Adverse Childhood Experiences Are Associated with Childhood-Onset Arthritis in a National Sample of US Youth: An Analysis of the 2016 National Survey of Children's Health

Tamar B. Rubinstein, MD, MS[1,2], Danielle R. Bullock, MD, MPH[3], Kaveh Ardalan, MD, MS[4,5,6,7], Wenzhu B. Mowrey, PhD[8], Nicole M. Brown, MD, MPH, MHS[9,10], Laurie J. Bauman, PhD[11,12], and Ruth E. K. Stein, MD[13,14]

Objectives To determine whether there is an association between adverse childhood experiences (ACEs) and childhood-onset arthritis, comparing youth with arthritis to both healthy youth and youth with other acquired chronic physical diseases (OCPD); and to examine whether ACEs are associated with disease-related characteristics among children with arthritis.

Study design In a cross-sectional analysis of data from the 2016 National Survey of Children's Health we examined whether ACEs were associated with having arthritis vs either being healthy or having a nonrheumatologic OCPD. ACE scores were categorized as 0, 1, 2-3, ≥4 ACEs. Multinomial logistic regression models examined associations between ACEs and health status while adjusting for age, sex, race/ethnicity, and poverty status. Among children with arthritis, associations between ACEs and disease-related characteristics were assessed by Pearson χ^2 analyses.

Results Compared with children with no ACEs, children with 1, 2-3, and ≥4 ACEs had an increased odds of having arthritis vs being healthy (adjusted OR for ≥4 ACEs, 9.4; 95% CI, 4.0-22.1) and vs OCPD (adjusted OR for ≥4 ACEs, 3.7; 95% CI-1.7, 8.1). Among children with arthritis, ACEs were associated with worse physical impairment.

Conclusions Children with higher numbers of ACEs are more likely to have arthritis, when arthritis status is compared either with being healthy or with having OCPD. Further studies are needed to determine the direction of the association between ACEs and childhood arthritis, its impact on disease course, and potential intervention targets that might mitigate these effects. *(J Pediatr 2020;226:243-50)*.

The most common chronic childhood-onset arthritis is juvenile idiopathic arthritis (JIA), affecting an estimated 300 000 children in the US.[1] Although the etiology of JIA and other for ms of childhood-onset arthritis is largely unknown, genomic and epidemiologic studies indicate that it is likely multifactorial involving gene-environment interactions leading to immune dysregulation.[2-7] Chronic psychological stress has been hypothesized to play a role in triggering rheumatologic diseases, including JIA.[8] Mounting evidence suggests that exposure to chronic stress, especially in the formative years of childhood, predispose to worse general health and chronic disease.[9,10] There are particular effects that stress has on the immune system, suggested by associations in animal and human studies between precedent stress and the development of proinflammatory states that may help to explain how chronic stress could potentiate inflammatory and autoimmune disease.[11-15]

Patients with childhood-onset arthritis are more likely to report several forms of precedent personal and family stressful events when compared with healthy controls.[16] Several studies indicate that psychological stress is elevated in families affected by juvenile arthritis, and may be a reaction to the disease experience.[17-19]

Adverse childhood experiences (ACEs) are experiences that are associated with chronic stress in childhood, such as neglect, violence, and household dysfunction. Although recent literature points to an association between childhood trauma and arthritis in adults, the relationship between ACEs and childhood-onset arthritis has not been investigated in a large representative community sample.[20-22] Furthermore, it is unknown how children with arthritis compare

ACE	Adverse childhood experience
JIA	Juvenile idiopathic arthritis
NSCH	National Survey of Children's Health
OCPD	Other acquired chronic physical disease

From the [1]Division of Pediatric Rheumatology, Department of Pediatrics, Albert Einstein College of Medicine, [2]Division of Pediatric Rheumatology, Children's Hospital at Montefiore, Bronx, NY; [3]Division of Pediatric Rheumatology, Department of Pediatrics, University of Minnesota, Minneapolis, MN; [4]Division of Pediatric Rheumatology, Department of Pediatrics, Duke University School of Medicine, Durham, NC; [5]Division of Rheumatology, Ann and Robert H. Lurie Children's Hospital of Chicago, Departments of [6]Pediatrics, [7]Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL; [8]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY; [9]Albert Einstein College of Medicine, Bronx, NY; [10]Strong Children Wellness Medical Group Jamaica, NY; [11]Division of Academic General Pediatrics, Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY; [12]Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Bronx, NY; [13]Division of Developmental Medicine, Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY and [14]Division of Developmental Medicine, Children's Hospital at Montefiore, Bronx, NY

Supported by a Rheumatology Research Foundation K-Bridge Award (to T.R.). The funders were not involved in the study design, data collection, analysis, or interpretation, nor in the manuscript development or decision to submit for publication. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.06.046

with children with other acquired chronic physical disease (OCPD) regarding their exposure to ACEs.

Based on the strong relationship in the literature between ACEs and acquired chronic physical disease, our primary aim was to investigate whether there was an association between ACEs and childhood arthritis compared with healthy children and those with OCPD. We hypothesized that ACEs would be associated with childhood arthritis compared with healthy children and children with OCPD. Our second aim was to investigate the associations between the ACE score and disease-related characteristics in children with arthritis to explore whether ACEs may impact the severity of arthritis as well as pain and physical impairment.

Methods

We used cross-sectional data from the 2016 National Survey of Children's Health (NSCH), a nationally representative sample of youth with data on ACEs. This survey of sampled households with children <18 years old is conducted by the US Census Bureau and sponsored by the Maternal and Child Health Bureau of the Health Resources and Services Administration and the National Center for Health Statistics at the Centers for Disease Control and Prevention. For the 2016 NSCH, parent/guardian respondents were surveyed on behalf of their children by mail or online questionnaires. The survey includes questions on demographics and individual (child's) and family measures of health and wellness. The NSCH uses a complex weighted survey design to represent the US population of uninstitutionalized children. The 2016 NSCH contains data on 50 212 children, representing a population of 73 350 040 US children. This analysis of the 2016 NSCH data was designated as exempt by the Einstein-Montefiore Institutional Review Board.

Variable Definitions and Measurements

Arthritis, Disease, and Health Status. Three groups of children from the NSCH were compared in our main analysis, the arthritis group, and 2 comparison groups including the healthy group and the OCPD group (**Figure 1**; available at www.jpeds.com). Children were classified as having an acquired chronic physical disease by positive responses to the questions: "Has a doctor or other health care provider EVER told you that this child has [condition]" and "Does this child currently have the condition?" for the conditions of arthritis, allergies, asthma, diabetes, and epilepsy. Children with current arthritis, with and without the presence of other acquired chronic diseases, were included in the arthritis group. Children with resolved arthritis were excluded from the analysis to focus on children who were more likely to have chronic inflammatory arthritis as opposed to infectious or postinfectious arthritis.

Healthy status was defined by a negative response to the Children with Special Health Care Needs Screener and no history of physical disease, that is, no report of any of the physical conditions specifically queried in the NSCH which include the above acquired chronic diseases and 9 other physical diseases and conditions (blood disorder, brain injury, cerebral palsy, cystic fibrosis, Down syndrome, heart conditions, headache, or other genetic or inherited condition).[23]

A second comparison group, the OCPD group, included children without a history of arthritis but who had reported one or more of the other 4 acquired chronic diseases: allergies, asthma, diabetes, and epilepsy.

ACEs. ACE scores were calculated from responses from the Adverse Family Experience questionnaire included in the NSCH, which is a modified Adverse Childhood Experience questionnaire. Nine different ACEs were queried: (1) financial hardship, (2) divorced/separated parents, (3) death of a parent, (4) incarceration of a parent, (5) witnessing physical abuse at home, (6) witnessing violence in the neighborhood, (7) household member with mental illness, (8) alcohol/drug abuse at home, and (9) racial/ethnic discrimination. All except financial hardship were queried as yes/no questions, with the option of deferment: "To the best of your knowledge, has this child EVER experienced any of the following?" For financial hardship, respondents were asked "SINCE THIS CHILD WAS BORN, how often has it been very hard to get by on your family's income – hard to cover the basics like food or housing?" with response options never, rarely, somewhat often, and very often. Responses for this question were dichotomized with somewhat often and very often defined as positive, consistent with instructions for scoring the scale.[24] Based on the ACE literature, we categorized ACE scores between 0 and ≥4 ACEs.[25-27] Owing to the overall small number of children with arthritis, we collapsed scores of 2 and 3 into 1 category, like other studies with smaller sample sizes, to ensure sufficient power to assess the sample of children with arthritis.[28,29] This strategy resulted in 4 groups: 0, 1, 2-3, and ≥4 ACEs.

Disease-Related Characteristics. Following positive responses to both whether children had ever been diagnosed with a condition, and whether the condition was current, parents/guardians were asked to grade whether the condition was mild, moderate, or severe. We used these responses to assess for the severity of arthritis and OCPD. To analyze whether ACEs were associated with arthritis severity, we dichotomized responses into mild vs moderate/severe to ensure approximately even groups.

Chronic pain and physical impairment were queried independently of answers to any specific conditions and were asked of all respondents. The presence of chronic pain was assessed by the question, "During the past 12 months, has this child had frequent or chronic difficulty with repeated or chronic physical pain, including headaches or other back or body pain?" Responses were dichotomous (yes/no). Physical impairment was assessed with the question: "During the past 12 months, how often has this child's health conditions or problems affected his or her ability to do things other children his or her age do?" Responses were sometimes, usually,

always, or never. These were dichotomized to analyze the presence of physical impairment with never being negative and all other responses considered positive.

The presence of comorbid depression or anxiety was defined as having positive responses to both the questions: "Has a doctor or other health care provider EVER told you that this child has depression" and "Does this child currently have the condition?" or similar paired questions for anxiety.

Covariates

We examined variables known to be associated with both arthritis and ACEs to examine potential confounders to include in adjusted models. These included sex, age, race/ethnicity, and income. Prior literature has shown that children who identified as Black/non-Hispanic or Hispanic race/ethnicity have a higher prevalence of ACEs; thus, we defined race/ethnicity as a combined variable (White/non-Hispanic, Black/non-Hispanic, Hispanic, other/non-Hispanic).[30,31] Children from households with an income of <100% of the federal poverty line are known to have higher prevalence of ACEs; we dichotomized income as below the poverty line and not, using the Department of Health and Human Services poverty guidelines.[32]

Statistical Analyses

Statistical analysis was performed using Stata 14 (StataCorp, College Station, Texas) and weighted point estimates and variances were calculated using Stata survey procedures to account for the complex sample design. We examined differences in sociodemographics between the groups using bivariate analyses with Pearson χ^2 tests for categorical variables and adjusted Wald tests to compare estimated means between groups. We investigated whether the ACE score was associated with arthritis vs healthy and arthritis vs OCPD using multinomial logistic regression. The models were expressed first with the reference group as healthy and then as OCPD to determine the increased odds of arthritis vs these outcomes. Adjusted models included covariates for age, sex, race/ethnicity, and low household income (dichotomized as above or below the federal poverty line). Subsequently, we investigated whether the ACE score was associated with disease-related characteristics in bivariate analyses using Pearson χ^2 tests among children with arthritis.

Sensitivity Analysis for Missing ACE Data

Respondents were allowed to decline to answer any ACE question. Missing ACE data were not missing at random. A higher proportion of children with missing ACE data were black, Hispanic, or other race/ethnicity and were more likely to be from low-income households. More children with arthritis were missing ACE data than healthy children (20% vs 9%; $P = .02$) and children with OCPD (7%; $P = .003$). The majority of children with missing ACE data were missing data for one ACE question and each ACE question had a similar number of missing responses (3%-4% missing). There were no missing data in the NSCH dataset for the sociodemographic variables because multiple imputation was used in the design of the dataset. For all demographic variables, <1% of respondents had imputed data, with the exception of income, for which 17% of healthy and OCPD classified children had imputed values and 20% of children with arthritis. No significant differences in proportions of imputed data were found across health status groups. Two sensitivity analyses were performed (counting each unanswered ACE question as no exposure and counting each unanswered ACE question as a positive exposure) to assess for any differences from the main results.

Results

This study included 37 283 children with complete ACE questionnaires who were classified as having current arthritis with or without OCPD (n = 123), healthy (n = 25 058), or having OCPD (n = 12 102) (**Figure 1**). By percentage estimates, among children with arthritis, the majority had comorbid OCPD (70%), most commonly allergies (31%), followed by asthma, with or without allergies (29%).

Demographic Characteristics

Age, sex, race/ethnicity, and household income differed across the 3 groups. Pairwise comparisons showed that children with arthritis were significantly older than healthy children and children with OCPD (both $P < .0001$). Additional pairwise comparisons between arthritis and the other groups were not statistically significant (**Table I**).

Comparison of ACEs in Arthritis, Healthy, and OCPD Groups

Among all US children represented by the NSCH, the calculated point estimate for children with any ACE was 46%; 39% of healthy children, 55% of children with OCPD, and 74% of children with arthritis had any ACE. Prevalence estimates for high exposure to ACEs (≥4 ACEs) were 4% among healthy children, 9% among children with OCPD, and 26% among children with arthritis (**Figure 2**; available www.jpeds.com).

An analysis of ACE type showed that for each specific type of ACE there were significant differences among the 3 groups of children. Children with arthritis had the highest prevalence for each of the 9 ACEs, except for financial hardship. Pairwise comparisons showed significant differences in the prevalence between the arthritis group and the other 2 groups in every ACE type except for financial hardship and death of a parent (**Table II**; available at www.jpeds.com).

Association between ACE Score and Arthritis

Categorical ACE scores at each level were significantly associated with having arthritis or having OCPD compared with being healthy by multinomial logistic regression. In adjusted models for age, sex, race/ethnicity, and low household income, the association of an ACE score of 1 with arthritis did not remain statistically significant. In both unadjusted and adjusted models, we observed increasing odds with each rising category of ACE score of arthritis vs healthy (**Table III**) and arthritis vs OCPD (**Table IV**).

Table I. Demographic characteristics for children in the 2016 NSCH

Demographics	Healthy* (n = 25 058)	OCPD† (n = 12 102)	Arthritis (n = 123)
Age, years	7.6 ± 0.7	9.9 ± 0.9	12.9 ± 0.6‡
Female sex	51% (0.7)	46% (1.0)	55% (7.0)
Race			
White, non-Hispanic	52% (0.7)	53% (1.0)	58% (7.2)
Black, non-Hispanic	11% (0.5)	15% (0.7)	15% (5.4)
Hispanic	26% (0.8)	21% (1.1)	13% (4.8)
Other	11% (0.4)	10% (0.6)	13% (5.9)
Low household income§	19% (0.7)	22% (1.0)	29% (6.5)
Acquired chronic disease	–		
Arthritis, alone		–	30% (5.7)
OCPD			
Allergies, alone		62% (1.0)	31% (6.3)
Asthma (with or without allergies)		34% (1.0)	29% (7.1)
Epilepsy (with or without allergies/asthma)		2.3% (0.3)	7.3% (3.6)
Diabetes (with or without allergies/asthma)		1.6% (0.2)	3.0% (2.8)
Diabetes and epilepsy (with or without allergies/asthma)		0.1% (0.1)	0
Moderate-severe disease¶	–	42% (1.0)	57% (6.9)**
Physical impairment	3.2% (0.3)	30% (0.9)	71% (6.5)‡
Chronic pain	2% (0.2)	12.6% (0.7)	64% (7.0)‡
Depression/anxiety	1.4% (0.2)	13.5% (0.7)	36% (0.7)‡

Values are weighted proportions with SE given or mean ± SD. Adjusted Wald analyses used to compare weighted mean estimates of age and Pearson χ^2 analyses used to compare weighted percentages of other variables.
*Healthy children defined as those with a negative screen for special health care needs and with no reported chronic diseases.
†OCPDs include physician-diagnosed allergies.
‡$P < .0001$ for pairwise comparisons between arthritis vs OCPD, arthritis vs healthy asthma, diabetes, and epilepsy.
§From households with annual income of <100% the federal poverty line.
¶Presence of moderate to severe disease activity for any disease.
**$P < .05$ for pairwise comparisons between arthritis vs OCPD.

In the adjusted multinomial model, children with ≥4 ACEs were 9.4 times as likely to have arthritis as healthy children (95% CI, 4.0-22.1; $P < .001$) and 3.7 times as likely to have arthritis than OCPD (95% CI, 1.7-8.1; $P = .001$).

Sensitivity analyses for missing data yielded similar results. Because of the large percentage of children with arthritis having comorbid OCPD, we conducted an additional analysis to look at the association between arthritis and categorical ACE scores while adjusting for OCPD. The results show that current arthritis was associated with categorical ACE scores (OR, 3.4; 95% CI, 1.9, 6.1; $P < .001$) while adjusting for the presence or absence of OCPD. In addition, to address the difference in age between the analysis groups, we analyzed the subsample of children whose age was ≥11 years old where the median age was similar between the 3 groups (14-15 years of age) and the main conclusions were still valid. We tested for interactions between covariates and categorical ACE scores in adjusted multinomial models, and no significant interactions were found.

Association between ACEs and Disease-Related Characteristics among Children with Arthritis

We compared disease-related characteristics of arthritis to children with OCPD. Data show that, compared with children with OCPD, children with arthritis had higher estimated prevalence of moderate to severe disease (65% vs 45%; $P = .005$), impaired physical functioning (71% vs 30%; $P < .0001$), chronic pain (64% vs 13%; $P < .0001$), and comorbid depression or anxiety (36% vs 14%; $P < .0001$). Among children with arthritis, we investigated whether the categorical ACE score was associated with disease-related characteristics (Table V). Although there were no significant associations between ACE scores and the disease severity or chronic pain, the prevalence of physical impairment was associated with the ACE score ($P = .01$). The estimated prevalence of physical impairment among children with arthritis who were unexposed to ACEs was 44%, however that for children with arthritis with ≥4 ACEs it was 97%. The association between comorbid depression/anxiety did not attain statistical significance ($P = .08$).

In alternate analyses where we included children with resolved arthritis (excluded from the main analyses), a slightly lower total point prevalence estimates were observed in physical impairment (63% vs 71%), pain (59% vs 64%), and comorbid depression/anxiety (30% vs 36%). However, the associations between disease-related features with ACE scores remained similar.

Discussion

In this large, nationally representative survey of US children, we found that ACEs were strongly associated with arthritis. Children with ≥4 ACEs were >9 times as likely to have arthritis compared with healthy children and nearly 4 times as likely to have arthritis compared with children with other

Table III. Odds of arthritis vs healthy* in 2016 NSCH by ACE score

ACEs	Unadjusted model OR (95% CI)	Unadjusted model *P* value	Adjusted model† OR (95% CI)	Adjusted model† *P* value
0	1	–	1	–
1 vs 0	2.3 (1.1-4.8)	.03	1.9 (0.9-4.0)	.09
2-3 vs 0	5.1 (2.4-10.5)	<.001	3.2 (1.5-6.6)	.002
≥4 vs 0	16.2 (7.3-35.9)	<.001	9.4 (4.0-22.1)	<.001

ORs, 95% CIs, and *P* values are results from the multinomial logistic regression models comparing children with arthritis and children with other chronic diseases to the reference group of healthy children.
*Healthy children defined as those with a negative screen for special health care needs and with no reported medical conditions.
†Adjusted for age, sex, race/ethnicity, poverty.

Table IV. Odds of arthritis vs OCPD* in 2016 NSCH by ACE score

	Unadjusted model		Adjusted model†	
ACEs	OR (95% CI)	*P* value	OR (95% CI)	*P* value
0	1	–	1	–
1 vs 0	1.6 (0.8-3.3)	.23	1.4 (0.7-3.0)	.35
2-3 vs 0	2.1 (1.6-4.4)	.048	1.7 (0.8-3.6)	.14
≥4 vs 0	5.0 (2.3-11.0)	<.0001	3.7 (1.7-8.1)	.001

ORs, 95% CIs, and *P* values are results from the multinomial logistic regression models comparing children with arthritis and children with other chronic diseases to the reference group of healthy children.
*OCPDs include physician-diagnosed allergies, asthma, diabetes, and epilepsy.
†Adjusted for age, sex, race/ethnicity, poverty.

OCPD in models adjusting for sociodemographic confounders. We observed increasing ORs with each successive categorical ACE score. This finding is consistent with a prior study that demonstrated a dose-response between the ACE scores and risk of disease.[9]

Studying the relationship between ACEs and disease in children requires noting that ACEs are still accumulating in childhood. In contrast with studies of exposure to ACEs in adults, the temporal relationship between ACEs and disease in this study is unclear. An earlier study of children with juvenile arthritis showed that some stressful life experiences are more likely to occur among newly diagnosed patients compared with healthy controls.[16] In our study, ACEs may have preceded or followed disease diagnoses. The adversity may come before or after the illness and the relationship may be bidirectional.

The mechanisms by which ACEs are associated with health outcomes in adulthood may differ from those in childhood. ACEs may predispose to disease, but childhood diseases may also be a risk factor for future exposure to ACEs. Although emerging evidence links precedent psychosocial stress and psychological distress to the development of rheumatologic disease, stress on a family from taking care of a child with chronic illness can lead to financial difficulties, marital problems, and household dysfunction. Several previous studies have indicated that parents of children with chronic arthritis experience high levels of emotional distress.[33-36] This finding may be a result of the disease rather than a trigger.

We observed a diminished effect size in the association between ACEs and arthritis when compared with OCPD (including other inflammatory diseases, such as asthma) vs when compared with healthy children. Furthermore, it is worth emphasizing that the majority (70%) of children with arthritis in this study had comorbid OCPD. However, ≥4 ACEs were highly associated with arthritis compared with OCPD and categorical ACE scores were associated with arthritis, independent of the presence of OCPD. This finding raises the question of whether the relationship between ACEs and arthritis may also arise from mechanisms that are independent of those connecting ACEs and general chronic disease, or whether similar mechanisms may be involved, but have an even stronger effect of linking ACEs to arthritis compared with other diseases.

The population of children with arthritis described in this study has significant physical and mental comorbidities. Associations between allergies, asthma, and inflammatory arthritis in children and adults have been described.[37,38] Relatively high prevalence of depression and anxiety among youth with arthritis and other rheumatologic diseases is also described.[39]

The process by which stress is hypothesized to induce lasting biologic changes, termed biological embedding, provides an explanation for the potential role that stress may play in altering the proclivity for rheumatologic disease.[40] Changes in responsiveness of the hypothalamic-pituitary-adrenal axis occur as a result of stress, particularly chronic stress.[41] Through these hormonal changes and other mechanisms, chronic stress may affect both the development and the function of the immune system.[13,42] Changes that have been observed may reflect an individual's susceptibility to proinflammatory states and immune-mediated disease, for instance elevated IL-6 responses to acute stress.[11,43] In addition, epigenetic changes have been hypothesized to occur in response to stress based on animal models of stress and early human studies of epigenetic differences associated with stress exposure.[44,45]

Although chronic psychological stress has long been hypothesized to play a role in the pathophysiology of

Table V. ACEs and disease-related features among children with arthritis

Disease-related feature	Total (n = 123)	0 ACEs (n = 45)	1 ACE (n = 24)	2-3 ACEs (n = 34)	≥4 ACEs (n = 20)	*P* value*
Moderate/severe disease	43% (6.8)	34% (11.4)	63% (12.9)	41% (13.0)	36% (13.6)	.4
Physical impairment	71% (6.5)	44% (12.0)	78% (13.1)	65% (13.6)	97% (3.3)	.01
Chronic pain	64% (7.0)	56.4% (12.5)	69% (13.4)	57% (13.7)	72% (16.3)	.8
Depression/anxiety	36% (6.7)	10% (5.3)	46% (14.3)	36% (16.7)	56% (16.7)	.08

Weighted proportions with SE given.
**P* value given for Pearson χ^2 analysis.

rheumatologic disease, only recently have large epidemiologic studies been leveraged to investigate this hypothesis.[15] Trauma and post-traumatic stress disorder have been associated with systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in studies of military personnel.[22] Studies from a prospective cohort of >50 000 women from the Nurses' Health Study, found that trauma exposure was associated with incident systemic lupus erythematosus and rheumatoid arthritis.[20,21] Regarding ACEs specifically, a large retrospective study found that ACEs were associated with odds of hospitalization for autoimmune disease in adults and a Canadian cohort study showed that childhood exposure to abuse was associated with arthritis in adults.[46,47]

We did not find an association between disease severity and ACEs. This finding is consistent with a smaller study from 30 years ago that found that neither the presence of chronic family stress nor stressful life events was associated with disease severity or type of disease in children with juvenile rheumatoid arthritis.[48] Likewise, no association was seen between pain and ACEs in children with arthritis in our study. An association between ACEs and chronic pain in adults has been previously described, and findings of a relationship between ACEs and pain in children have been inconsistent.[49-53]

Although acute daily stress has previously been associated with worse physical functioning in children with arthritis, our findings that ACEs were associated with physical impairment implies that chronic stress may also be linked to impaired physical functioning.[54] This difference may reflect irreversible disease damage, access to physical therapy, or differences in treatment. This finding may also reflect differences in coping abilities, differences in emotional reserves to handle chronic disease, or differences in social resources that may hinder achieving optimal functional outcomes.

Chronic stress and ACEs in particular, are highly associated with mental health conditions such as depression and anxiety, which are known to influence social, emotional, but also physical functioning in children with chronic disease.[10,55-57] Our investigations of an association between ACEs, physical functioning, depression, and anxiety among children with arthritis were exploratory and limited by the relatively small sample size of children with arthritis included in the NSCH. In addition, in this study, pain and physical impairment were queried independently of arthritis status and may be related to other comorbid conditions and not arthritis.

The relationships between disease severity, pain, physical impairment, comorbid psychiatric symptoms, and ACEs should be examined in larger studies of children with arthritis. Adding ACE questionnaires to registry studies, such as that currently piloted by the Childhood Arthritis and Rheumatology Research Alliance in children with JIA, may provide important information about the relationship between ACEs and specific rheumatologic diseases.

A strength of this study is the use of a large nationally representative sample, making these findings widely generalizable within the US. Although the sample of children with arthritis was small, it is as large as expected based on the prevalence of inflammatory arthritis.[1] Limitations of the study include the lack of characterization of type of arthritis and the inability to confirm parent-reported diagnosis with medical records. Most juvenile arthritis is inflammatory and not osteoarthritis, but arthritis in childhood includes a heterogeneous group of diseases, including autoimmune and autoinflammatory arthritis, like JIA and juvenile forms of systemic lupus erythematosus, scleroderma, inflammatory myositis, and sarcoidosis. Arthritis as classified in this study may also include infectious arthritis and postinfectious arthritis. Parents may have reported a diagnosis of arthritis with joint problems or joint pain that is not consistent with physician-diagnosed inflammatory arthritis. Hence, the examination of ACE data in formal rheumatologic disease registries will enhance our understanding of the relationship between ACEs, childhood arthritis, and disease-related outcomes.

The NSCH ACE questions are not all inclusive and there are areas of chronic adversity that may be associated with arthritis and other diseases not explored in this study. For instance, deportation of a parent or family member is not included in the questionnaire. Expanded ACE screeners that include this and other examples of serious childhood adversity have been proposed to better reflect family experiences of specific populations, such as immigrant and urban populations.[58,59] Finally, the NSCH data were not granular enough to determine the duration, timing, or severity of the reported ACEs.

The association between ACEs and arthritis and between ACEs and impairment in children with arthritis suggests that ACE screening may be important and informative in pediatric rheumatology clinics. Currently, psychoeducation and social and family support are being studied to determine whether early interventions can buffer against the development of new ACEs and engender resilience to their deleterious impact.[60] Further studies are needed to illuminate the pathways by which ACEs associate with childhood-onset rheumatologic disease and to determine whether supportive interventions around psychosocial health for children exposed to ACEs have a role in improving disease-related outcomes in childhood arthritis. ■

We thank the Maternal and Child Health Bureau of the Health Resources and Services Administration for their sponsorship of the National Survey of Children's Health, the participants who made this research possible, and Dr Jim Jarvis for his contributions to the concept of this study.

Submitted for publication Feb 26, 2020; last revision received Jun 8, 2020; accepted Jun 10, 2020.

Reprint requests: Tamar B. Rubinstein, MD, MS, Children's Hospital at Montefiore, 3415 Bainbridge Ave, Bronx, NY 10467. E-mail: trubinst@montefiore.org

References

1. Petty RE, Laxer RM, LR W. Juvenile idiopathic arthritis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn L, eds. Textbook of pediatric rheumatology. 7th ed. Philadelphia: Elsevier; 2016.
2. Berkun Y, Padeh S. Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. Autoimmun Rev 2010;9:A319-24.
3. Meyer B, Chavez RA, Munro JE, Chiaroni-Clarke RC, Akikusa JD, Allen RC, et al. DNA methylation at IL32 in juvenile idiopathic arthritis. Sci Rep 2015;5:11063.
4. Jiang K, Zhu L, Buck MJ, Chen Y, Carrier B, Liu T, et al. Disease-associated single-nucleotide polymorphisms from noncoding regions in juvenile idiopathic arthritis are located within or adjacent to functional genomic elements of human neutrophils and CD4+ T cells. Arthritis Rheumatol 2015;67:1966-77.
5. Okubo H, Itou K, Tanaka S, Watanabe N, Kashiwagi N, Obata F. Analysis of the HLA-DR gene frequencies in Japanese cases of juveniles rheumatoid arthritis and rheumatoid arthritis by oligonucleotide DNA typing. Rheumatol Int 1993;13:65-9.
6. Franca CMP, Sallum AME, Braga ALF, Strufaldi FL, Silva CAA, Farhat SCL. Risk factors associated with juvenile idiopathic arthritis: exposure to cigarette smoke and air pollution from pregnancy to disease diagnosis. J Rheumatol 2018;45:248-56.
7. Bell SW, Shenoi S, Nelson JL, Bhatti P, Mueller BA. Juvenile idiopathic arthritis in relation to perinatal and maternal characteristics: a case control study. Pediatr Rheumatol Online J 2017;15:36.
8. Herrmann M, Scholmerich J, Straub RH. Stress and rheumatic diseases. Rheum Dis Clin North Am 2000;26:737-63. viii.
9. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14:245-58.
10. Dube SR, Felitti VJ, Dong M, Giles WH, Anda RF. The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. Prev Med 2003;37:268-77.
11. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology 2010;35:2617-23.
12. Caserta MT, O'Connor TG, Wyman PA, Wang H, Moynihan J, Cross W, et al. The associations between psychosocial stress and the frequency of illness, and innate and adaptive immune function in children. Brain Behav Immun 2008;22:933-40.
13. Danese A, Lewis SJ. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? Neuropsychopharmacology 2017;42:99-114.
14. Ligier S, Sternberg EM. Neuroendocrine host factors and inflammatory disease susceptibility. Environ Health Perspect 1999;107(Suppl 5):701-7.
15. Stojanovich L, Marisavljevich D. Stress as a trigger of autoimmune disease. Autoimmun Rev 2008;7:209-13.
16. Neufeld KM, Karunanayake CP, Maenz LY, Rosenberg AM. Stressful life events antedating chronic childhood arthritis. J Rheumatol 2013;40:1756-65.
17. Vuorimaa H, Tamm K, Honkanen V, Komulainen E, Konttinen YT, Santavirta N. Parents and children as agents of disease management in JIA. Child Care Health Dev 2009;35:578-85.
18. Reisine ST. Arthritis and the family. Arthritis Care Res 1995;8:265-71.
19. Frank RG, Hagglund KJ, Schopp LH, Thayer JF, Vieth AZ, Cassidy JT, et al. Disease and family contributors to adaptation in juvenile rheumatoid arthritis and juvenile diabetes. Arthritis Care Res 1998;11:166-76.
20. Roberts AL, Malspeis S, Kubzansky LD, Feldman CH, Chang SC, Koenen KC, et al. Association of trauma and posttraumatic stress disorder with incident systemic lupus erythematosus in a longitudinal cohort of women. Arthritis Rheumatol 2017;69:2162-9.
21. Lee YC, Agnew-Blais J, Malspeis S, Keyes K, Costenbader K, Kubzansky LD, et al. Post-traumatic stress disorder and risk for incident rheumatoid arthritis. Arthritis Care Res 2016;68:292-8.
22. O'Donovan A, Cohen BE, Seal KH, Bertenthal D, Margaretten M, Nishimi K, et al. Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder. Biol Psychiatry 2015;77:365-74.
23. Bethell CD, Read D, Stein RE, Blumberg SJ, Wells N, Newacheck PW. Identifying children with special health care needs: development and evaluation of a short screening instrument. Ambul Pediatr 2002;2:38-48.
24. Child and Adolescent Health Measurement Initiative (CAHMI). 2016 National Survey of Children's Health: child and family health measures and subgroups. SPSS Codebook, Version 2.0. College Station (TX): StataCorp; 2018.
25. Brown NM, Brown SN, Briggs RD, German M, Belamarich PF, Oyeku SO. Associations between adverse childhood experiences and ADHD diagnosis and severity. Acad Pediatr 2017;17:349-55.
26. Dietz PM, Spitz AM, Anda RF, Williamson DF, McMahon PM, Santelli JS, et al. Unintended pregnancy among adult women exposed to abuse or household dysfunction during their childhood. JAMA 1999;282:1359-64.
27. Anda RF, Dong M, Brown DW, Felitti VJ, Giles WH, Perry GS, et al. The relationship of adverse childhood experiences to a history of premature death of family members. BMC Public Health 2009;9:106.
28. Heard-Garris N, Davis MM, Szilagyi M, Kan K. Childhood adversity and parent perceptions of child resilience. BMC Pediatr 2018;18:204.
29. Frankenberger DJ, Clements-Nolle K, Yang W. The association between adverse childhood experiences and alcohol use during pregnancy in a representative sample of adult women. Womens Health Issues 2015;25:688-95.
30. Strompolis M, Tucker W, Crouch E, Radcliff E. The intersectionality of adverse childhood experiences, race/ethnicity, and income: implications for policy. J Prev Interv Community 2019;47:310-24.
31. Bethell CD, Davis MB, Gombojav N, Stumbo S, Powers K. Issue brief: adverse childhood experiences among US children. In: Child and Adolescent Health Measurement Initiative (CAHMI). Baltimore: Johns Hopkins Bloomberg School of Public Health; 2017.
32. Halfon N, Larson K, Son J, Lu M, Bethell C. Income inequality and the differential effect of adverse childhood experiences in US children. Acad Pediatr 2017;17(7 Suppl):S70-8.
33. Cox A, Ostring G, Piper S, Munro J, Singh-Grewal D. Maternal stress associated with juvenile idiopathic arthritis. Int J Rheum Dis 2014;17:541-7.
34. Manuel JC. Risk and resistance factors in the adaptation in mothers of children with juvenile rheumatoid arthritis. J Pediatr Psychol 2001;26:237-46.
35. Lustig JL, Ireys HT, Sills EM, Walsh BB. Mental health of mothers of children with juvenile rheumatoid arthritis: appraisal as a mediator. J Pediatr Psychol 1996;21:719-33.
36. Gerhardt CA, Vannatta K, McKellop JM, Zeller M, Taylor J, Passo M, et al. Comparing parental distress, family functioning, and the role of social support for caregivers with and without a child with juvenile rheumatoid arthritis. J Pediatr Psychol 2003;28:5-15.
37. Patel MR, Leo HL, Baptist AP, Cao Y, Brown RW. Asthma outcomes in children and adolescents with multiple morbidities: findings from the National Health Interview Survey. J Allergy Clin Immunol 2015;135:1444-9.
38. Schmitt J, Schwarz K, Baurecht H, Hotze M, Folster-Holst R, Rodriguez E, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol 2016;137:130-6.
39. Fair DC, Rodriguez M, Knight AM, Rubinstein TB. Depression and anxiety in patients with juvenile idiopathic arthritis: current insights and impact on quality of life, a systematic review. Open Access Rheumatol 2019;11:237-52.
40. Berens AE, Jensen SKG, Nelson CA 3rd. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. BMC Med 2017;15:135.

41. Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr Physiol 2016;6:603-21.
42. Vitlic A, Lord JM, Phillips AC. Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system. Age (Dordr) 2014;36:9631.
43. de Punder K, Entringer S, Heim C, Deuter CE, Otte C, Wingenfeld K, et al. Inflammatory measures in depressed patients with and without a history of adverse childhood experiences. Front Psychiatry 2018;9:610.
44. Maddox SA, Schafe GE, Ressler KJ. Exploring epigenetic regulation of fear memory and biomarkers associated with post-traumatic stress disorder. Front Psychiatry 2013;4:62.
45. Bearer EL, Mulligan BS. Epigenetic changes associated with early life experiences: saliva, a biospecimen for DNA methylation signatures. Curr Genomics 2018;19:676-98.
46. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. Psychosom Med 2009;71:243-50.
47. Badley EM, Shields M, O'Donnell S, Hovdestad WE, Tonmyr L. Childhood maltreatment as a risk factor for arthritis: findings from a population-based survey of Canadian adults. Arthritis Care Res (Hoboken) 2019;71:1366-71.
48. Vandvik IH, Hoyeraal HM, Fagertun H. Chronic family difficulties and stressful life events in recent onset juvenile arthritis. J Rheumatol 1989;16:1088-92.
49. Brown RC, Plener PL, Braehler E, Fegert JM, Huber-Lang M. Associations of adverse childhood experiences and bullying on physical pain in the general population of Germany. J Pain Res 2018;11:3099-108.
50. Sachs-Ericsson NJ, Sheffler JL, Stanley IH, Piazza JR, Preacher KJ. When emotional pain becomes physical: adverse childhood experiences, pain, and the role of mood and anxiety disorders. J Clin Psychol 2017;73:1403-28.
51. Van Houdenhove B, Egle U, Luyten P. The role of life stress in fibromyalgia. Curr Rheumatol Rep 2005;7:365-70.
52. Nelson S, Simons LE, Logan D. The incidence of adverse childhood experiences (ACEs) and their association with pain-related and psychosocial impairment in youth with chronic pain. Clin J Pain 2018;34:402-8.
53. Nelson SM, Cunningham NR, Kashikar-Zuck S. A conceptual framework for understanding the role of adverse childhood experiences in pediatric chronic pain. Clin J Pain 2017;33:264-70.
54. Schanberg LE, Gil KM, Anthony KK, Yow E, Rochon J. Pain, stiffness, and fatigue in juvenile polyarticular arthritis: contemporaneous stressful events and mood as predictors. Arthritis Rheum 2005;52:1196-204.
55. Giovanelli A, Reynolds AJ, Mondi CF, Ou SR. Adverse childhood experiences and adult well-being in a low-income, urban cohort. Pediatrics 2016;137:10.1542.
56. Kenney MK, Singh GK. Adverse childhood experiences among American Indian/Alaska Native children: the 2011-2012 National Survey of Children's Health. Scientifica (Cairo) 2016;2016:7424239.
57. Green AE, Ferrand J, Aarons GA. Functioning among youth with comorbid mood disorder and chronic physical illness in public sector care. J Dev Behav Pediatr 2016;37:637-46.
58. Wade R Jr, Cronholm PF, Fein JA, Forke CM, Davis MB, Harkins-Schwarz M, et al. Household and community-level Adverse Childhood Experiences and adult health outcomes in a diverse urban population. Child Abuse Negl 2016;52:135-45.
59. Flores AR, Olsen RJ, Cantu C, Pallister KB, Guerra FE, Voyich JM, et al. Increased pilus production conferred by a naturally occurring mutation alters host-pathogen interaction in favor of carriage in Streptococcus pyogenes. Infect Immun 2017;85:e00949-16.
60. Garner AS, Shonkoff JP , Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics 2012;129:e224-31.

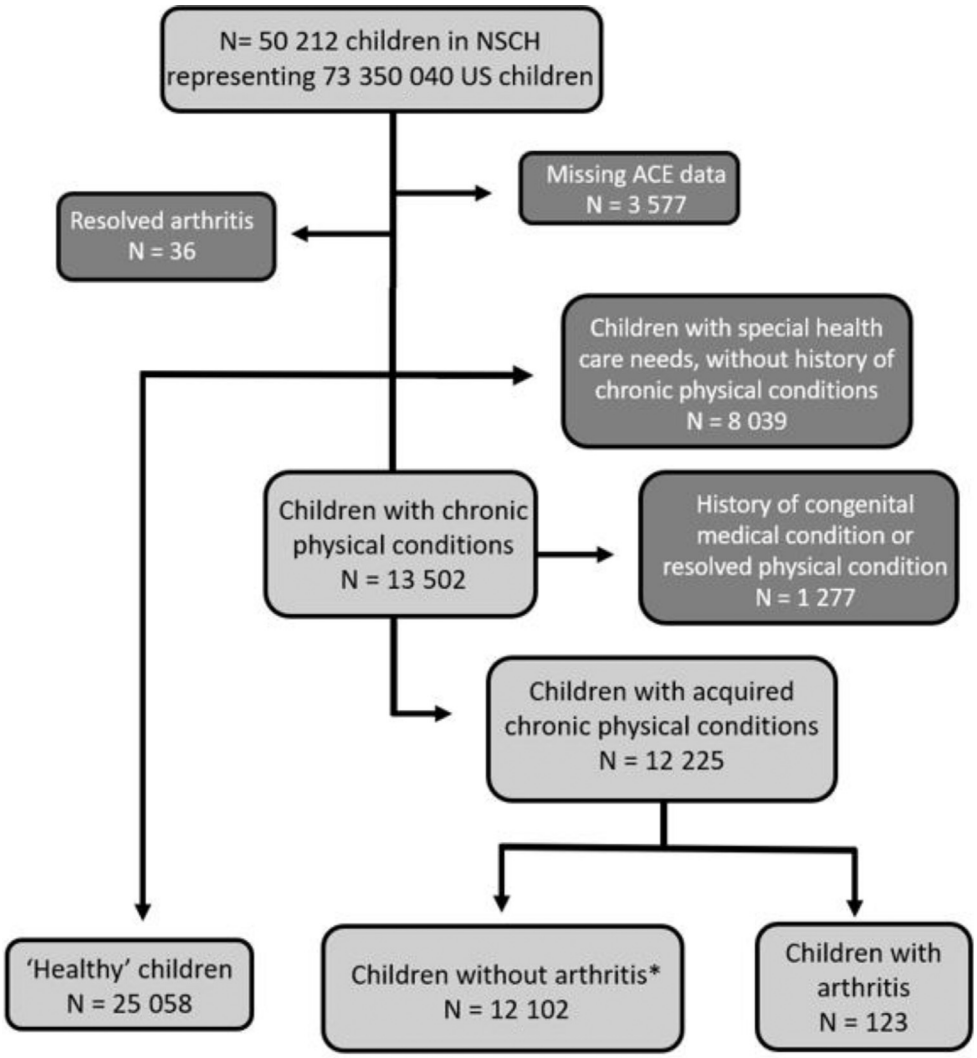

Figure 1. Included subpopulations of the 2016 NSCH are shown in *light gray*; the subgroups that were excluded are shown in *dark gray*. Chronic mental disorders were not excluded from any of the subgroups, including 'healthy' children. *Children with other chronic physical conditions, not arthritis, include children with physician-diagnosed allergies, asthma, diabetes, and epilepsy.

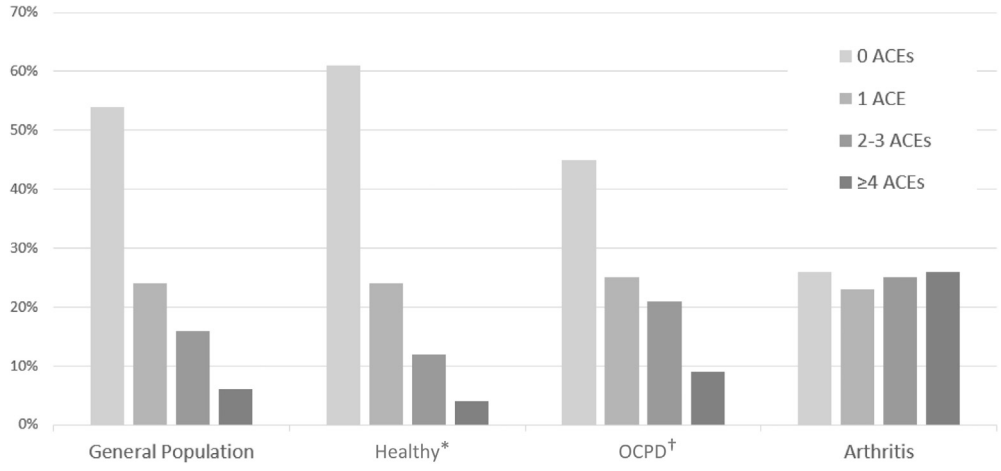

Figure 2. Weighted proportions of children with each categorical ACE score shown among the general population of all children from the NSCH and among NSCH subgroup populations. *Healthy children were defined as those with a negative screen for special health care needs and with no reported medical diseases. †OCPD include physician-diagnosed allergies, asthma, diabetes, and epilepsy.

Table II. ACEs in healthy children, children with OCPDs, and children with arthritis from the 2016 NSCH

ACEs	Healthy* (n = 25 058)	OCPD† (n = 12 102)	Arthritis (n = 123)
Any ACEs	39% (0.7)	55% (1.0)‡	74% (5.8)§
Specific ACEs			
Financial hardship	21% (0.6)	32% (1.0)	31% (5.7)
Divorced/separated parents	20% (0.6)	31% (0.9)¶	47% (7.0)§
Death of a parent	2% (0.2)	4% (0.4)	7% (3.6)
Incarceration of a parent	6% (0.4)	11% (0.8)¶	19% (5.2)§
Witnessed physical abuse at home	4% (0.3)	7% (0.5)**	22% (6.3)§
Witnessed violence in neighborhood	2% (0.2)	5% (0.4)††	21% (6.6)§
Mental illness in home	5% (0.3)	12% (0.7)††	36% (7.3)§
Alcohol/drug abuse in home	7% (0.4)	11% (.6)‡	24% (6.5)§
Racial/ethnic discrimination	3% (0.2)	5% (0.5)¶	14% (6.0)§

Weighted proportions with SE given. *P* values from Pearson χ^2 tests.
Pairwise comparisons of arthritis vs other chronic diseases: ¶$P < .05$, ‡$P < .01$, **$P < .001$, ††$P < .0001$.
Pairwise comparisons of arthritis vs healthy: §$P < .0001$.
*Healthy children defined as those with a negative screen for special health care needs and with no reported chronic diseases.
†OCPDs include physician-diagnosed allergies, asthma, diabetes, and epilepsy.