

# Prevalence of Juvenile Idiopathic Arthritis in the Alaska Native Population

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**Objective.** To determine the prevalence and clinical characteristics of juvenile idiopathic arthritis (JIA) in Alaska Native children.

**Methods.** Potential cases of JIA were identified by querying administrative data from hospitals and clinics in the Alaska Tribal Health System for codes possibly identifying JIA. Medical record abstraction was performed to confirm criteria met for JIA, demographic and clinical characteristics, and treatment patterns. Individuals age  $\leq 18$  years with a confirmed diagnosis of JIA were included. The denominator for prevalence was the 2015 Alaska Area Indian Health Service user population age of  $\leq 18$  years.

**Results.** The unadjusted prevalence of JIA in Alaska Native children was 74.6 per 100,000 (age-adjusted 79.0 per 100,000). JIA was more common in females than males (unadjusted prevalence 105.8 versus 45.0 per 100,000). Oligoarthritis was the most common subtype (31% of cases), but polyarthritis and enthesitis-related arthritis were also common (26% and 24% of cases, respectively), with a notably high prevalence of enthesitis-related arthritis. The median age at diagnosis was 9 years. Of the combined cohort with results available, 56% were antinuclear antibody positive, 23% were rheumatoid factor positive, 19% were anti-cyclic citrullinated peptide antibody positive, and 57% had the presence of HLA-B27. Uveitis had been diagnosed in 16% of cases.

**Conclusion.** The prevalence of JIA in Alaska Native children may be higher than the general US population. Enthesitis-related arthritis makes up a higher proportion of cases than in other populations described likely because of the high prevalence of HLA-B27 in this population.

## INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. By definition, JIA encompasses a heterogeneous group of chronic inflammatory forms of arthritis with onset prior to age 16 years (1). Although the onset is in childhood, a substantial proportion of patients with JIA have active disease lasting into adulthood (2). JIA can include joint disease with related functional limitation as well as extraarticular manifestations, most commonly uveitis, which has been reported in 11–30% of established JIA cases (3). The terminology for juvenile arthritis has changed over time, with the International League of Associations for Rheumatology (ILAR) criteria for JIA having replaced older classification schemes (4). The ILAR classification criteria include conditions previously classified as juvenile rheumatoid arthritis (JRA) by the American College of Rheumatology (ACR) (5) as well as a broader set of conditions causing inflammatory arthritis. The ILAR

criteria include 7 different subtypes, 4 of which were previously considered to be JRA. Epidemiologic studies of JIA have been limited by changing criteria, varying study methodology, and different populations studied. Estimates of incidence have ranged from 1.6 to 23 per 100,000 and prevalence from 3.8 to 400 per 100,000 in the general population of North America and Europe, as summarized in a systematic review in 2014 (6). A recent epidemiologic study in the US reported overall JIA incidence of 10.3 per 100,000 between 1994 and 2013 and prevalence of 57.6 per 100,000 in 2010 (7).

High rates of several autoimmune diseases have been described in indigenous North American adults (8), including rheumatoid arthritis (9,10), systemic lupus erythematosus (11,12), and spondyloarthritis (13). Few studies have investigated the prevalence or incidence of JIA in indigenous North American populations, and none have used the current JIA classification criteria. One study of JRA using administrative billing codes in 2 regions

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### SIGNIFICANCE & INNOVATIONS

- This study provides the first description of the prevalence of juvenile idiopathic arthritis (JIA) in the Alaska Native population.
- Data from this study suggest that the prevalence of JIA overall and enthesitis-related arthritis in Alaska Native children may be higher than other populations.

of the Indian Health Service (IHS) from 1998 to 2000 estimated a high prevalence with variation by region (14). A study of the Canadian Inuit population in the 1970s to 1980s found that spondyloarthritis was present at higher rates than JRA in children, but the incidence of both was high (15). A study of the Alaska Native population in Southeast Alaska found a high incidence of JRA, with average annual incidence of 38.6 per 100,000 in the period from 1970 to 1984 (16).

The objective of this study was to determine the prevalence of JIA in the Alaska Native population statewide. Secondary objectives were to determine the prevalence of specific JIA subtypes and to define the clinical characteristics and treatment patterns of JIA in this population.

## PATIENTS AND METHODS

**Study population and clinical services.** The Alaska Native population includes ~160,000 people of all ages distributed over a vast geographic area. In Alaska, all IHS services are managed by tribal organizations under a self-governance compact agreement. The Alaska Tribal Health System (ATHS) is the statewide affiliation of tribal health organizations providing health services to Alaska Native people. In 2015, the total user population for the ATHS was ~152,000, of whom ~56,000 were age ≤18 years. In the ATHS, adult rheumatologists travel to 12 regional field clinics, and the care is supplemented by patient travel to Anchorage or by telemedicine follow-up. Pediatric rheumatologists from Seattle Children's Hospital travel to Anchorage every 2 months and provide clinics at the Alaska Native Medical Center (ANMC) in Anchorage, the tertiary care hospital for Alaska Native patients statewide. Children with JIA are preferentially referred to pediatric rheumatologists, but in some cases may see adult rheumatologists in field clinics if they are unable to travel to Anchorage or Seattle. This research project was approved by the Alaska Area Institutional Review Board. Tribal approval was obtained from participating tribal health organizations in the ATHS.

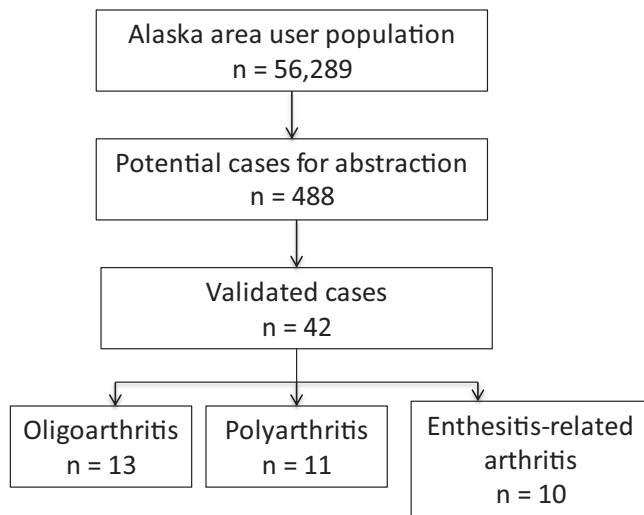
**Case ascertainment.** Potential cases of JIA were ascertained from several sources. First, a query of the ANMC electronic health record (EHR) was performed for International Classification of Diseases, Ninth Revision (ICD-9) codes possibly identifying JIA for visits during the period from October 1, 2011 to September 30,

2015. This time period corresponded with the interval between EHR adoption and conversion from ICD-9 to ICD-10 coding. This query included individuals age <18 years as of September 30, 2015 and excluded non-Indian beneficiaries, as defined by the IHS. A broad list of ICD-9 codes was used, including 714.x (includes rheumatoid arthritis, JIA, and related conditions), 720.x (includes spondyloarthritis and related conditions), 696.x (includes psoriatic arthritis and related conditions), 726.x (includes enthesopathy of specific joints and unspecified enthesopathy), 719.0 (effusion of joint), 364.x (iritis and related conditions), 099.3 (reactive arthritis), and 713.1 (arthritis associated with gastrointestinal conditions other than infections).

In addition to querying the ANMC EHR, we performed queries at regional field clinic facilities in the ATHS to identify individuals with a diagnosis of JIA who might not have been seen for JIA at the ANMC but had been seen in other tribal health clinics. These queries were performed according to local EHR or other information technology protocols and were modeled after queries at the ANMC. Finally, additional sources of potential cases included adult and pediatric rheumatology clinic databases for the ANMC and other clinics in the ATHS.

The denominator for this project was defined as the 2015 Alaska Area IHS user population age ≤18 years. The user population as defined by the IHS represents the count of individuals who received care at a tribal facility in Alaska ≥1 times in the prior 3 years. This denominator was selected to capture data on children who receive some health care at tribal facilities because data collection was occurring at tribal facilities.

**Medical record abstraction.** For each potential case, medical record abstraction was performed using a standardized data abstraction form. This form included data elements required to confirm the classification criteria for JIA by ILAR criteria (both inclusions and exclusions) and JRA by the older ACR criteria (both inclusion and exclusion criteria), which subtype was confirmed, and demographic characteristics (age, sex, type of community of residence, age at diagnosis, year of diagnosis, and duration of symptoms prior to diagnosis). Abstraction also determined whether a pediatric rheumatologist confirmed the diagnosis, whether specified disease features were present or not (uveitis, bone erosions on plain radiographs), the presence of autoantibodies (antinuclear antibody [ANA], rheumatoid factor [RF], and anti-cyclic citrullinated peptide [anti-CCP] antibody) or HLA-B27. The medications ever prescribed for JIA were abstracted from both physician notes in the EHR as well as pharmacy records from the ANMC. The number of visits with a rheumatologist in the year prior to the prevalence data was also collected. Medical record abstraction was initially performed by a researcher (BK) and was validated by a senior researcher (EDF), with potential cases adjudicated by the second researcher (EDF).



**Figure 1.** Flowchart for inclusion of potential cases. The denominator represents the Alaska user population age of  $\leq 18$  years in 2015. Potential cases were identified as possibly having juvenile idiopathic arthritis (JIA) based on International Classification of Diseases, Ninth Revision codes or recorded diagnoses. After detailed medical record abstraction, cases were classified as JIA or not based on International League of Associations for Rheumatology classification criteria, including subtype. Subtypes listed were the most common, but cases were also identified with systemic, psoriatic, and undifferentiated JIA. These were excluded from the figure to protect confidentiality, given the cell size of  $<5$ .

**Case definitions.** Our primary case definition was fulfillment of ILAR criteria for JIA as documented in the medical record. To be considered a case by our definition, patients were required to have the onset of JIA prior to age 16 years. Cases were included as prevalent if individuals were up to 18 years of age as of September 30, 2015. Prevalence was calculated as of September 30, 2015, requiring a diagnosis of JIA to be confirmed on that date or earlier. We used a secondary case definition of fulfillment of the 1977 JRA classification criteria.

**Statistical analysis.** The prevalence of JIA was calculated using the number of cases meeting the case definition divided by the number of children in the population denominator, expressed as a rate per 100,000. Prevalence was calculated overall and by sex. Age-adjusted rates were calculated overall using the 2000 projected US population (17). Male and female rates and rates for subtypes with  $<5$  cases were not age-adjusted due to the small number of cases. 95% confidence intervals (95% CIs) were calculated around each proportion. Statistical analyses were performed using Stata, version 11.2.

## RESULTS

The flow chart for inclusion of potential cases is presented in Figure 1. The total user population age  $\leq 18$  years was 56,289. Of 488 potential cases identified for medical record abstraction using broad search criteria, 42 were confirmed as having JIA. Of the 42 cases identified, 39 had been identified in our initial query of the ANMC EHR, while additional queries identified only 3 cases not previously identified. One additional case not found on regional query was identified from the adult rheumatology database.

The prevalence of JIA in Alaska Native children is shown in Table 1. The age-adjusted overall prevalence was 79 per 100,000 (95% CI 55.1–102.9). JIA was  $>2$  times as common in females compared to males (105.8 per 100,000 versus 45.0 per 100,000). The prevalence of JIA subtypes is also shown in Table 1. Oligoarthritis was the most common subtype, followed by polyarthritis and enthesitis-related arthritis with similar prevalence. When using the JRA criteria, the overall age-adjusted prevalence was 65.7 per 100,000, and the most common subtype was pauciarticular JRA.

The clinical characteristics of all JIA cases are summarized in Table 2. The median age at diagnosis was 9.1 years, with a median of 6 months of symptoms prior to diagnosis. Most individuals with JIA resided in rural or urban cluster locations. Uveitis was diagnosed in 16.7% of cases. Although autoan-

**Table 1.** Prevalence of juvenile idiopathic arthritis (JIA) and juvenile rheumatoid arthritis (JRA) by disease subtypes in the Alaska Native population\*

Case definition	No. cases	Overall		Female, unadjusted	Male, unadjusted
		Unadjusted	Age-adjusted		
ILAR criteria met for JIA, any subtype (primary)	42	74.6 (52.0–97.2)	79.0 (55.1–102.9)	105.8 (67.3–144.4)	45.0 (20.5–69.5)
Oligoarthritis	13	23.1 (10.5–35.6)	24.4 (11.1–37.6)	43.8 (19.0–68.6)	3.5 (0.0–10.2)
Polyarthritis	11	19.5 (8.0–31.1)	20.5 (8.4–32.7)	36.5 (13.9–59.1)	3.5 (0.0–10.2)
Enthesitis-related arthritis	10	17.8 (6.8–28.8)	19.0 (7.2–30.8)	7.3 (0.0–17.4)	27.7 (8.5–46.9)
Psoriatic arthritis	$<5$	5.3 (0.0–11.4)	NA	NA	NA
Systemic	$<5$	1.8 (0.0–5.3)	NA	NA	NA
Undifferentiated	$<5$	7.1 (0.1–14.1)	NA	NA	NA
Criteria met for JRA, any subtype (secondary)	35	62.2 (41.6–82.8)	65.7 (43.9–87.4)	94.9 (58.4–131.4)	31.1 (10.8–51.5)
Pauciarticular	20	35.5 (20.0–51.1)	37.5 (21.1–54.0)	58.4 (29.8–87.0)	13.8 (0.3–27.4)
Polyarticular	13	23.1 (10.5–35.6)	24.3 (11.1–37.6)	36.5 (13.9–59.1)	10.4 (0.0–22.1)
Systemic	$<5$	3.6 (0.0–8.5)	NA	NA	NA

\* Prevalence values are the number per 100,000 (95% confidence interval) unless indicated otherwise. ILAR = International League of Associations for Rheumatology; NA = not applicable.

**Table 2.** Clinical characteristics of juvenile idiopathic arthritis cases\*

Characteristic	Sample size, no.	Value
Median age at diagnosis, years	42	9.1
Female sex	42	29 (69)
Location of residence†		
Urban	42	9 (21.4)
Urban cluster	42	16 (38.1)
Rural	42	17 (40.5)
Median time from symptoms to diagnosis, months	35	6
Uveitis	42	7 (16.7)
ANA positive	36	20 (55.6)
RF positive	39	9 (23.1)
Anti-CCP antibody positive	31	6 (28.6)
HLA-B27 positive	21	12 (57.1)
Erosive changes on radiographs	39	7 (17.9)

\* Values are the number (%) unless indicated otherwise. ANA = antinuclear antibody; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide.

† Urban population >50,000; urban cluster population 2,500–50,000; rural population <2,500.

tibody, HLA typing, and radiographic data were not available on all cases, ANA test results were positive in a substantial proportion (55.6% of those tested; 20 of 36), and HLA-B27 findings were positive in 57.1% of those tested (12 of 21). Anti-CCP antibody was present in a slightly higher proportion than RF in those tested (28.6% versus 23.1%), and in 2 cases anti-CCP results were positive while RF results were negative. Sensitivity analysis using the assumption that all those not tested were negative gives a minimal prevalence of positive ANA of 47.6% (20 of 42), HLA-B27 of 28.6% (12 of 42), anti-CCP of 14.3% (6 of 42), and RF of 21.4% (9 of 42). Erosive changes were noted on plain radiographs in 17.9% of cases (7 of 39 with radiographic data).

Treatment patterns and medications ever prescribed for JIA are shown in Table 3. Most cases (81%) had been diagnosed by a pediatric rheumatologist, and the mean number of visits in the past year was just under 2 visits. Just over one-half of cases (52.4%) had been treated with oral or parenteral steroids at any time, and a slightly lower proportion (47.6%) had received intra-articular steroids. Nonsteroidal antiinflammatory drugs (NSAIDs) had been prescribed commonly. The most common disease-modifying antirheumatic drug (DMARD) was methotrexate, ever prescribed in 64.3% of cases. Just over 60% of patients had ever received biologics for treatment.

## DISCUSSION

In Alaska Native children statewide, the age-adjusted prevalence of JIA was 79.0 per 100,000. The most common subtype was oligoarthritis, but polyarthritis and enthesitis-related arthritis were almost as common, with enthesitis-related arthritis accounting for 24% of cases. The median age at onset was 9.1 years, and

JIA was more common in females than males. More than one-half of those tested were HLA-B27 positive.

There is limited information about the prevalence of JIA in different populations (18). An estimate of pooled JIA prevalence for white patients was recently developed in a systematic review and was found to be 32.6 per 100,000 (6). Pooled estimates could not be calculated by race or ethnicity due to insufficient data. A recent study in the US described the incidence and prevalence of JIA in Olmsted County, Minnesota using similar methodology to our study. The prevalence of JIA in our study was higher than that found in Olmsted County (79 versus 51 per 100,000). However, given the small number of cases and wide confidence intervals in this study, we cannot determine whether this difference is due to chance. A study of the Maori population in New Zealand found lower incidence of JIA than in children of European ancestry, although a greater number of poor prognostic factors was identified in the Maori children (19). A study of a diverse population by Kaiser Permanente in Northern California found an age-adjusted JIA prevalence of 44.7 per 100,000, which is slightly lower but only included the population of age ≤15 years (18).

In most studies, oligoarthritis is the most common subtype of JIA, which is consistent with the findings of our study. However, despite oligoarthritis being the most common subtype, its overall prevalence was not higher than described in other populations. Enthesitis-related arthritis is a category of JIA that includes features of spondyloarthropathy, with the presence of HLA-B27 as 1 of the criteria used for classification. Enthesitis-related arthritis is typically an uncommon presentation among cases of JIA, and the estimated pooled prevalence by systematic review was 3.1 per 100,000 (approximately one-fifth as common as oligoarthritis) (6). However, enthesitis-related arthritis accounted for a significant proportion of JIA cases in our study (24%), compared with only 1.4% of cases in Olmsted County and 3% of cases in the Kaiser Permanente study. The prevalence of enthesitis-related arthritis may be higher among African American children with JIA (reported to be present in 12.4% of cases in a recent study) (20) but still does not appear to be as high as in our study. The higher prevalence of enthesitis-related arthritis might be expected in Alaska Native children given the known high prevalence of HLA-B27 in the

**Table 3.** Treatment patterns of juvenile idiopathic arthritis\*

Characteristic	Value
Diagnosis confirmed by a pediatric rheumatologist	34 (81)
No. of visits to a rheumatologist in the past year, mean ± SD	1.8 ± 1.6
Oral or parenteral steroids ever	22 (52.4)
Intraarticular steroids ever	20 (47.6)
NSAIDs ever	36 (85.7)
Methotrexate ever	27 (64.3)
Any nonbiologic DMARD ever	33 (78.6)
Biologics ever	26 (61.9)

\* Values are the number (%) unless indicated otherwise. N = 42 for all characteristic sample sizes. NSAIDs = nonsteroidal antiinflammatory drugs; DMARD = disease-modifying antirheumatic drug.



population (range 25–40% in different regional studies) (8) as well as the high prevalence of spondyloarthropathy in Alaska Native adults (range 1.1–2.5% based on studies in the 1980s to 1990s in different regions of the state) (8,13). In addition, data from Canadian indigenous children in the 1980s, before enthesitis-related arthritis criteria were developed, suggested high rates of spondyloarthropathy. One study found that spondyloarthropathy was relatively more common than JRA in indigenous Canadian children compared to white children (21), and a second study found that although spondyloarthropathy was relatively more common, both conditions occurred with high prevalence (15). It is possible that some cases of oligoarthritis in our study might be undifferentiated spondyloarthritis or enthesitis-related arthritis. The median age at onset of oligoarthritis was 5 years, with some cases occurring in children up to age 13 years. We followed the ILAR exclusion criteria and did not consider cases in males with positive HLA-B27 and age at onset after 6 years to be oligoarthritis. In one case, a female patient was considered to have oligoarthritis with onset of arthritis after age 6 years and HLA-B27 positivity. In some cases, because we were reviewing existing medical records, HLA-B27 status was unknown. Cases were classified based on the ILAR criteria using the information available in the medical record.

For comparison to older studies, we determined the prevalence of JRA and its subtypes according to the 1977 classification criteria. The overall prevalence of JRA was lower than JIA because it does not include some forms of arthritis (including enthesitis-related arthritis) that are included within the JIA classification scheme. We found an overall age-adjusted prevalence of JRA of 65.7 per 100,000, slightly higher than the pooled prevalence estimated in a recent systematic review but lower than described in Olmsted County, Minnesota (6,7). This prevalence is intermediate between estimates from the Oklahoma and Billings IHS areas in an IHS study from 1998 to 2000 (53 and 115 per 100,000, respectively) (14). Of the 3 subtypes of JRA, pauciarticular (similar to oligoarticular JIA) was the most common, representing 57% of cases of JRA. This is similar to other population-based studies where the pauciarticular subtype is the most common form, including Olmsted County, where it accounts for 80% of cases classified as JRA in the most recent cohort (7). However, it differs from a previous description of JRA in First Nations populations in Canada, where RF-positive polyarticular JRA was present in 42% of patients, and pauciarticular JRA in only 22% (22).

There are few contemporary studies describing the clinical characteristics of JIA in different populations, but a recent study described the phenotype of JIA in African American children in comparison to non-Hispanic white children enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry (20). The age at onset of JIA in African American children was higher than in non-Hispanic white children in the CARRA study (8.9 versus 5.2 years) and was more comparable to the age at onset that we found in our study (9.1 years). In comparison to the findings on African American children in the CARRA study, we

found a similar female predominance, a similar proportion of cases with positive RF and anti-CCP antibody, a slightly higher proportion with positive ANA, and a much higher proportion of patients positive for HLA-B27 (57.1% in our study versus 13.2% of African American patients in the CARRA study). Uveitis was more common in our study population (16.7% versus 6.1%). In non-Hispanic white patients with JIA in the CARRA study, RF and anti-CCP antibody positivity was less likely (8.1% and 7.7%), as was HLA-B27 (positive in 15.2% of cases). Uveitis was intermediate, present in 11.7% of non-Hispanic white patients with JIA. The Kaiser Permanente Northern California study found a similar female predominance (64%), a slightly higher proportion with positive ANA (70%), a lower proportion with positive RF (9%), and a much lower proportion with HLA-B27 (2%) or uveitis (3%) (18). A study of Maori or Pacific Island children in New Zealand found a higher frequency of RF positivity (although not anti-CCP positivity) than in children of European background, as well as increased likelihood of joint space narrowing or erosions on radiographs. The proportion of Maori children with JIA with erosions on radiographs (19%) was similar to the proportion in our study (17.9%) (19).

A few population-based studies have described treatment patterns in JIA. In the cases of African American and non-Hispanic white patients in the CARRA Registry described above, the proportions treated with steroids (65% and 54%, respectively, versus 52.4% in our study), DMARDs (71% and 73.6% versus 78.6% in our study), and biologics (53% and 43.7% versus 61.9% in our study) were similar to those in our study (20). Compared to a study of a population-based cohort in Olmsted County, Minnesota, we found that a higher proportion of cases had received methotrexate (64% versus 35%), any DMARD (78.6% versus 37%), and any biologic drug (62% versus 13%), while a lower proportion had received NSAIDs (85.7% versus 100%), and a very similar proportion had received intraarticular corticosteroid injections (48% in both studies) (23).

This study has some limitations. First, data collection was limited to the existing medical record. Some criteria for JIA might have been met but not documented in the medical record, and we were not able to examine, interview, or collect serum from potential cases to validate the criteria. Second, for the cases diagnosed at an older age, we were not able to follow them longitudinally to know if their clinical characteristics or treatment patterns might evolve over time. Third, the small number of cases limited the precision of our estimates. Because of the small number of cases, we focused on prevalence and not incidence and are not able to compare incidence of JIA to other population-based studies. This limitation is inherent in studies of small populations, especially American Indian/Alaska Native populations, and should not preclude studies of small populations. Fourth, cases seen in regional clinics from tribal health organizations not included in the study and never at the ANMC would not have been captured, and cases seen outside of the tribal health system are not captured. However, we were able to query most

regional clinics and only identified a small number of cases not seen at the ANMC. In addition, we used the IHS user population as the denominator in order to identify children who were accessing care in the tribal health system. Some Alaska Native children receive health care in other health systems, but those children were not in the denominator for this study. Fifth, we did not distinguish between acute and chronic uveitis on medical record abstraction. It is possible that acute anterior uveitis could be more common in this population with high rates of HLA-B27, but we are unable to comment on specific characteristics of uveitis. Finally, our search strategy identified a large number of patients who did not have JIA. However, the strategy to query a broad set of codes that include JIA and other conditions allowed us to ensure that cases coded in several different ways would be captured. Strengths of this project include the opportunity to assess the prevalence and clinical characteristics of JIA in a population not previously described and the ability to use several different sources for case ascertainment.

In conclusion, we found the prevalence of JIA to be slightly higher than described in the US population, with a higher proportion of enthesitis-related arthritis and HLA-B27 positivity. This study significantly adds to the limited literature on JIA epidemiology. Epidemiologic studies of JIA in other populations are warranted. Ideally, descriptions of health disparities in minority populations can be used to improve service delivery or develop interventions designed to improve outcomes. In clinical practice, although JIA may be slightly more common than in other populations, it remains relatively uncommon. The high prevalence of enthesitis-related arthritis and HLA-B27 in this population is useful information for clinicians and should be incorporated into educational programs. Finally, the high prevalence of JIA in the Alaska Native population suggests that studies of risk factors in this population would be informative and could lead to insight into the etiology of JIA.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ferucci had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Stevens, Ferucci.

**Acquisition of data.** Khodra, Ferucci.

**Analysis and interpretation of data.** Stevens, Ferucci.

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