50	14.5
RF-negative polyarthritis ((RF-neg. PA)	91	26.5
RF-positive polyarthritis (RF-pos. PA)	37	10.8
Enthesitis-related arthritis (ERA)	75	21.8
Psoriatic arthritis (PsA)	37	10.8
Other arthritis	11	3.2
Female	196	70.5
Age in years, mean (SD)	19.7 (2.8)	
Years since symptom onset, mean (SD)	10.6 (5.6)	
Number of DMARDs ever received, mean (SD)	3.5 (2.2)	
Patients ever treated with etanercept	278	81
Years of etanercept treatment[a], mean (SD)	4.2 (2.8)	
Positive ANA test[b]	92	35
Positive HLA-B27 test[b]	77	30
Current treatment with biologic or conventional DMARDs[d]		
Etanercept	144	42
Methotrexate	151	44
Adalimumab[e]	42	12
Other biologics[f]	29	9
Other conventional DMARDs	64	19
Disease activity (NRS 0–10), mean (SD)	2.6 (2.5)	
Fatigue (NRS 0–10), mean (SD)	2.8 (2.7)	
Pain (NRS 0–10), mean (SD)	2.8 (2.4)	
HAQ-score, mean (SD)[c]	0.4 (0.6)	
SF36, mental component summary (MCS) score, mean (SD)	49.7 (9.8)	
SF36, physical component summary (PCS) score, mean (SD)	45.0 (11.0)	

[a]Years of etanercept treatment in patients ever treated with etanercept; [b]percentages refer to 239 ANA tests and 234 HLA-B27 tests; [c]Health Assessment Questionnaire; [d]combination treatment or multiple drug use results in more than 100%; [e]years of adalimumab treatment, mean (SD): 2.7 (1.7); [f]years of infliximab treatment, mean (SD): 2.4 (1.6); years of abatacept treatment, mean (SD):1.0 (0.6); years of rituximab treatment,mean (SD): 0.9 (1.3); years of anakinra treatment, mean (SD): 4.0 (0.5); years of tocilizumab treatment, mean (SD): 1.4 (0.8).

eases, haematological diseases, allergic diseases, thyroid/endocrine diseases, skin diseases, eye diseases (especially uveitis), tuberculosis, chronic viral infections, tumours, neurologic diseases, psychic disorders, and "others" to be specified. Examples in each category were provided.

Data regarding disease onset, JIA subgroup, disease modifying anti-rheumatic drug (DMARD) treatment ever received, and positivity for antinuclear antibodies (ANAs) and HLA-B27 were obtained from the physician reports in Biker. For the purpose of this study, comorbidity was defined (in accordance with others [14, 19]) as a medical condition that co-exists along with arthritis. This condition may be linked to the rheumatic disease itself and/or its treatment such as uveitis, psoriasis or osteoporosis, or it may be completely independent of these.

According to the patients' ratings, inactive disease was defined as a value of 0 on the NRS 0–10. In addition, the Wallace criteria (20) were applied to define inactive disease and remission in patients (n=234) for whom physician reports were available.

Statistical analysis

The prevalence rates of the specific comorbidities were compared with those of an age- and gender-matched control cohort that was sampled from the general population. The control cohort was selected from the German Health Survey GEDA (Public Use File GEDA 2009, Robert Koch Institute, Berlin, Germany, 2011). The survey investigated the sociodemographic status and the self-reported health state in a representative group of the general population. To select a control group from the population cohort for this study, propensity score matching was applied to achieve balance with respect to gender and age between the study sample and the population sample. The propensity score is the conditional probability of being in the study sample given a particular age and gender.

The matching was performed with the nearest neighbourhood method with a ratio of 1:2 (mean age: JuMBO 20±2.7, controls 20±2.8; female: JuMBO 71%, controls 73%). The comorbidity rates for the case control analyses were compared using the McNemar test.

The association of the clinical characteristics and the patients' current health status with the existence of at least one comorbid disease was analysed with linear regression models for continuously distributed variables and logistic regression models for categorical data (21). The standard errors were estimated with a Taylor series linearisation method (22).

A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS software (version 9.1.3; SAS Institute, Cary, NC).

Results

Patient characteristics

Comorbidity self-reports were available for 344 (84%) patients with JIA. The patients with no comorbidity self-report did not significantly differ in respect to sociodemographic variables and clinical characteristics from the analysis sample (data not shown). Patients had a mean age of 19.7 years and a mean disease duration of 10.6 years. Their characteristics are summarised in Table I. Twenty-five percent of the patients had an inactive disease according to patients' self-ratings. According to physicians' ratings, 22.2% had an inactive disease and 20.1% were in remission on drugs at the last visit.

Prevalence of comorbidities

Sixty two percent of the JIA patients reported at least one comorbid condition. All queried disease categories are shown in Table II with the most frequently reported individual conditions. Two of the patients who reported having amyloidosis had soJIA and one RF-negative PA. In one patient, the

amyloidosis led to renal insufficiency. There were no malignant tumours, tuberculosis, chronic viral infection (*e.g.* hepatitis B or C) or drug abuse reported. The prevalence of a disease among the JIA patients was compared with certain diseases in the population from which data were available from the population survey (see Table II). With regard to those comorbid conditions for which comparative data were available from the general population, no significantly increased frequency was observed in the JIA cohort. This even applied to depression, which was reported significantly less often by the JIA patients compared to the controls (4.9% *vs*. 9.0%, p=0.04). The prevalence of comorbidities differed significantly among the various JIA subgroups (Table III). The highest prevalence of comorbidities was found among the patients with soJIA (80.0%), even though these patients had no disease-related comorbid conditions such as uveitis or psoriasis. In soJIA, cardiovascular diseases (40.6%), in particular hypertension (26.7%), were the most commonly reported comorbidities in 6 patients. Most of the CVD cases had hypertension (73.4%). In addition, 1 case each with aortic insufficiency and thrombosis was reported. Coronary heart disease, myocardial infarction or stroke was not reported. Thirty-three percent of the JIA-patients had never been treated with corticosteriods. The treatment rate was 48.2% in patients with CVD and 31.7% in patients without CVD, respectively. This difference was not significant. Patients with soJIA received corticosteriods in 69.2%.

Table II. Lifetime prevalence of comorbidity in JIA patients. If available, comparator prevalence in an age- and gender-matched control group from a community sample is given.

	JIA patients		Control cohort[a]		
	n	%	n	%	Statistics[b]
n	344		688		
Any comorbid condition	214	62.2			
Cardiovascular diseases	34	9.9	57	8.3	S=1.09; p=0.343
Hypertension	25	7.3	54	7.9	S=0.17; p=0.759
Cardiac insufficiency	1	0.3	8	1.2	S=3.60; p=0.111
Pulmonary diseases	28	8.1			
Asthma	26	7.6	69	10.1	S=3.06; p=0.098
Gastrointestinal diseases	14	4.1	72	10.5	S=19.76; p<0.001
Crohn's disease	4	1.2			
Ulcerative colitis	3	0.9			
Gastrointestinal ulcer	1	0.3	9	1.3	S=4.45; p=0.065
Liver and gallbladder diseases	3	0.9	6	0.8	S=3.57; p=0.125
Diseases of the kidneys or the					
Urinary tract	16	4.7			
Renal insufficiency	1	0.3	9	1.3	S=4.45; p=0.064
Kidney stone	4	1.2			
Amyloidosis	3	0.9			
Gynecological diseases	12	5.0			
Haematological diseases	23	6.7			
Anaemia	11	3.2			
Iron deficiency	6	1.7			
Allergic diseases	84	24.4			
Allergic rhinitis	50	14.5			
House dust mite allergy	16	4.7			
Thyroid/endocrine diseases	23	6.7			
Hypothyroidism	7	2.0			
Hashimoto thyreoiditis	4	1.2			
Diabetes mellitus	3	0.9	11	1.6	S=1.47; p=0.332
Skin diseases	67	19.5			
Psoriasis	22	6.4			
Atopic dermatitis	30	8.7			
Eye diseases	80	23.3			
Uveitis	59	17.7			
Cataract	3	0.9	6	0.9	S=0.05; p=0.956
Glaucoma	9	2.6			
Other eye diseases	8	1.6			
Neurologic diseases	41	11.9			
Migraine	30	8.7			
Epilepsy	5	1.5			
Psychiatric disorders	32	9.3			
Depression	17	4.9	62	9.0	S= 8.91; p=0.004
Anxiety disorder	7	2.0			
Other comorbidities	30	8.7			
Osteoporosis	11	3.2	0	0.0	-

[a]Controls drawn from a community sample in Germany (GEDA), matched by age and gender by propensity scores; [b]McNemar test for matched pairs, S: test statistics; [c]Other eye diseases: episcleritis (n=1), scleritis (n=2), sicca syndrome, sicca symptoms (n=3) chronic conjunctivitis (n=1), astigmatism (n=1), benign eye tumour (n=1).

Correlation of comorbidity with clinical and demographic parameters

Patients with at least one comorbidity had received significantly more DMARDs in the past and were significantly more often ANA positive (Table IV). In contrast, we did not find any association of age, gender, duration of disease, cumulative duration of etanercept treatment or HLA-B27 positivity with comorbidity.

Impact of comorbidities on patients' self-reported current health state

The group of patients with at least one comorbid condition had a significantly higher disease activity, suffered significantly more often from fatigue and pain, had a significantly lower functional capacity, and valued their physical but not their psychosocial health significantly less than those without any comorbidity (Table IV). The presence of any comorbidity (SF-36 PCS:beta =-6.1, p<0.001; SF-36 MCS:beta =-2.6, p=0.017) and the level of disease activity (SF-36 PCS:beta =-2.6, p<0.001; SF-36 MCS:beta =-0.5, p<0.001) were independent predictors of a lower SF-36 PCS score and SF-36 MCS score, respectively. A more detailed analysis

Table III. Distribution of characteristics in the JIA subgroups (n=344).

	Years since symtom onset[a]	Ever treated with etanercept[b] (n=278)	Any comorbidity[b] (n=214)	Number of comorbidities[a]	Uveitis[b] (n=59)	Cardiovascular disease[b] (n=34)
	Mean (SD)	n (%)	n (%)	Mean (SD)	n (%)	n (%)
soJIA	13.8 (6.8)	14 (93.3)	12 (80.0)	1.8 (1.4)	0 (0.0)	6 (40.6%)
Pers. OA	9.1 (5.3)	7 (25.0)	15 (53.6)	0.8 (1.0)	4 (14.3)	1 (3.6%)
Ext. OA	14.6 (5.2)	43 (86.0)	33 (66.0)	1.3 (1.3)	21 (42.0)	7 (14.0%)
RF-neg. PA	11.1 (6.0)	81 (89.0)	50 (54.9)	1.0 (1.2)	10 (11.0)	7 (7.7%)
RF-pos. PA	10.0 (4.9)	36 (97.3)	24 (64.9)	1.3 (1.3)	1 (2.7)	2 (5.4%)
ERA	7.9 (3.9)	61 (81.3)	44 (58.7)	1.3 (1.3)	18 (24.0)	6 (9.3%)
PsA	9.6 (4.7)	27 (73.0)	28 (75.7)	1.3 (1.2)	5 (13.5)	3 (8.1%)
Other arthritis	10.8 (5.3)	9 (81.8)	8 (72.7)	1.7 (1.5)	0 (0.0)	2 (18.2%)

[a]Group effect by F-Test: years since symptom onset: F=8.45, $p<0.001$; mean number of comorbidities: F=1.48, $p=0.173$; [b]Group effect by Wald-Test: ever treatment with etanercept $\chi^2=45.2$, $p<0.001$; any comorbid condition: $\chi^2=8.9$, p=0.264; Uveitis: Chi2=24.8, $p=0.001$; cardiovascular disease: $\chi^2=15.2$, $p=0.033$.

Table IV. Association of current health status and patients characteristics with the occurrence of at least one comorbid condition.

	No comorbidity[a]	Any comorbid condition	
	Mean (SD)	Mean (SD)	MD (p-value)/ OR (p-value)[b]
n	130	214	
Female, n (%)	85 (65.4)	153 (71.5)	1.3 (0.235)
Years since symtom onset	10.3 (5.3)	10.8 (5.8)	0.5 (0.396)
Number of DMARDs ever received	2.4 (0.9)	2.6 (1.3)	0.4 (0.026)
Cumulative years of etanercept treatment	4.3 (2.8)	4.1 (2.7)	-0.1 (0.740)
Positive ANA test, n (%)	20 (21.7)	72 (42.9)	2.7 (0.003)
Positive HLA-B27 test, n (%)	31 (34.1)	46 (28.2)	0.8 (0.331)
Patient's current self-reported health status			
Disease activity (NRS 0–10)	2.0 (2.1)	2.9 (2.7)	0.9 (<0.001)
Fatigue (NRS 0–10)	2.1 (2.2)	3.2 (2.8)	1.1 (<0.001)
Pain (NRS 0–10)	2.1 (2.0)	3.2 (2.5)	1.2 (<0.001)
HAQ (score 0–3)	0.2 (0.5)	0.5 (0.6)	0.3 (<0.001)
SF36, MCS	51.3 (8.0)	48.8 (10.6)	-2.6 (0.017)
SF36, PCS	48.8 (9.0)	42.7 (11.5)	-6.1 (<0.001)

[a]Reference group; [b]MD: mean difference between patients with no comorbidity and patients with at least one comorbid condition for continuously distributed variables; OR: Odds ratio for categorical variable.

suggested that the comorbidity status and disease activity contributed equally to a lower SF-36 MCS score, whereas disease activity was a stronger predictor of a lower SF-36 PCS score.

In contrast to this, an influence of the most common comorbidity, *i.e.* uveitis, on the current self-reported health status was not found. While disease duration was significantly associated with uveitis ($p<0.001$), the patient's current functional status or HRQoL was not influenced by the whether a patient had ever had uveitis. Patients with psoriasis, however, had a lower SF-36 MCS score (44.8 [SD 13.9], beta =-5.3, $p=0.013$) and a lower SF-36 PCS score (39.4 [SD 13.7], beta =-6.0, $p=0.013$) than those without psoriasis.

Discussion

Comorbidity is known to affect the long-term outcome of patients with rheumatic diseases. The presence of comorbidities is associated with reductions in HRQoL and predicts future health care utilisation, additional comorbidity and mortality in adult-onset diseases (23). Using data from the German biologics register for young adults, we studied the prevalence and impact of comorbidity in a collective of severely affected patients with juvenile-onset arthritis.

Comorbidity in rheumatic diseases can be causally linked to the process, to the treatment or independently found. It is hardly possible to assess whether comorbidity is caused by the disease itself or the therapy. In this study, all conditions reported were regarded as comorbidities, whether or not related to JIA or its treatment. Of note, patients may have different thresholds for reporting. Patients report on a "disease" or "condition" if signs or symptoms occur to a sufficient level of severity and/or frequency and are acknowledged by the patient as a problem (14). Thus, recorded comorbid conditions may comprise a spectrum that ranges from symptoms to serious illnesses.

In this study, the most frequently reported comorbid condition was uveitis, with a prevalence of 17.7%. It has been repeatedly shown that uveitis persists in half of the JIA patients into adult life and results in a relevant vision loss in one third of the affected patients (24). Given this, it is noteworthy that patients with uveitis rated their HRQoL as not significantly worse than those without uveitis. It could be speculated that either uveitis was inactive in a relevant portion of patients or that the SF-36 might not correctly reflect the impact caused by uveitis, as was shown for other instruments by Angeles-Han *et al*. (25).

In contrast to uveitis, psoriasis, another extra-articular JIA manifestation, was associated with lower psychosocial and physical health. Several studies have shown the great impact of psoriasis on HRQoL (26, 27). Much of the impact of psoriatic arthritis on mental health was attributed to the skin disease (28). Additionally, it is known that depression and anxiety are associated with psoriasis (27). However, in this study, these psychological comorbidities were not observed more frequently in the psoriasis patients.

In addition to the extra-articular JIA manifestations, allergic disorders and asthma were the most common comorbidities, with a prevalence of asthma that was equal to that in the general population. These data do not support

the hypothesis of an inverse correlation of allergic diseases and asthma with JIA, which was deduced from the immunological paradigm of Th1 and Th2-dominated diseases (29).

Cardiovascular diseases (CVDs) were the next most frequently stated comorbid conditions after extra-articular JIA manifestations and allergic disorders. CVDs are of particular importance for the patients' long-term outcomes. In RA and systemic lupus erythematosus (SLE), the increase in CVD prevalence is due in part to both the cumulative burden of inflammation and the increased prevalence – or altered properties – of traditional cardiovascular risk factors (30). RA and SLE patients have accelerated arteriosclerosis and a higher prevalence of coronary heart disease and congestive heart failure than the general population (30-32). Subclinical atherosclerosis has been recently also verified in children with JIA, in particular in those with soJIA (33). Consistent with this trend, we demonstrate that patients with soJIA have a higher prevalence of CVDs in their very early adult years compared with the general population. More than 40% of these patients reported CVDs, whereas in the other JIA subgroups, CVD prevalence ranged from only 4 to 18%. Given the high level of systemic inflammation and the frequent use of corticosteroids in patients with soJIA, it is not surprising that they are at highest risk for developing CVD among all JIA patients (34, 35). Most of the soJIA patients with CVD had hypertension, while coronary heart disease, myocardial infarction or stroke were not reported. Hypertension is regarded as a traditional CVD risk factor and has been more commonly observed in patients with SLE than in the general population. It is not clear whether hypertension is also more common among RA patients. A recent meta-analysis of seven case-control studies has found the prevalence of hypertension to be the same in patients with RA as in controls (OR 1.09, 95%CI 0.91–1.31) (36). However, there is evidence to link hypertension with disease activity in RA, and with several anti-rheumatic drug treatments including steroids (30). Those factors may have played a role with regard to the higher CVD prevalence found in the soJIA patients, but this requires verification in additional studies.

Coexisting conditions substantially affect the outcomes of interest such as physical functioning and overall health status (37). This was demonstrated in this study, where in addition to disease activity, comorbidity had a significant influence on the patients' health status. In fact, the group of JIA patients with comorbidities judged their current health and functioning lower than those without comorbidities. Altogether, more than 60% of the adult JIA patients reported at least one comorbid condition. This prevalence is similar to that reported in other studies on adult patients with RA, AS and PsA (23, 37, 38). With regard to the entire JIA cohort, conditions for which comparative data from the general population were available were not observed more frequently. Depression was even found to be significantly less frequent among the JIA patients. This finding is in contrast to those of other studies of patients with chronic diseases and requires further investigation (39-41).

The results presented have to be considered in light of the study limitations. First, our sample did not comprise an incidence-based JIA cohort but rather involved a severely affected JIA cohort, and therefore, the data are not representative of the entire JIA group. We may have therefore overestimated the comorbidity in JIA. Second, the presence of comorbidities was determined through patient questionnaires. The ascertainment of comorbidity in the self-report research setting is associated with problems, as already discussed above. For example, different patients, but also patients and controls, may have different thresholds to report conditions, which may have biased our results.

Furthermore, the cross-sectional design limits the analysis of the associated factors with physical function and HRQL and does not allow definitive conclusions to be drawn about the strength of the cause-effect relationships.

Despite these limitations, our study is the first to provide detailed data on comorbidities in adult JIA that have not yet been reported. It demonstrates that comorbidity which is mainly disease-related has a significant impact on patients' perceived health. Prospective long-term studies are needed to identify modifying factors to prevent comorbidity in adult JIA.

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References

1. FLATO B, LIEN G, SMERDEL A *et al*.: Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. *J Rheumatol* 2003; 30: 386-93.
2. OEN K: Long-term outcomes and predictors of outcomes for patients with juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2002; 16: 347-60.
3. PACKHAM JC, HALL MA: Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology* (Oxford) 2002; 41: 1428-35.
4. RUSSO RA, KATSICAS MM: Global damage in systemic juvenile idiopathic arthritis: preliminary early predictors. *J Rheumatol* 2008; 35: 1151-6.
5. SARMA PK, MISRA R, AGGARWAL A: Physical disability, articular, and extra-articular damage in patients with juvenile idiopathic arthritis. *Clin Rheumatol* 2008; 27: 1261-5.
6. VIOLA S, FELICI E, MAGNI-MANZONI S *et al*.: Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 2092-102.
7. NORDAL E, ZAK M, AALTO K *et al*.: Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. *Arthritis Rheum* 2011; 63: 2809-18.
8. BALDINI C, DELLE SEDIE A, BOMBARDIERI S: From clinical trials to the bedside: how can we treat patients with rheumatoid arthritis and concurrent morbidities who are generally excluded from randomised controlled clinical trials? *Clin Exp Rheumatol* 2005; 23: 893-904.
9. WASKO MC: Comorbid conditions in patients with rheumatic diseases: an update. *Curr Opin Rheumatol* 2004; 16: 109-13.
10. MINDEN K, NIEWERTH M, ZINK A *et al*.:

Long-term outcome of patients with JIA treated with etanercept, results of the biologic register JuMBO. *Rheumatology* (Oxford) 2012; 51: 1407-15.
11. BAYLISS EA, ELLIS JL, STEINER JF, MAIN DS: Initial validation of an instrument to identify barriers to self-management for persons with co-morbidities. *Chronic Illn* 2005; 1: 315-20.
12. GREENFIELD S, SULLIVAN L, DUKES KA, SILLIMAN R, D'AGOSTINO R, KAPLAN SH: Development and testing of a new measure of case mix for use in office practice. *Med Care* 1995; 33 (Suppl.): AS47-AS55.
13. KATZ JN, CHANG LC, SANGHA O, FOSSEL AH, BATES DW: Can comorbidity be measured by questionnaire rather than medical record review? *Med Care* 1996; 34: 73-84.
14. WOLFE F, MICHAUD K, LI T, KATZ RS: Chronic conditions and health problems in rheumatic diseases: comparisons with rheumatoid arthritis, noninflammatory rheumatic disorders, systemic lupus erythematosus, and fibromyalgia. *J Rheumatol* 2010; 37: 305-15.
15. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-2.
16. HORNEFF G, SCHMELING H, BIEDERMANN T *et al*.: The German etanercept registry for treatment of juvenile idiopathic arthritis. *Ann Rheum Dis* 2004; 63: 1638-44.
17. BRUCE B, FRIES JF: The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003; 30: 167-78.
18. WARE JE, JR., SHERBOURNE CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-83.
19. GABRIEL SE, MICHAUD K: Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009; 11: 229.
20. WALLACE CA, GIANNINI EH, HUANG B, ITERT L, RUPERTO N: American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res* (Hoboken) 2011; 63: 929-36.
21. MCCULLAGH P, NELDER JA: Generalized Linear Models. 2nd Edition.
22. WOLTER KM: Introduction to Variance Estimation. 2nd Edition; 2003; New York: Springer.
23. GABRIEL SE, CROWSON CS, O'FALLON WM: Comorbidity in arthritis. *J Rheumatol* 1999; 26: 2475-9.
24. SKARIN A, ELBORGH R, EDLUND E, BENGTSSON-STIGMAR E: Long-term follow-up of patients with uveitis associated with juvenile idiopathic arthritis: a cohort study. *Ocul Immunol Inflamm* 2009; 17: 104-8.
25. ANGELES-HAN ST, GRIFFIN KW, LEHMAN TJ *et al*.: The importance of visual function in the quality of life of children with uveitis. *J AAPOS* 2010; 14: 163-8.
26. VARNI JW, GLOBE DR, GANDRA SR, HARRISON DJ, HOOPER M, BAUMGARTNER S: Health-related quality of life of pediatric patients with moderate to severe plaque psoriasis: comparisons to four common chronic diseases. *Eur J Pediatr* 2012; 171: 485-92.
27. MEASE PJ, MENTER MA: Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. *J Am Acad Dermatol* 2006; 54: 685-704.
28. STRAND V, SHARP V, KOENIG AS *et al*.: Comparison of health-related quality of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept treatment. *Ann Rheum Dis* 2012; 71: 1143-50.
29. HEINZMANN A, JERKIC SP, GANTER K *et al*.: Association study of the IL13 variant Arg110Gln in atopic diseases and juvenile idiopathic arthritis. *J Allergy Clin Immunol* 2003; 112: 735-9.
30. SYMMONS DP, GABRIEL SE: Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. *Nat Rev Rheumatol* 2011; 7: 399-408.
31. MARADIT-KREMERS H, NICOLA PJ, CROWSON CS, BALLMAN KV, GABRIEL SE: Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005; 52: 722-32.
32. HERSH AO, TRUPIN L, YAZDANY J *et al*.: Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2010; 62: 1152-9.
33. VLAHOS AP, THEOCHARIS P, BECHLIOULIS A *et al*.: Changes in vascular function and structure in juvenile idiopathic arthritis. *Arthritis Care Res* (Hoboken) 2011; 63: 1736-44.
34. MAZZANTINI M, TALARICO R, DOVERI M *et al*.: Incident comorbidity among patients with rheumatoid arthritis treated or not with low-dose glucocorticoids: a retrospective study. *J Rheumatol* 2010; 37: 2232-6.
35. FROSCH M, ROTH J: New insights in systemic juvenile idiopathic arthritis--from pathophysiology to treatment. *Rheumatology* (Oxford) 2008; 47: 121-5.
36. BOYER JF, GOURRAUD PA, CANTAGREL A, DAVIGNON JL, CONSTANTIN A: Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. *Joint Bone Spine* 2011; 78: 179-83.
37. SALAFFI F, CAROTTI M, GASPARINI S, INTORCIA M, GRASSI W: The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. *Health Qual Life Outcomes* 2009; 7: 25.
38. RUPP I, BOSHUIZEN HC, JACOBI CE, DINANT HJ, VAN DEN BOS G: Comorbidity in patients with rheumatoid arthritis: effect on health-related quality of life. *J Rheumatol* 2004; 31: 58-65.
39. GOULIA P, PAPADIMITRIOU I, MACHADO MO *et al*.: Does psychological distress vary between younger and older adults in health and disease? *J Psychosom Res* 2012; 72: 120-8.
40. PINQUART M, SHEN Y: Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. *J Pediatr Psychol* 2011; 36: 375-84.
41. CHITTLEBOROUGH CR, WINEFIELD H, GILL TK, KOSTER C, TAYLOR AW: Age differences in associations between psychological distress and chronic conditions. *Int J Public Health* 2011; 56: 71-80.