Risk Markers of Juvenile Idiopathic Arthritis-associated Uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry

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ABSTRACT. ***Objective.*** To characterize the epidemiology and clinical course of children with juvenile idiopathic arthritis-associated uveitis (JIA-U) in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry and explore differences between African American (AA) and non-Hispanic white (NHW) children.

Methods. There were 4983 children with JIA enrolled in the CARRA Registry. Of those, 3967 NHW and AA children were included in this study. Demographic and disease-related data were collected from diagnosis to enrollment. Children with JIA were compared to those with JIA-U. Children with JIA-U were also compared by race.

Results. There were 459/3967 children (11.6%) with JIA-U in our cohort with a mean age (SD) of 11.4 years (± 4.5) at enrollment. Compared to children with JIA, they were younger at arthritis onset, more likely to be female, had < 5 joints involved, had oligoarticular JIA, and were antinuclear antibody (ANA)-positive, rheumatoid factor (RF)-negative, and anticitrullinated protein antibody-negative. Predictors of uveitis development included female sex, early age of arthritis onset, and oligoarticular JIA. Polyarticular RF-positive JIA subtype was protective. Nearly 3% of children with JIA-U were AA. However, of the 220 AA children with JIA, 6% had uveitis; in contrast, 12% of the 3721 NHW children with JIA had uveitis.

Conclusion. In the CARRA registry, the prevalence of JIA-U in AA and NHW children is 11.6%. We confirmed known uveitis risk markers (ANA positivity, younger age at arthritis onset, and oligoarticular JIA). We describe a decreased likelihood of uveitis in AA children and recommend further exploration of race as a risk factor in a larger population of AA children. (J Rheumatol First Release Nov 1 2013; 10.3899/jrheum.130302)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS UVEITIS RISK MARKERS OUTCOMES

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood, with an annual incidence of 2 to 20 per 100,000 children, and a prevalence of 16 to 150 per 100,000[1,2]. It is a chronic arthritis of unknown etiology with 7 subtypes — oligoarticular persistent, oligoarticular extended, polyarticular rheumatoid factor (RF)-positive, polyarticular RF-negative, systemic, psoriatic, enthesitis-related, and undifferentiated JIA. Although JIA is the most commonly used classification scheme, other categorizations include juvenile rheumatoid arthritis (JRA), consisting of 3 subtypes (pauciarticular, polyarticular, and systemic) and juvenile chronic arthritis with 4 subtypes (pauciarticular, polyarticular, systemic, and juvenile psoriatic).

JIA-associated uveitis (JIA-U), also known as iritis or iridocyclitis, is the most prevalent extraarticular manifestation of JIA in North America and occurs in 10-20% of

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children with JIA[3,4,5,6,7,8,9,10,11,12]. It is a nongranulomatous chronic anterior eye inflammation that can cause vision loss and blindness and accounts for up to 80% of all pediatric anterior uveitis[3].

Risk factors for uveitis. Uveitis is potentially blinding with a chronic and often relapsing course. Almost 80% of children have bilateral disease[13,14]. Risk factors associated with uveitis development include early age of arthritis onset, sex, short disease duration, arthritis subtype, and antinuclear antibody (ANA) seropositivity[15,16,17,18]. The American Academy of Pediatrics (AAP) Sections on Rheumatology and Ophthalmology have recommended screening guidelines for uveitis in children with JRA based on ANA seropositivity, JRA subtype, age at arthritis onset, and arthritis duration[19,20].

Few studies on JIA-U focus on African American (AA) children[21,22,23]. In this population, the role of ANA is unclear, predisposition to JIA subtype differs, and there appears to be a lower risk of uveitis compared to non-Hispanic white (NHW) children. Hence, the risk for JIA-U may differ by race and should be explored.

Most studies in JIA-U are conducted in small samples. Our objective is to characterize the epidemiology and clinical characteristics of children with JIA-U in a large sample of AA and NHW children with JIA in a multicenter registry, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

MATERIALS AND METHODS

This is a cross-sectional study based on a multicenter registry with 56 participating centers in the United States. The registry actively enrolls children with varied rheumatic diseases. Children with JIA alone and JIA-U were enrolled from May 2010 to June 2012. JIA was diagnosed by the treating physician based on the International League of Associations for Rheumatology JIA classification[24]. Investigational Review Board approval was obtained. Demographic and disease-related data were collected from time of diagnosis to enrollment visit. Race and ethnicity were self-reported by the parent, and we included only children reported exclusively as NHW or AA. We excluded children with missing data on race and ethnicity, and children with > 1 race listed.

Data collection. Data collection was based on medical chart review, physician assessment, patient/parent recall, and physician/parent/patient completion of subjective measures. Disease-related data included age at arthritis onset, JIA subtype, presence of uveitis, number of joints ever affected (< 5 or > 5 joints that have had swelling, pain on movement, tenderness, or limitation of movement), radiographic evidence of joint damage, laboratory measures [ANA, RF, and anticitrullinated protein antibody (ACPA) positivity or negativity] and HLA-B27 status.

Quality of life (QOL), function, and disease activity were assessed at time of enrollment. Children completed assessments if > 10 years of age. Measures included (1) physician global assessment of disease activity (0, not active to 10, very active), (2) health-related QOL ("How do you rate your child's health?" — excellent, very good, good, poor, very poor), and (3) parent/patient overall well-being score ("Considering all the ways that your child's rheumatic condition affects your child, rate how your child is doing": 0, very well to 10, very poor). A patient/parent pain scale score ("How much pain do you think your child had because of his/her rheumatic condition in the past week?" 0, no pain to 10, very severe pain) was also recorded. Children > 9 years of age completed the Faces Pain Scale-Revised[25,26]. The Childhood Health Assessment Questionnaire (CHAQ), a valid and reliable instrument that measures physical disability, was also completed. Twenty questions encompass 8 functional components: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each domain consists of 3 measures: (1) difficulty in performing daily functions, (2) use of special aids or devices, and (3) activities that require assistance from another person. Scores range from 0 to 3[27]. Greater scores indicate worse QOL, activity level, pain, or physical function.

Statistics. All statistical analyses were conducted in SAS 9.2. Statistical significance was assessed at the 0.05 level of significance. Differences in demographic and clinical characteristics between children with JIA alone and JIA-U were compared using chi-squared tests, 2-sample tests, or Wilcoxon rank-sum tests, as appropriate. Logistic regression was used to calculate OR to estimate univariate associations between patient characteristics and the primary outcome, disease type (JIA or JIA-U). We analyzed the following characteristics as potential risk factors: sex, race, age at arthritis onset (yrs), JIA subtype, HLA-B27 positivity, ANA positivity, RF positivity, and ACPA positivity. For all analyses, the reference group was JIA alone.

Based on the results from the univariate analysis, we constructed multivariable logistic regression models using significant predictors ($p < 0.1$) from the univariate results to identify an optimal subset of risk markers that best predicted JIA-U. Prior to model construction, potential predictors were correlated to identify any potential sources of multicolinearity. If 2 or more predictors were significantly correlated with one another and the outcome ($p > 0.4$), then the most predictive characteristic was chosen. The final multivariate models were constructed using a modified backward elimination procedure. In short, nonsignificant predictors ($p > 0.05$) were systematically removed until a significant increase in model fit (based on Akaike information criteria and log-likelihood) could no longer be obtained or all of the predictors in the model were significant at the 0.05 level. The predictive power of the final model was assessed by calculating the area under the curve for the receiver-operating characteristic curve.

RESULTS

Demographics. In our cohort of 3967 children, the overall mean age (± SD) at study enrollment was 11.4 years (± 4.7). Females comprised 72%, and 5.6% were AA (Table 1). There were 459 of 3967 children (11.6%) diagnosed with uveitis, of whom 13 (2.8%) were AA. However, of the 220 AA children diagnosed with JIA, only 6% developed uveitis compared to 12% (446/3747) of NHW children with JIA ($p = 0.007$).

Disease characteristics. Children with JIA-U had a mean age (± SD) of 4.2 years (± 3.6) at time of arthritis diagnosis and were significantly younger compared to children with JIA alone, with a mean age of 6.7 years (± 4.5; $p < 0.001$). They were more frequently of the oligoarticular persistent (42.4% vs 27.4%, $p < 0.001$) and extended (14.7% vs 7.4%, $p < 0.001$) JIA subtypes, and more likely to have fewer than 5 joints ever involved compared to JIA alone (54.8% vs 43.3%, $p < 0.001$; Figure 1). Children with JIA-U were also more frequently ANA-positive (65.4% vs 47.1%, $p < 0.001$). There was no significant difference in joint damage as evidenced by radiographic examination.

Children with JIA alone were more frequently of the systemic (8.4% vs 0.4%, $p < 0.001$), polyarticular RF-negative (31.1% vs 24.2%, $p = 0.003$), polyarticular

Table 1. Comparison of JIA and JIA-U among African American and non-Hispanic white children. Data are n (%) unless otherwise indicated.

	All JIA, n = 3967	JIA-U, n = 459	JIA Alone, n = 3508	p**
Demographic Characteristics				
Age at time of study, yrs, mean ± SD	11.4 ± 4.7	11.1 ± 4.5	11.5 ± 4.7	0.096
Sex, female	2857 (72.0)	353 (76.9)	2504 (71.4)	0.013*
Race				0.010*
Non-Hispanic white	3747 (94.5)	446 (97.2)	3301 (94.1)	
African American	220 (5.6)	13 (2.8)	207 (5.9)	
Disease Characteristics				
Age at arthritis onset, yrs ± SD	6.4 ± 4.4	4.2 ± 3.6	6.7 ± 4.5	< 0.001*
JIA subtype				< 0.001*
Systemic	295 (7.5)	2 (0.4)	293 (8.4)	< 0.001*
Polyarticular RF-negative	1188 (30.3)	109 (24.2)	1079 (31.1)	0.003*
Polyarticular RF-positive	214 (5.5)	3 (0.7)	211 (6.1)	< 0.001*
Oligoarticular persistent	1140 (29.1)	191 (42.4)	949 (27.4)	< 0.001*
Oligoarticular extended	321 (8.2)	66 (14.7)	255 (7.4)	< 0.001*
Psoriatic	251 (6.4)	31 (6.9)	220 (6.3)	0.655
Enthesitis-related	416 (10.6)	34 (7.6)	382 (11.0)	0.025*
Undifferentiated	95 (2.4)	14 (3.1)	81 (2.3)	0.313
Laboratory measures				
ANA-positive, n = 3525	1736 (49.3)	270 (65.4)	1466 (47.1)	< 0.001*
RF-positive, n = 1414	129 (9.1)	2 (1.4)	127 (10.0)	0.001*
HLA-B27–positive, n = 2165	324 (15.0)	47 (19.0)	277 (14.4)	0.057
ACPA-positive, n = 1524	145 (9.5)	4 (2.9)	141 (10.2)	0.006*
QOL Measures, mean ± SD				
Physician global assessment	1.6 ± 1.9	1.3 ± 1.7	1.6 ± 2.0	< 0.001*
CHAQ	0.36 ± 0.60	0.26 ± 0.50	0.37 ± 0.61	< 0.001*
Patient/parent pain scale score	2.6 ± 2.6	2.0 ± 2.5	2.7 ± 2.7	< 0.001*
Patient/parent overall well-being score	2.3 ± 2.3	1.9 ± 2.1	2.4 ± 2.3	< 0.001*
Health-related QOL				0.271
Excellent	957 (24.4)	124 (27.4)	833 (24.0)	
Very good	1642 (41.9)	193 (42.7)	1449 (41.8)	
Good	1196 (30.5)	119 (26.3)	1077 (31.1)	
Poor	116 (3.0)	15 (3.3)	101 (2.9)	
Very poor	10 (0.3)	1 (0.2)	9 (0.3)	
Parent/subject assessment of disease activity	2.6 ± 2.7	2.1 ± 2.6	2.6 ± 2.7	< 0.001*

* $p < 0.05$; chi-squared, 2-sample or Wilcoxon rank-sum tests; [a] Higher scores indicate worse disease; ** p value based on comparison of JIA-U vs JIA alone. CHAQ: Childhood Health Assessment Questionnaire; JIA: juvenile idiopathic arthritis; JIA-U: JIA-associated uveitis; RF: rheumatoid factor; ANA: antinuclear antibody; ACPA: anticitrullinated protein antibodies; QOL: quality of life.

RF-positive (6.1% vs 0.7%, $p < 0.001$), and enthesitis-related JIA subtypes (11% vs 7.6%, $p = 0.025$; Figure 1). They were also more frequently RF-positive (10% vs 1.4%, $p = 0.001$) and ACPA-positive (10.2% vs 2.9%, $p = 0.006$).

Measures of QOL and function. Children with JIA alone had worse physician global assessment scores (1.6 ± 2.0 vs 1.3 ± 1.7, $p < 0.001$), parent/patient overall well-being scores (2.4 ± 2.3 vs 1.9 ± 2.0, $p < 0.001$), and parent/patient assessment of disease activity (2.6 ± 2.7 vs 2.1 ± 2.6, $p < 0.001$) compared to children with JIA-U. As expected, they also had worse CHAQ scores (0.37 ± 0.61 vs 0.26 ± 0.50; $p < 0.001$), and reported higher pain scores (2.7 ± 2.7 vs 2.0 ± 2.5; $p < 0.001$). However, there were no significant differences in health-related QOL scores.

Risk factors for JIA-U. The results of the univariate and multivariate analyses are provided in Tables 2 and 3. Of the 15 risk factors examined, 12 were significantly associated with JIA-U. Prior to multivariate analysis, potential risk factors were correlated to identify potential sources of multicolinearity. Polyarticular RF-negative and oligoarticular persistent JIA were found to be significantly negatively correlated (r –0.42, $p < 0.001$) because these 2 subtypes accounted for about 67% (300/450) of all JIA-U cases. Thus, if a patient did not have the oligoarticular persistent subtype, then they were highly likely to have the polyarticular RF-negative subtype or vice versa. Because patients with JIA-U had a higher prevalence of the oligoarticular persistent subtype, the polyarticular RF-negative subtype was eliminated from model consideration. In

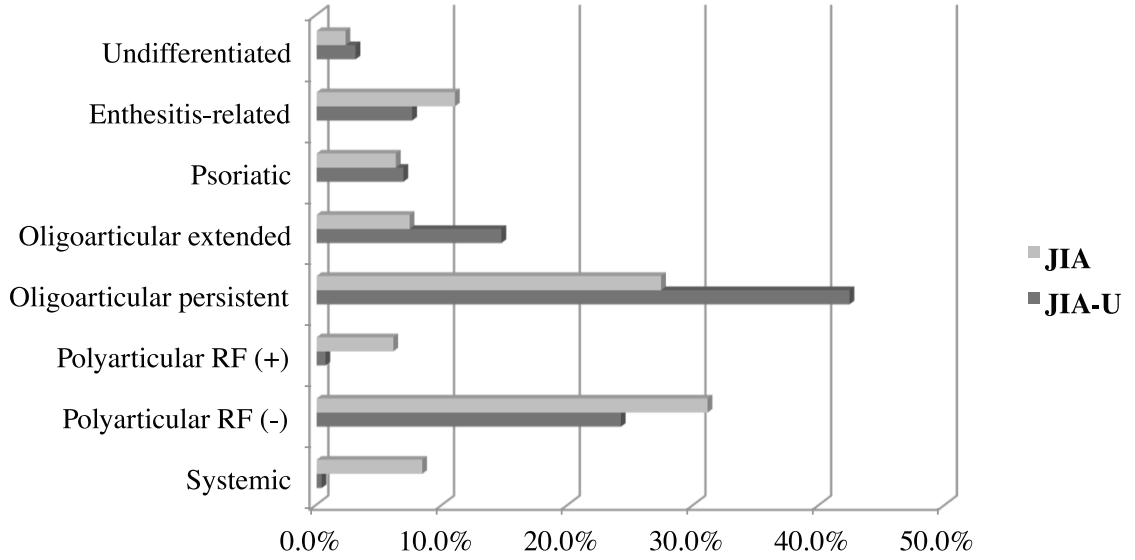

Figure 1. Frequency of juvenile idiopathic arthritis (JIA) subtypes in children with and without JIA-associated uveitis. JIA-U: JIA-associated uveitis; RF: rheumatoid factor.

Table 2. Patient risk factors associated with juvenile idiopathic arthritis-associated uveitis (JIA-U).

Risk Factor	Univariate OR (95% CI)
Sex (female)	1.34 (1.00–1.68)*
Race (African American)	0.47 (0.26–0.82)**
Age at arthritis onset	0.86 (0.83–0.88)***
JIA subtype	
Systemic	0.05 (0.01–0.19)***
Polyarticular RF-negative	0.70 (0.56–0.88)**
Polyarticular RF-positive	0.10 (0.03–0.32)***
Oligoarticular persistent	1.93 (1.58–2.36)***
Oligoarticular extended	2.15 (1.61–2.87)***
Psoriatic	1.08 (0.74–1.60)
Enthesitis related	0.66 (0.46–0.94)*
Undifferentiated	0.75 (0.42–1.33)
Laboratory data	
ANA-positive	2.12 (1.71–2.63)***
RF-positive	0.13 (0.03–0.54)**

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. RF: rheumatoid factor; ANA: antinuclear antibody.

addition, systemic JIA was associated with JIA but not with uveitis. However, with only 2 patients in the JIA-U sample, this did not retain significance in the multivariate model.

After multivariate logistic modeling (Table 3), significant positive predictors of JIA-U were female sex, younger age of onset, ANA positivity, oligoarticular persistent JIA, and oligoarticular extended JIA. In addition, polyarticular RF-positive JIA was protective against JIA-U. A significant interaction between sex and age of onset was detected ($p = 0.049$). Regardless of disease (JIA or JIA-U), females had earlier onset of arthritis than males; however, the difference in age of onset between males and females with JIA was not as pronounced as in JIA-U. For JIA alone, the average age of onset of symptoms in males was 7.3 years (95% CI 6.9–7.5) and in females was 6.5 years (95% CI 6.3–6.7). In contrast, in patients with JIA-U, the average age of onset of symptoms in males was 5.9 years (95% CI 5.0–6.7) and in females was 3.8 years (95% CI 3.4–4.1). The area under the receiver-operating curve for the final model was 0.714, indicating fair accuracy of the model.

Table 3. OR and 95% CI for significant predictors of juvenile idiopathic arthritis-associated uveitis.

Predictor	OR	95% CI
Sex (female vs male)	1.36	(0.86–2.11)
Age of onset	0.92	(0.87–0.98)
Sex × age of onset (female only)	0.93	(0.87–0.999)
ANA-positive (yes vs no)	1.61	(1.27–2.05)
Polyarticular RF-positive (yes vs no)	0.26	(0.08–0.82)
Oligoarticular persistent (yes vs no)	1.61	(1.27–2.05)
Oligoarticular extended (yes vs no)	1.89	(1.34–2.67)

ANA: antinuclear antibody; RF: rheumatoid factor.

Racial differences in uveitis. Although these results are underpowered because there were few AA children with uveitis in our cohort, we performed a subanalysis comparing AA and NHW children to provide preliminary data and assess racial differences in uveitis that have not been previously explored (Table 4). Of the 459 children with JIA-U, 446 were NHW and 13 were AA. NHW children had a higher prevalence of uveitis compared to AA children

Table 4. Comparison of African American (AA) and non-Hispanic white children with juvenile idiopathic arthritis-associated uveitis (JIA-U).

	AA, n = 13	White, n = 446	p*
Demographic characteristics			
Age at time of study, yrs, mean ± SD	12.3 ± 4.6	11.1 ± 4.5	0.352
Sex, female, n (%)	8 (61.5)	345 (77.4)	0.315
Disease characteristics			
Age at arthritis onset, yrs ± SD	8.0 ± 5.1	4.2 ± 3.5	0.035*
JIA subtype, n (%)			0.138
Systemic	0 (0.0)	2 (0.4)	1.000
Polyarticular RF-negative	1 (7.7)	108 (24.7)	0.168
Polyarticular RF-positive	0 (0.0)	3 (0.7)	1.00
Oligoarticular persistent	5 (38.5)	186 (42.7)	0.815
Oligoarticular extended	2 (15.4)	64 (14.7)	0.917
Psoriatic	0 (0.0)	31 (7.1)	0.325
Enthesitis-related	4 (30.8)	30 (6.9)	0.001*
Undifferentiated	1 (7.7)	13 (3.0)	0.323
No. current active joints, mean ± SD	0.9 ± 2.0	0.8 ± 1.6	0.879
< 5 joints ever affected, n (%)	5 (41.8)	202 (45.3)	0.803
Imaging evidence of joint damage, n (%)	5 (41.7)	86 (23.1)	0.135
Laboratory data, n (%)			
ANA-positive	4 (44.4)	69 (49.6)	1.000
RF-positive	0 (0.0)	2 (1.5)	1.000
HLA-B27–positive	4 (40.0)	43 (18.1)	0.100
ACPA-positive	1 (20.0)	3 (2.3)	0.140
QOL measures[a]			
Physician global assessment	2.2 ± 1.9	1.2 ± 1.7	0.050
CHAQ	0.35 ± 0.60	0.26 ± 0.50	0.604
Patient/parent pain scale score	2.31 ± 2.18	2.02 ± 2.49	0.650
Parent/subject overall well-being score	2.38 ± 2.43	1.90 ± 2.10	0.417
Health-related QOL, n (%)			
Excellent	2 (15.4)	122 (27.8)	0.323
Very good	8 (61.5)	185 (42.1)	0.164
Good	3 (23.1)	116 (26.4)	0.787
Poor	0 (0)	15 (3.4)	0.497
Very poor	0 (0)	1 (0.2)	1.000
Parent/subject assessment of disease activity	2.38 ± 2.40	2.11 ± 2.63	0.689

* $p < 0.05$, chi-squared, 2-sample, or Wilcoxon rank-sum tests; [a] Higher scores indicate worse disease. CHAQ: Childhood Health Assessment Questionnaire; RF: rheumatoid factor; ANA: antinuclear antibody; ACPA: anti-citrullinated protein antibodies; QOL: quality of life.

(11.9% vs 5.9%, p = 0.007). AA children were more frequently older at age of arthritis onset (8.0 ± 5.1 vs 4.2 ± 3.5; p = 0.035) and were more likely to be diagnosed with enthesitis-related JIA (30.8% vs 6.9%; p = 0.001). There was no significant difference in sex, joint involvement, or laboratory status (ANA, RF, HLA-B27, and ACPA).

AA children with JIA-U also had worse physician global assessment scores, which approached significance (2.2 ± 1.9, p = 0.050). There were no significant differences in the CHAQ, the pain scale, overall well-being, health-related QOL, or parent/subject disease activity assessment scores.

DISCUSSION

In the CARRA registry, the prevalence of uveitis in AA and NHW children with JIA is 11.6%. This comprises the largest database of children with JIA and JIA-U to date. The reported prevalence of uveitis in a juvenile arthritis population has ranged widely from 10–20%, which can be attributed to the use of different juvenile arthritis classification schemes and varied followup[5,6,7,8,10,11]. There are various risk factors associated with uveitis, and race appears to be an important determinant of uveitis development because AA children developed uveitis (6%) significantly less often in comparison to NHW children (12%).

Risk factors for uveitis development. Common risk markers for uveitis development include ANA positivity, young age at arthritis onset, JIA subtypes such as oligoarticular, psoriatic, enthesitis-related, and undifferentiated JIA, and female sex[11,14,16,28,29,30,31,32,33]. The AAP guidelines recommend uveitis screening every 3 months for a child who is ANA-positive, of oligoarticular or polyarticular JRA

subtypes, has arthritis onset < 6 years of age, and < 4 years arthritis duration[19,20].

On initial analysis of our sample, a higher likelihood of having uveitis appeared to be associated with female sex, younger age at arthritis onset, oligoarticular persistent and extended JIA, and ANA positivity. Lower prevalence of JIA-U was associated with AA race, systemic JIA, polyarticular RF-negative JIA, enthesitis-related JIA, and RF-positivity. However, after performing multivariate logistic regression, only female sex, early age of arthritis onset, and oligoarticular persistent and extended JIA subtypes remained significantly associated with higher prevalence of uveitis, whereas polyarticular RF-positive JIA was associated with a lower prevalence. After controlling for these factors, race, systemic JIA, polyarticular RF-negative JIA, enthesitis-related JIA, and ACPA positivity were no longer associated with uveitis. However, these findings may be related to the small number of AA patients with uveitis and patients in the less common JIA subtypes.

JIA subtype appears to play a role in a child's susceptibility to uveitis, where oligoarticular and polyarticular RF-negative JIA have an increased likelihood of uveitis development. The significance of the extended vs persistent oligoarticular subtypes differs[11,12,14,16,28,32,34]. Of the JIA subtypes with associated uveitis in our cohort, there were 191 children (42.4%) with oligoarticular persistent JIA, 109 with polyarticular RF-negative JIA (24.2%), 66 with oligoarticular extended JIA (14.7%), 34 with enthesitis-related JIA (7.6%), 31 with psoriatic JIA (6.9%), 14 with undifferentiated JIA (3.1%), 3 with polyarticular RF-positive JIA (0.7%), and 2 with systemic JIA (0.4%; Figure 1). Hence, we confirm that children with uveitis were more likely to have oligoarticular and polyarticular RF-negative JIA and less likely to have polyarticular RF-positive and systemic JIA[10,12,29]. An important clinical application of these findings is the noted association between JIA subtype and frequency of uveitis, which can affect uveitis screening schedule and patient/parent counseling. Hence, because the current AAP guidelines focus on children with JRA, it is important to determine optimal timing for screening for children with other JIA subtypes. Heiligenhaus, *et al*[16] recommended guidelines specific for JIA and suggested assessments every 3 months for children with oligoarticular, RF-negative polyarticular, psoriatic, and undifferentiated JIA who are ANA-positive, < 6 years old at JIA onset, and have had arthritis for < 4 years[16]. Although our study also demonstrated that children with psoriatic JIA have a greater frequency of uveitis, this only approached significance. Likewise, we also showed increased JIA-U in polyarticular RF-negative JIA. Hence, the importance of other JIA subtypes requires further exploration because risk for uveitis development and need for screening may differ and are not all included in the current AAP guidelines. Studies have noted an increase in uveitis susceptibility in females and an increase in ocular complications in males[33,35]. Interestingly, we observed an interaction between female sex and young age of arthritis onset. So in our sample, the influence of age of arthritis onset on uveitis development was affected by female sex. We could hypothesize that children who are diagnosed with JIA at a very young age have an increased risk for JIA-U if they are female.

Overall, our results are consistent with the AAP guidelines and also confirm previous studies in which we noted the significance of ANA positivity, age at arthritis onset, JIA subtypes, and female sex on uveitis susceptibility, while RF did not appear to be associated with increased risk[36,37]. Only 2 reports have noted an increased association between ACPA positivity and uveitis[38,39].

The role of race in uveitis. Little is known about the effect of race on uveitis. We note that AA children appear to have a decreased risk for uveitis development because only 2.8% of all children with uveitis were AA, and there were fewer AA children diagnosed with JIA who developed uveitis compared to NHW (6% vs 12%, p = 0.007). Race plays a significant role in other conditions such as sarcoidosis and systemic lupus erythematosus. Likewise, there appears to be an association between JIA subtype and race in which children who are AA or native North American are more likely to develop polyarticular RF-positive JIA, NHW children to develop extended oligoarticular JIA and psoriatic JIA, and Asians to develop enthesitis-related JIA[23,40]. Because different races have varied risk for JIA subtypes, and the JIA subtypes vary in their risk for uveitis, race may influence uveitis susceptibility.

Most studies of JIA-U have been in children of European ancestry with only a few focused on children of AA descent[21,22,23]. In 3 studies, JIA-U prevalence ranged from 4–8% in AA children, with absence of ANA positivity. In a 1984 study, none of the 8.3% of 42 South African children diagnosed with JIA-U were ANA-positive[41]. Similarly, in 1997, 20% of 172 children with JRA were AA, 8.7% of these had uveitis, and none were ANA-positive[22]. In 2007, a study of 758 children with JIA consisting of 4% blacks demonstrated that black children had a lower risk of developing JIA-U compared to children of European ancestry[23]. In a sample of 859 children with JIA, there was a relative risk (RR) of 1.27 (p = 0.036) for developing uveitis in European children and an RR of 0.36 (p < 0.0001) in non-European children[23].

In concurrence with the literature, most children with JIA-U in our sample were NHW, because AA accounted for only 3% of the cases. As expected in children with uveitis, there were more children of the oligoarticular persistent subtype in both groups. They were similar in RF-negative status and percentage of females. AA children with uveitis were older at time of arthritis onset (8.0 ± 5.1 vs 4.2 ± 3.5,

p = 0.035). Because young age at arthritis onset is a risk factor for uveitis, this may explain why AA children have decreased uveitis[11].

Interestingly, there was no difference in ANA status. Previous studies have shown that the ANA is usually absent in AA children with uveitis. Further investigation in a larger sample of AA children is important because the ANA is taken into consideration in determining the schedule for uveitis screening in the AAP guidelines[22,41].

Because AA children appear to have a decreased risk for uveitis, and our preliminary data demonstrated significant differences in their clinical characteristics compared to NHW children, risk factors for JIA-U may differ between races. Further study into the contribution of race should be conducted. To our knowledge, no studies have examined the role of JIA subtype and race in uveitis susceptibility or severity.

QOL and function. Most studies on QOL and function in children with JIA focus on musculoskeletal disability secondary to arthritis. There is a paucity of information on vision-related QOL and visual function. In our sample, children with JIA alone had worse disease activity, overall well-being, physical function, and pain as evidenced by their scores in subjective measures. Because they were more frequently diagnosed with the JIA subtypes with greater joint involvement, they may have increased functional disability. However, information was collected later in the disease course because most children had about 5 years of arthritis prior to enrollment in the registry (age at arthritis onset 6.4 ± 4.4 yrs and age at study enrollment 11.4 ± 4.7 yrs). Their arthritis may have been better controlled, and the children may have adapted to their disease. Hence, scores may have differed if measured earlier in the disease course.

We expected children with JIA-U to score worse because they had both ocular and musculoskeletal involvement, but our results indicate otherwise. This may be due to several reasons. There were no data on the status of uveitis; therefore disease may have been quiescent or asymptomatic. Likewise, these QOL measures did not focus on the specific effect of vision-related factors. In future studies, it will be important to consider uveitis activity at time of questionnaire administration because this may affect visual function and vision-related QOL. The use of vision-specific instruments should be considered to better identify the effects of uveitis[42,43,44].

Strengths and limitations. Our sample consisted of the largest population of children with JIA and JIA-U from diverse geographic regions, which may be a true representation of JIA and uveitis in the US population. Although our sample of AA children with uveitis was small (2.8%), this was similar to findings in the literature (4-8%).

Our study was largely based on retrospective data. However, followup prospective data are currently being collected, with more detailed information on uveitis.

Owing to the large scale of this registry and limitations in data collection, not all details of arthritis or uveitis are known (i.e., date of uveitis onset, visual symptoms, disease activity, and uveitis complications such as cataracts and glaucoma). The classification of children with and without uveitis may be incorrect, especially early in the JIA disease course. Likewise, uveitis in some patients may be undiagnosed because the disease is often asymptomatic. Uveitis is known to develop in the first 4–7 years after arthritis onset; hence some children classified as JIA may later be reclassified as JIA-U[16]. However, the duration of arthritis in this sample was a mean of 5 years, and uveitis would have been expected to develop. A survival analysis would have been a better analysis of uveitis risk factors because the duration of arthritis varied. The authors currently are conducting a longitudinal study on risk factors of uveitis.

Measures of QOL and function were administered at a mean of 5 years after arthritis onset. Therefore, results may not be reflective of true disease status (damage or activity) because children may have adapted to their illness, and the resiliency and adaptability of children should be considered. Likewise, there were minimal data on uveitis at time of questionnaire completion, a factor that could affect interpretation of these measures if uveitis were active.

Only joint counts and the CHAQ were used to measure physical disability secondary to arthritis. Additionally, joint counts were measured as < or > 5 joints and not as total number of joints. In the literature, there is limited information on the QOL and function of children with JIA and uveitis because most QOL studies focus on musculoskeletal disability secondary to arthritis.

The clinical ocular examination (i.e., slit lamp examination or visual acuity) and other validated subjected measures such as the Pediatric Quality of Life Inventory to measure overall QOL, or the Effects of Youngsters' Eyesight on Quality of Life to measure visual function and vision-related QOL could be considered but may be difficult to implement in such a large sample because they are time-consuming to administer[42,43].

JIA-U was found in 11% of children with JIA in the CARRA registry, which consists of the largest sample of JIA-U to date. Although we confirm known risk markers of uveitis, we newly demonstrate that race may be a factor in uveitis development, because AA children in our sample had a decreased likelihood to develop uveitis. The role of race in uveitis should be further explored.

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APPENDIX.

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