Received: 15 May 2022 | Revised: 9 June 2022 | Accepted: 21 August 2022

DOI: 10.1111/1756-185X.14431

International Journal of Rheumatic Diseases WILEY

ORIGINAL ARTICLE

An overview of the relationship between juvenile idiopathic arthritis and potential environmental risk factors: Do early childhood habits or habitat play a role in the affair?

Oya Koker[1,2] | Ayten Aliyeva[1] | Sezgin Sahin[1] | Amra Adrovic[1] | Mehmet Yildiz[1] | Fatih Haslak[1] | Aybuke Gunalp[1] | Kenan Barut[1] | Ozgur Kasapcopur[1]

[1]Pediatric Rheumatology, Cerrahpasa Medical School, Istanbul University-Cerrahpasa, Istanbul, Turkey

[2]Pediatric Rheumatology, Marmara University-Pendik Training and Research Hospital, Istanbul, Turkey

Correspondence
Ozgur Kasapcopur, Department of Pediatric Rheumatology, Cerrahpasa Medical School, Istanbul University-Cerrahpasa, Kocamustafapasa Caddesi No:53, Cerrahpasa, 34098 Fatih, Istanbul, Turkey.
Email: ozgurkasapcopur@hotmail.com

Abstract

Aim: The current study was undertaken to evaluate the influence of breastfeeding on the development and outcome measures of juvenile idiopathic arthritis (JIA). The second aim was to determine the consequences of particular sociodemographic and sociocultural characteristics and nutritional behavior of early childhood on JIA.

Methods: The study includes the patients diagnosed with JIA and regularly followed up at the Department of Pediatric Rheumatology in Istanbul University-Cerrahpasa. The comparison group consisted of healthy subjects and patients with juvenile systemic lupus erythematosus (jSLE). A face-to-face survey method was conducted with the parents of the participants between February 1, 2021, and September 1, 2021.

Results: The mean age of the JIA cohort (n = 324) was 12.2 ± 4.7 years, with a female ratio of 64.8%. The breastfeeding rate differed from the control groups (253 healthy subjects and 88 patients with jSLE) but was higher with a value of 94.8%. There was no difference between the groups ($P = .097$, $P = .064$) or within the subgroups of JIA ($P = .12$) regarding breastfeeding duration. Cow's milk introduction time ($P = .02$, $P = .0001$), household pet-keeping ($P = .001$), income level ($P = .0001$), maternal literacy ($P = 0.013$) made a statistical difference vs the control groups.

Conclusion: No relationship was established between the rate or duration of breastfeeding and the development or severity of JIA. The early introduction of cow's milk was found to be higher in the patient cohorts. The income level and maternal literacy appeared to be relevant with the high disability and damage scores, and frequent relapse rates. Secondhand smoking, higher in JIA, may prompt the basis of primary preventable strategies in JIA.

KEYWORDS
breastfeeding, early childhood exposures, environmental factors, juvenile idiopathic arthritis, outcome

1 | INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease complex in childhood which encompasses 7 heterogenous subtypes, demonstrating a broad clinical distribution.[1–3] The disease, although not fully elucidated, arises with the interaction of genetic and environmental factors, leading to immune dysregulation and displaying both autoimmune and inflammatory features.[4] Advances in molecular medicine and elucidation of the cytokine network shed light on the etiopathogenesis for a better understanding of the disease. However, individual differences in the course of the disease strongly suggest the influence of external factors.

There seems to be an intricate interplay of genetic predisposition and environmental influences, with varying balances between ethnic groups and even individually at the root of autoimmune diseases.[5] The increase in the incidence of certain autoimmune disorders over the past few decades may well be associated with raised awareness, but is also a consequence of the potential impact of environmental alterations. Furthermore, the variation in clinical phenotypes of diseases is attributed to more than genetic divergence, strongly suggesting the growing role of environmental triggers.[6] Investigators have endeavored to determine the position of various environmental factors such as early childhood nutrition, lifestyle, microbiota, passive smoking, infections and medications in the etiology of largely known autoimmune diseases, such as diabetes mellitus, celiac disease, rheumatoid arthritis, inflammatory bowel disease (IBD).[5,7] Considering that they may have shared risks besides the overlapping genetic features with other autoimmune diseases, certain environmental factors have been focused on for JIA, but the heterogeneity in the definition and classification have brought methodological limitations to the studies. Among the environmental factors investigated, the most striking is the controversial protective effect of breastfeeding on the incidence and severity of JIA.[6,8] There is ample evidence respecting the fact that breastfeeding acts as a bridge to transfer the maternal immunological memory and essential compounds such as cytokines, and through this connection, supports building the infant's immune system as well as enriching the microbiome. Disruption of this balance is considered to lead to an increased risk of immune disorders, including autoimmune diseases.[9] On the other hand, the relationship between the early introduction of formula or cow's milk and the development of JIA is a matter of debate, with conflicting study results.[10–12]

The current study was undertaken to evaluate the influence of breastfeeding on the development and outcome measures of JIA according to the subtypes. The second aim of our work was to further broaden current knowledge of the consequences of particular sociodemographic and sociocultural characteristics and nutritional behavior of early childhood on JIA.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was performed with patients with JIA who were diagnosed and regularly followed up at Department of Pediatric Rheumatology in Cerrahpasa Medical School in Istanbul University-Cerrahpasa, a tertiary care referral hospital in Turkey. The comparison group consisted of healthy subjects and patients with juvenile systemic lupus erythematosus (jSLE). A face-to-face survey method was conducted with the parents of the participants between February 1, 2021 and September 1, 2021.

2.2 | Identification of study groups

The study cohort consisted of patients who were diagnosed with JIA before the age of 16 and completed a year follow-up period. The patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria and identified as oligoarthritis (oJIA), polyarthritis (pJIA) rheumatoid factor (RF) positive, polyarthritis RF negative, enthesitis-related arthritis (ERA), systemic juvenile idiopathic arthritis (sJIA), juvenile psoriatic arthritis (jPsA) and undifferentiated arthritis; each was evaluated separately in the study.[3] Nevertheless, patients in the category of undifferentiated arthritis were excluded due to insufficient number and oJIA was evaluated in 2 groups as extended and persistent.

The comparison group consisted of healthy relatives of the hospital staff and students from surrounding schools who did not have any known disease or use of any medication and patients diagnosed with juvenile systemic lupus erythematosus (jSLE), our largest cohort representing autoimmune diseases after JIA.

Inclusion and exclusion criteria were established to provide standardization among the participants. Subjects with a comorbid disease, a first-degree relative with an inflammatory rheumatic disease, and a familial genetic burden were excluded from the study. Patients with incomplete data regarding the content of the survey and those whose parents refused to participate in the study were also excluded. The patients with insufficient medical data or without regular follow-up were not included. Each participant and his/her legal representative approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients prior to their inclusion in the study. The written consent and signature were obtained from the participants. Approval was obtained from the Ethics Committee of Cerrahpasa Medical School (approval: 09.01.2020-4116) for the study.

2.3 | Data collection and content of the survey

The patients were surveyed during their routine visits, their medical records were reviewed, and their inclusion and exclusion criteria were established. The content of the survey, consisting of open-ended and closed-ended questions, was formulated by the authors of the study. The subjects were surveyed for their sociodemographic and sociocultural characteristics, parental behaviors, gestation and breastfeeding period, and nutritional status in early childhood. The medical records of the patients diagnosed with JIA were reviewed for demographic data, clinical follow-up,

and treatment modalities. The disease characteristics including subtype, age at diagnosis, disease duration, medication, outcome measures were documented.

The number of active joints, functional ability, the number of joints with a limited range of motion, presence of systemic features such as fever, rash, serositis, splenomegaly, lymphadenopathy attributable to JIA, treatment responses, C-reactive protein level (normal <5 mg/L), erythrocyte sedimentation rate (normal ≤20 mm/h), pain and well-being assessments of the physician (PGA) and patient/parents (PtGA), recorded during the routine visits of the patients at 3-month intervals, were evaluated. Visual analog scale (VAS; 0 = no pain, 10 = worst pain) was used to access pain intensity.

Disease activity score of each patient was calculated individually according to disease subtype and disease duration. The Wallace criteria, Juvenile Arthritis Disease Activity Score (JADAS) 27, systemic JADAS (sJADAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), Psoriasis Area Severity Index (PASI) were used for the assessments.[13–19] In the calculation of disease activity, JADAS for patients with extended and persistent oJIA, RF negative and positive pJIA; sJADAS for patients with sJIA; JSpADA for ERA; both PASI (skin involvement) and JADAS (joint involvement) for jPsA were used.

Juvenile arthritis damage index (JADI) and childhood health assessment questionnaire (CHAQ; 0 = normal, 3 = worst score) which were administered to the patients at 6-month intervals were used for the assessment of articular and extra-articular damage and functional disability, respectively.[20,21] In order to ensure standardization, the scores were calculated cumulatively according to disease duration. First clinical remissions (CR) determined according to Wallace clinical inactive disease criteria (CID) for oligoarticular, polyarticular and systemic subtypes, and relapse frequencies were recorded.[13] CR on medication was defined as CID for at least 6 months. CR off medication was defined as CID for 12 months after all medication was withdrawn. Since there is no standard evaluation method for patients with ERA and jPsA, the CID evaluation was based on the absence of active arthritis or rash or inflammatory pain. The state of the patient who did not meet the CID criteria in at least one visit was defined as a relapse.

2.4 | Statistical analysis

Statistical analyses were performed by using the IBM SPSS Statistics for Windows 25.0 software (Statistical Package for the Social Sciences) and Microsoft Excel. The visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's normality tests) were used to analyze the distribution of the variables. The demographic and clinical data were evaluated using descriptive analysis. Mean values with standard deviations (mean ± SD) or median (med) with minimum and maximum values (min-max) were given for demonstration of the data according to the distribution. Categorical variables were presented as counts or frequencies and compared using Chi-square test or Fisher test statistics. One-way analysis of variance or Student's *t* test was used for parametric distribution. Kruskal-Wallis test or Mann-Whitney *U* test was used for nonparametrically distributed variables. The statistical significance level was taken as .05.

3 | RESULTS

3.1 | Patient characteristics

Among the patients diagnosed with JIA, 26 were excluded owing to missing data or insufficient follow-up period, 21 due to comorbid diseases, while 47 patients were excluded because of a history of inflammatory rheumatic disease in their first-degree relatives. Ultimately, 324 patients met the inclusion criteria. Table 1 demonstrates the demographic and clinical characteristics of the patients in the JIA cohort.

3.2 | Comparison of the study groups

In the comparison group, 253 healthy subjects and 88 patients with jSLE were included. The JIA cohort and the healthy controls demonstrated statistical differences in maternal and paternal age, breastfeeding and formula feeding rate, cow's milk introduction period, preschool participation, household pet-keeping, passive smoking, and maternal literacy. The mean disease duration was 6.1 ± 4.1 years in JIA and 4.6 ± 2.6 years in jSLE. In the comparison of the JIA and jSLE cohorts, statistical differences were observed in terms of age, gender, breastfeeding rate, cow's milk introduction period, immunization status, household pet-keeping, and income level. Table 2 reflects the comparisons of the study groups by the early childhood exposures and environmental risk factors.

3.3 | The impact of potential environmental factors on disease outcome measures

Outcome measures of the JIA cohort according to the subtypes and disease duration are presented in Table 3, along with their current age and age at diagnosis. No statistical difference was observed when the subgroups (oJIA, pJIA, ERA, and sJIA) were compared as per the breastfeeding duration ($P = .12$). The reflections of the rate and duration of breastfeeding on the outcome measures were assessed and are presented in Table 4. In addition to breastfeeding, the impacts of immunization and certain socioeconomic and cultural factors, which differ from the control group, on disease outcome measurements were evaluated. The impacts of immunization, cigarette exposure, family income level, and maternal literacy on the disease were compared and are presented in Table 5.

TABLE 1 Clinical characteristics of patients in the juvenile idiopathic arthritis cohort.

Subtypes of JIA, n (%)	
Persistent oligoarthritis	100 (30.9)
Extended oligoarthritis	29 (9)
Seronegative polyarthritis	52 (16)
Seropositive polyarthritis	30 (9.3)
Psoriatic arthritis	16 (4.9)
Enthesitis-related arthritis	53 (16.3)
Systemic JIA	44 (13.6)
Age at diagnosis, y	
Mean ± SD	6.5 ± 4.1
Med (min-max)	6 (1-15)
Disease duration, y	
Mean ± SD	6.1 ± 4.1
Med (min-max)	5.0 (1-17)
Non-biologic DMARDs, n (%)	
Methotrexate	285 (88)
Sulfasalazine	6 (1.9)
Cyclosporine	5 (1.6)
Biologic DMARDs	
Anti-TNF	164 (50.6)
Anti-IL1	26 (8)
Anti-IL6	13 (4)
Biologic switching due to reactivation	64 (19.8)
First mo of clinical remission	5.8 ± 4.1
On medication	52 (16)
Off medication	32 (9.9)
Rates of relapse	
Mean ± SD	1.9 ± 1.8
Med (min-max)	2 (0-10)
CHAQ[a]	
Mean ± SD	1.26 ± 1.1
Med (min-max)	1.1 (0-4)
JADI[a]	
Mean ± SD	0.96 ± 1.6
Med (min-max)	0 (0-10)

Abbreviations: CHAQ, childhood health assessment questionnaire; DMARDs, disease-modifying anti-rheumatic drugs; JADI, juvenile arthritis damage index; JIA, juvenile idiopathic arthritis.

[a]Cumulative values are presented for the JADI and CHAQ scores.

4 | DISCUSSION

This study focuses on the possible role of early childhood exposures and environmental risk factors in JIA. Primarily the paper seeks to evaluate the influence of breastfeeding on the development and outcome measures according to the subtypes of the disease. While the early introduction of cow's milk was found to be higher in the patient cohorts, no relationship has been established between the rate or duration of breastfeeding and the development or severity of JIA. A few researchers addressed the issue in the early 1990s and revealed controversial results.[22,23] The small sample size, patient selection bias, and lack of a patient control group were the constraining factors in the studies. On the other hand, the modification in the classification and terminology suggested reinterpretation of the results as per the subtypes. A report including healthy controls as well as the patients with primary nephrotic syndrome as a comparison group underlined that although there was no difference respecting the breastfeeding rate within the groups, the breastfeeding duration in the oligoarticular type has been found shorter.[24] In our study, the breastfeeding rate of JIA differed vs jSLE and healthy individuals yet it was quite high with a value of 94.8%. Further, there was no difference between the 3 main groups or within the subgroups of JIA in terms of breastfeeding durations analyzed in 5 categories in our study. Alongside studies examining the role of breastfeeding in the development of JIA, Hyrich and co-workers discussed its association with the severity of the disease and concluded that breastfeeding was relevant to less occurrence, and milder or later onset of JIA yet without a comparison group as the major limitation. The study pointed out that breastfed children were more likely to be diagnosed at younger ages and had better physician or parent global pain and physical function scores, with longer durations of breastfeeding corresponding to progressively lower scores. Curiously, the authors have observed a higher rate of early disease onset in never-breastfed patients in JPsA and ERA.[25] Furthermore, in a report evaluating 203 patients with human leukocyte antigen B27 positive ankylosing spondylitis fulfilling the modified New York criteria, attention was drawn to the protective role of breastfeeding, referring to its effect on microbiota.[26] While the correlation between microbiota and ERA is currently on the agenda, these assumptions seem well-founded. Correspondingly, a recent report from Brazil observed a high prevalence of breastfeeding in the low-income JIA cohort, and breastfeeding over 6 months has been associated with less disease activity, CHAQ score, and less joint deformity.[27] Although there was no difference in outcome measures between the breastfed and non-breastfed groups, a reliable comparison could not be achieved in our study, since the breastfeeding rate was high in the entire JIA cohort, but the duration of breastfeeding did not create a statistical difference in this regard.

On top of the retrospective studies, 32 patients have been reached in a prospective study reported in accordance with the national registry from southeastern Sweden, and the 4-month time frame has been determined as the cutoff for breastfeeding duration. Ultimately it has been highlighted that the longer breastfeeding may be protective against JIA.[10] The same study has asserted that low parental literacy may influence breastfeeding,[10] but this assertion was not backed by other reports.[27] In our study, the rate of maternal literacy was lower vs the healthy control group, but did not negatively impact the breastfeeding rate. However, low maternal literacy was associated with high disease activity, frequent relapse, high CHAQ and JADI scores.

TABLE 2 Comparison of the juvenile idiopathic arthritis cohort with healthy subjects and juvenile systemic lupus erythematosus patients according to environmental risk factors.

Survey questions	JIA (n = 324)	Healthy (n = 253)	P*	jSLE (n = 88)	P**
Age, y					
Mean ± SD	12.2 ± 4.7	11.5 ± 4.1	.056	14.9 ± 3.3	.001
Med (min-max)	13 (2-18)	12 (2-18)		16 (6-18)	
Gender, n (%)					
Female	210 (64.8)	153 (60.5)	.298	69 (78.4)	.015
Male	114 (35.2)	100 (39.5)		19 (21.6)	
BMI, n (%)					
Underweight	12 (3.7)	9 (3.5)	.08	3 (3.4)	.06
Healthy weight	292 (90.1)	229 (90.6)		79 (89.8)	
Overweight	20 (6.2)	15 (5.9)		6 (6.8)	
Maternal pregnancy age					
<20	32 (9.9)	43 (17.0)	.002	9 (10.2)	.310
20-34	251 (77.5)	162 (64.0)		73 (83.0)	
≥35	41 (12.7)	48 (19.0)		6 (6.8)	
Paternal age					
<20	-	8 (3.2)	.001	-	.162
20-34	241 (74.4)	165 (65.2)		72 (81.8)	
≥35	83 (25.6)	80 (31.6)		16 (18.2)	
Birth order					
First	136 (42.0)	122 (48.2)	.07	33 (37.5)	.450
Second	99 (30.6)	84 (33.2)		33 (37.5)	
Third or later	89 (27.5)	47 (18.6)		22 (25)	
Mother's marital status					
Married	293 (90.4)	218 (86.2)	.11	78 (88.6)	.688
Divorced/single	31 (9.6)	35 (13.8)		10 (11.4)	
Smoking during pregnancy	66 (20.4)	38 (15.0)	.10	18 (20.7)	1.000
Major illness during pregnancy	28 (8.6)	22 (8.7)	1.000	7 (8.0)	1.000
Any medication during pregnancy	20 (6.2)	18 (7.1)	.736	6 (6.8)	.807
Alcohol during pregnancy	3 (0.9)	8 (3.2)	.066	2 (2.3)	.290
Has the child ever breastfed?	307 (94.8)	224 (88.5)	.008	76 (86.4)	.016
Breastfeeding duration, mo					
<6	62 (20)	31 (13.8)	.097	10 (13.2)	.064
6-12	44 (14.2)	40 (17.9)		20 (26.3)	
12-18	73 (23.5)	66 (29.5)		21 (27.6)	
18-24	85 (27.4)	64 (28.6)		15 (19.7)	
≥24	46 (14.8)	23 (10.3)		10 (13.2)	
Cow's milk introduction, mo					
<12	60 (18.5)	29 (11.5)	.020	39 (44.3)	.0001
>12	264 (81.5)	224 (88.5)		49 (55.7)	
Formula feeding	158 (48.8)	85 (33.6)	.001	43 (48.9)	1.000
Hospitalization due to infection in the first y of life?	54 (16.7)	36 (14.2)	.488	15 (17.0)	1.000
Immunization status					
Fully immunized	290 (89.5)	230 (90.9)	.674	85 (96.6)	.037
Partially immunized	34 (10.5)	23 (9.1)		3 (3.4)	

(Continues)

TABLE 2 (Continued)

Survey questions	JIA (n = 324)	Healthy (n = 253)	P*	jSLE (n = 88)	P**
Preschool/nursery	159 (49.1)	96 (37.9)	.009	40 (45.5)	.631
Household pet					
Cat-dog	21 (6.5)	31 (12.3)	.001	17 (19.3)	.001
Bird	34 (10.5)	17 (6.7)		5 (5.7)	
Hairless pet	2 (0.6)	12 (4.7)		2 (2.3)	
Household smoking	204 (63.0)	120 (47.4)	.0001	53 (60.2)	.710
Place of residence					
Urban area	305 (94.1)	241 (95.3)	.583	73 (83.0)	.624
Rural area	19 (5.9)	12 (4.7)		6 (6.8)	
Income level					
Below	184 (56.8)	122 (48.2)	.053	15 (17.0)	.0001
Minimum wage	125 (38.6)	110 (43.5)		69 (78.4)	
Above	15 (4.6)	21 (8.3)		4 (4.5)	
Maternal literacy					
Illiterate	65 (20.1)	28 (11.1)	.013	24 (27.3)	.085
Primary	134 (41.4)	101 (39.9)		44 (50.0)	
Secondary	89 (27.5)	78 (30.8)		15 (17.0)	
Higher	33 (10.2)	42 (16.6)		5 (5.7)	
Master's degree	3 (0.9)	4 (1.6)		-	
Paternal literacy					
Illiterate	29 (9.0)	16 (6.3)	.106	7 (8.0)	.682
Primary	153 (47.2)	98 (38.7)		42 (47.7)	
Secondary	97 (29.9)	90 (35.6)		30 (34.1)	
Higher	39 (12.0)	43 (17.0)		9 (10.2)	
Master's degree	6 (1.9)	6 (2.4)		-	

Abbreviations: BMI, body mass index; JIA, juvenile idiopathic arthritis; jSLE, juvenile systemic lupus erythematosus.
*P** represents comparison between JIA and healthy control group, and *P*** represents comparison between JIA and jSLE group.

TABLE 3 Outcome measures of the juvenile idiopathic arthritis cohort according to subgroups.

Subtypes of JIA	Current age	Age at diagnosis	Disease duration	Disease activity	CID	Relapse rate	CHAQ	JADI
Persistent oJIA (n = 100)	8 (3-18)	3 (1-15)	4 (1-15)	0.9 (0-14)	4 (1-24)	1 (0-6)	0.8 (0-3)	0 (0-4)
Extended oJIA (n = 29)	12 (5-18)	3 (1-10)	9 (2-17)	0 (0-8)	4 (0-9)	2 (0-4)	2 (0-4)	6 (3-20)
RF(−) pJIA (n = 52)	15 (7-18)	7 (1-15)	5 (1-15)	2 (0-18)	6 (1-24)	2 (0-8)	2 (0-3)	2 (0-8)
RF(+) pJIA (n = 30)	16 (10-18)	9 (2-15)	6 (1-17)	3 (0-12)	6 (3-16)	2 (0-7)	2.1 (0-4)	2 (0-10)
jPsA (n = 16)	12 (7-18)	8 (2-15)	5 (2-16)	2.5 (0.4-18.5)	6 (3-18)	2 (0-7)	1.7 (0-4)	1.5 (0-4)
ERA (n = 53)	16 (9-18)	10 (2-15)	5 (2-16)	1.5 (0-5)	6 (0-24)	1 (0-8)	1.8 (0-4)	0 (0-5)
sJIA (n = 44)	10 (2-18)	4 (1-14)	5 (1-15)	0 (0-3.9)	2 (1-12)	1 (0-10)	0 (0-3)	0 (0-8)

Abbreviations: CHAQ, childhood health assessment questionnaire; CID, clinically inactive disease; ERA, enthesitis-related arthritis; JADI, juvenile arthritis damage index; JIA, juvenile idiopathic arthritis; jPsA, juvenile psoriatic arthritis; oJIA, oligoarticular juvenile idiopathic arthritis; RF(−) pJIA, rheumatoid factor negative polyarticular juvenile idiopathic arthritis; RF(+) pJIA, rheumatoid factor positive polyarticular juvenile idiopathic arthritis; sJIA, systemic juvenile idiopathic arthritis.

Dietary intervention in infancy has been demonstrated to have a long-lasting effect on beta-cell autoimmunity markers, which may reflect an autoimmune process.[28] A recent review has stated that despite the shared roles of breastfeeding, maternal diet, and early nutrition in autoimmune diseases, each disease has specific dietary driver epigenetic mechanisms requiring further investigation.[29] The

TABLE 4 The influence of breastfeeding and breastfeeding duration on the outcome measures of the patients with juvenile idiopathic arthritis.

Breastfeeding as the risk factor	Disease duration	Disease activity	CID	Relapse rate	CHAQ	JADI
Rate						
Never breastfed	5 (1-16)	2.2 (0-7)	6 (1-16)	1 (0-4)	1.7 (0-3)	0 (0-4)
Breastfed	5 (1-17)	1.2 (0-18.5)	5 (0-24)	2 (0-10)	1 (0-4)	1 (0-10)
P	.171	.311	.869	.279	.798	.136
Duration, mo						
<6	5 (1-15)	1 (0-8)	6 (1-20)	2 (0-10)	1.1 (0-4)	1 (0-10)
6–12	4 (1-17)	2 (0-18)	5 (1-24)	2 (0-8)	1 (0-3)	0 (0-6)
12–18	6 (1-17)	1.2 (0-13)	5 (0-20)	2 (0-10)	1.4 (0-4)	1 (0-8)
18–24	4 (1-16)	1.2 (0-18.5)	4 (1-24)	2 (0-7)	1 (0-4)	0 (0-6)
>24	5 (1-15)	0.7 (0-6)	6 (1-24)	1 (0-6)	0.7 (0-4)	0 (0-5)
P	.398	.201	.139	.077	.098	.056

Abbreviations: CHAQ, childhood health assessment questionnaire; CID, clinical inactive disease; JADI, juvenile arthritis damage index.

TABLE 5 The influence of immunization, income, passive smoking and maternal literacy on the outcome measures of the juvenile idiopathic arthritis cohort.

Differentiating factors	Disease duration	Disease activity	CID	Relapse rate	CHAQ	JADI
Immunization						
Fully immunized	5 (1-17)	1.3 (0-18.5)	5 (0-24)	2 (0-10)	1 (0-4)	0 (0-10)
Partially immunized	5 (1-17)	1 (0-7.3)	6 (2-20)	2 (0-9)	1.4 (0-4)	0 (0-8)
P	.270	.531	.088	.139	.267	.050
Income level						
Below	5 (1-17)	1.5 (0-18.5)	6 (1-24)	2 (0-10)	1.4 (0-4)	1 (0-10)
Minimum wage	5 (1-17)	1.1 (0-18.0)	5 (0-24)	1 (0-10)	0.6 (0-4)	0 (0-8)
Above	5 (1-8)	0 (0-6)	4 (2-8)	1 (0-3)	0.6 (0-2)	0 (0-2)
P	.238	.080	.248	.004	.002	.009
Household smoking						
Yes	5 (1-17)	1.3 (0-18.5)	6 (0-24)	2 (0-10)	1.1 (0-4)	0 (0-10)
No	5 (1-15)	1.1 (0-18)	5 (1-20)	2 (0-10)	1 (0-4)	0 (0-8)
P	.453	.392	.559	.919	.543	.679
Maternal literacy						
Illiterate	6 (1-17)	3 (0-18)	6 (1-24)	2 (0-10)	2 (0-4)	2 (0-10)
Primary education	5 (1-17)	1.5 (0-18.5)	6 (1-24)	2 (0-8)	1.1 (0-4)	0 (0-8)
Secondary education	5 (2-15)	0.9 (0-8)	4 (0-20)	1 (0-6)	1 (0-3)	0 (0-8)
Higher education	3 (1-14)	0.6 (0-12)	3 (1-17)	1 (0-4)	0.6 (0-2)	0 (0-2)
P	.052	.0001	.0001	.0001	.0001	.0001

Abbreviations: CHAQ, childhood health assessment questionnaire; CID, clinical inactive disease; JADI, juvenile arthritis damage index.

Childhood Arthritis Risk Factor Identification Study (CLARITY) from Australia has supported the argument of neither breastfeeding duration nor the early introduction of cow's milk in determining JIA risk.[12] Nevertheless in another study, early introduction to the formula has been associated with an increased risk of JIA, while only a tendency of association has been detected concerning cow's milk.[10] Furthermore, few case reports have claimed that the removal of cow's milk, hence the allergens such as β-lactoglobulin and casein, from the diet in JIA patients improves the course of arthritis. The fact that early use of cow's milk was higher in both our patient cohorts vs the healthy controls may support this relationship and deserves further research.

Traditionally, the focus has always been on infections among the conspicuous environmental risk factors.[6] Given that joint involvement may accompany the course of an infection, the role of infectious factors in the development of the disease has been long argued. Streptococcus, Parvovirus B19 and Epstein-Barr virus were the main agents of concern.[30–34] Although a specific infectious agent

could not be revealed, the relationship between infections encountered in the first year of life and diseases such as type 1 diabetes mellitus and IBD has been identified.[35,36] Comparing a large cohort of patients with JIA vs a control group using Swedish registry data from 1973 to 2002, Carlens et al[37] have proposed a prospective association between hospitalization for any infection in the first year of life and the development of JIA. On the other hand, in a comprehensive study in which early-life risk factors were compared to playmate-matched controls, neither breastfeeding nor hospitalization has been associated with an increased risk.[11] Our experiments were consistent with Shenoi et al's findings. Thus, the results of our study do not support the relationship between a moderate–severe infection requiring hospitalization and the development of JIA. Research has tended to focus on infections requiring hospitalization, for the sake of easy recall and documentation. However, children may be faced with many infections in the early stages of their lives, and it seems challenging to evaluate the role of past infections in etiology as a whole. Conversely, there are also claims regarding a protective role of infection on the risk of autoimmune diseases by supporting the maturation of the immune system, particularly early in life, under the concept of the hygiene hypothesis.[38] The CLARITY study has assessed the impacts of sibling exposure on JIA with a comprehensive set of data including birth order and the number of siblings. The cumulative sibling exposure has been associated with a negative correlation which proposes that increased microbial exposure in childhood may confer protection against the development of the disease.[39] A case–control study evaluating perinatal and maternal characteristics according to the subgroups further supported the concept of hygiene or microchimerism hypotheses and declared a decreased risk with increasing parity.[40] However, possible inaccuracies in reporting maternal reproductive history and deficiencies in birth records have been indicated as the weakness of the study. Hence, the straight or consequential influences of infections are one of the controversial points in the etiopathogenesis of JIA. A meticulous screening with a larger sample size is essential in order to reach an explicit conclusion. Correspondingly, factors that have been associated with microbial exposure in early childhood, such as birth order, number of siblings, preschool attendance, and household pet-keeping were surveyed in our study. Among these variables, the rate of household pet-keeping in JIA was lower compared to the control group. Unexpectedly, in another study, contact with farm animals or pet contact during infancy has not been associated with oJIA, but with the development of IBD and SLE.[41] Since the overall cohort is heterogeneous, studies focusing on a subgroup and a straightforward factor may reflect more reliable results. While the comparisons were between the main groups in our study, the limitation of subgroup analyses due to numerical inadequacy was one of the drawbacks.

As a result of a systematic review and meta-analyses on environmental factors, one of the most intriguing correlations was with maternal smoking.[42] In the early 2000s, Jaakkola and co-workers examined the relationship between maternal smoking and the development of JIA in the first 7 years of life, based on Finnish birth registry records, and noticed 31 cases. They revealed a likely association between smoking 10 or more cigarettes per day during pregnancy and the development of JIA in females.[43] The results of the study, which were criticized methodologically, have not been confirmed by more extensive studies.[11,12,44] Although maternal smoking did not seem to pose a risk, according to our study results, the patients with JIA had higher indoor smoking exposure vs the healthy control group. Outcome measures demonstrated no association with cigarette exposure. However, considering that smoking is one of the unfavorable factors in the etiology of autoimmune diseases such as RA,[45,46] further investigations are needed to estimate the association between passive smoking and JIA.

Few researchers have addressed the question of whether several socioeconomic factors are associated with JIA.[47] The probability of developing JIA has been found to be higher in children from families with high incomes and living in urban dwellings by establishing a link with a hygienic early-life habitat. Our study results do not appear to corroborate their observations, and while the income levels of our patients with JIA did not differ from the healthy controls, their incomes were lower than the jSLE cohort. Moreover, income levels below the minimum wage were associated with frequent relapses, higher disability and damage. Our findings were consistent in that low socioeconomic status negatively affected the control of the disease.

Ultimately, we obtained comprehensive results that will shed light on our understanding of the relationship between breastfeeding and particular environmental factors and JIA. Compelling measurement and comparison of environmental data, the likely recall bias in the past inquiry, and the reflections of geographical and cultural discrepancies may render the results of studies in this field speculative. On the other hand, we know that many individual factors and confounders may come into play during the emergence and course of JIA, and clinical phenotypes, immunogenetic interactions and treatment processes may determine long-term outcomes. The strong point of our analysis in this respect was the binary comparison, including the healthy and patient groups. Further, categorized questions were asked to the parents face-to-face by the same researcher. The outcome measurements of each patient were calculated individually and cumulatively. Breastfeeding duration and striking differences between the main groups were compared according to these measures. Nevertheless, the overall high rate of breastfeeding in our study group prevented a robust assessment of outcome measures as planned in the breastfed and non-breastfed groups. Further, the decrease in the number of samples when divided into categories limited the analysis of the subgroups.

5 | CONCLUSION

Our observations have several implications for further research in determining the relationship between alternative environmental factors and autoimmunity by confirming the influence of the early introduction of cow's milk and suggesting a role for formula feeding

as a trigger for some autoimmune disorders. The results emphasize that socioeconomic factors such as income level and sociocultural aspects such as maternal literacy, as well as passive smoking, may affect the pecuniary and intangible dimensions of JIA and may reveal the necessity of determining preventive strategies. Although relevant environmental factors vary, many seem to intersect by disrupting microbiome diversity and immune balance in etiopathogenesis. The environmental factors examined so far require further investigation in well-designed studies with satisfactory samples to determine their position in the disease risk. While creating pertinent studies and interpreting the results, the heterogeneity of the disease itself and the fact that the interaction of genetic and environmental factors constitutes the infrastructure should not be overlooked. Environmental factors will inevitably soon become the issue of more research, under the influence of global climate changes.

AUTHOR CONTRIBUTIONS

All the authors contributed to the manuscript. Professor OK was responsible for the conception and design. All the authors were responsible for the acquisition, analysis and interpretation of data. Assistant Professor OK and Professor OK participated in drafting the work and all authors contributed to criticism of the manuscript. All authors read the manuscript and approved the submission. All authors of the study agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGEMENTS

We would like to thank our patients and their families for their sincere participation in our survey and study.

CONFLICT OF INTEREST

No conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ETHICAL APPROVAL

Informed consent was obtained from the legally authorized representatives of our patients. Approval was obtained from the Ethics Committee of Cerrahpasa Medical School (approval: 09.01.2020-4116) for the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

ORCID

Oya Koker https://orcid.org/0000-0002-0101-9585
Ayten Aliyeva https://orcid.org/0000-0002-8046-3907
Sezgin Sahin https://orcid.org/0000-0002-5365-3457
Amra Adrovic https://orcid.org/0000-0002-2400-6955
Mehmet Yildiz https://orcid.org/0000-0002-7834-4909
Fatih Haslak https://orcid.org/0000-0002-6963-9668
Aybuke Gunalp https://orcid.org/0000-0003-0137-0460
Kenan Barut https://orcid.org/0000-0001-8459-2872
Ozgur Kasapcopur https://orcid.org/0000-0002-1125-7720

REFERENCES

1. Barut K, Adrovic A, Şahin S, Kasapçopu Ö. Juvenile idiopathic arthritis. *Balkan Med J*. 2017;34(2):90-101.
2. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. *Rheumatol Ther*. 2016;3(2):187-207.
3. Petty RE, Southwood TR, Manners P, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-392.
4. Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw RA. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. *Pediatr Rheumatol Online J*. 2021;19(1):135.
5. Räisänen L, Viljakainen H, Sarkkola C, Kolho KL. Perinatal risk factors for pediatric onset type 1 diabetes, autoimmune thyroiditis, juvenile idiopathic arthritis, and inflammatory bowel diseases. *Eur J Pediatr*. 2021;180(7):2115-2123.
6. Ellis JA, Munro JE, Ponsonby AL. Possible environmental determinants of juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2010;49(3):411-425.
7. Richardson B. The interaction between environmental triggers and epigenetics in autoimmunity. *Clin Immunol*. 2018;192:1-5.
8. Vieira Borba V, Sharif K, Shoenfeld Y. Breastfeeding and autoimmunity: programing health from the beginning. *Am J Reprod Immunol*. 2018;79(1):e12778.
9. M'Rabet L, Vos AP, Boehm G, et al. Breast-feeding and its role in early development of the immune system in infants: consequences for health later in life. *J Nutr*. 2008;138(9):1782s-1790s.
10. Kindgren E, Fredrikson M, Ludvigsson J. Early feeding and risk of juvenile idiopathic arthritis: a case control study in a prospective birth cohort. *Pediatr Rheumatol Online J*. 2017;15(1):46.
11. Shenoi S, Shaffer ML, Wallace CA. Environmental risk factors and early-life exposures in juvenile idiopathic arthritis: a case-control study. *Arthritis Care Res (Hoboken)*. 2016;68(8):1186-1194.
12. Ellis JA, Ponsonby AL, Pezic A, et al. CLARITY - ChiLdhood arthritis risk factor identification sTudY. *Pediatr Rheumatol Online J*. 2012;10(1):37.
13. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol*. 2004;31(11):2290-2294.
14. Wallace CA, Giannini EH, Huang B, et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2011;63(7):929-936.
15. Consolaro A, Ruperto N, Bazso A, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;61(5):658-666.
16. Bulatović Calasan M, de Vries LD, Vastert SJ, et al. Interpretation of the juvenile arthritis disease activity score: responsiveness, clinically important differences and levels of disease activity in prospective cohorts of patients with juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2014;53(2):307-312.
17. Tibaldi J, Pistorio A, Aldera E, et al. Development and initial validation of a composite disease activity score for systemic juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2020;59(11):3505-3514.

18. Weiss PF, Colbert RA, Xiao R, et al. Development and retrospective validation of the juvenile spondyloarthritis disease activity index. *Arthritis Care Res (Hoboken)*. 2014;66(12):1775-1782.
19. Mease PJ. Measures of psoriatic arthritis: tender and swollen joint assessment, psoriasis area and severity index (PASI), nail psoriasis severity index (NAPSI), modified nail psoriasis severity index (mNAPSI), Mander/Newcastle Enthesitis index (MEI), Leeds Enthesitis index (LEI), Spondyloarthritis research consortium of Canada (SPARCC), Maastricht ankylosing spondylitis enthesis score (MASES), Leeds dactylitis index (LDI), patient global for psoriatic arthritis, dermatology life quality index (DLQI), psoriatic arthritis quality of life (PsAQOL), functional assessment of chronic illness therapy-fatigue (FACIT-F), psoriatic arthritis response criteria (PsARC), psoriatic arthritis joint activity index (PsAJAI), disease activity in psoriatic arthritis (DAPSA), and composite psoriatic disease activity index (CPDAI). *Arthritis Care Res (Hoboken)*. 2011;63(Suppl 11):S64-S85.
20. Viola S, Felici E, Magni-Manzoni S, et al. Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. *Arthritis Rheum*. 2005;52(7):2092-2102.
21. Ruperto N, Ravelli A, Pistorio A, et al. Cross-cultural adaptation and psychometric evaluation of the childhood health assessment questionnaire (CHAQ) and the child health questionnaire (CHQ) in 32 countries. Review of the general methodology. *Clin Exp Rheumatol*. 2001;19(4 Suppl 23):S1-S9.
22. Mason T, Rabinovich CE, Fredrickson DD, et al. Breast feeding and the development of juvenile rheumatoid arthritis. *J Rheumatol*. 1995;22(6):1166-1170.
23. Rosenberg AM. Evaluation of associations between breast feeding and subsequent development of juvenile rheumatoid arthritis. *J Rheumatol*. 1996;23(6):1080-1082.
24. Kasapçopur O, Taşdan Y, Apelyan M, et al. Does breast feeding prevent the development of juvenile rheumatoid arthritis? *J Rheumatol*. 1998;25(11):2286-2287.
25. Hyrich KL, Baildam E, Pickford H, et al. Influence of past breast feeding on pattern and severity of presentation of juvenile idiopathic arthritis. *Arch Dis Child*. 2016;101(4):348-351.
26. Montoya J, Matta NB, Suchon P, et al. Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case-control retrospective study. *Ann Rheum Dis*. 2016;75(5):879-882.
27. Rocha FAC, Landim J, Nour ML, et al. Long-term breastfeeding influences disease activity in a low-income juvenile idiopathic arthritis cohort. *Clin Rheumatol*. 2019;38(8):2227-2231.
28. Knip M, Virtanen SM, Seppä K, et al. Dietary intervention in infancy and later signs of beta-cell autoimmunity. *N Engl J Med*. 2010;363(20):1900-1908.
29. Bangarusamy DK, Lakshmanan AP, Al-Zaidan S, et al. Nutri-epigenetics: the effect of maternal diet and early nutrition on the pathogenesis of autoimmune diseases. *Minerva Pediatr (Torino)*. 2021;73(2):98-110.
30. Barash J, Goldzweig O. Possible role of streptococcal infection in flares of juvenile idiopathic arthritis. *Arthritis Rheum*. 2007;57(5):877-880.
31. Gonzalez B, Larrañaga C, León O, et al. Parvovirus B19 may have a role in the pathogenesis of juvenile idiopathic arthritis. *J Rheumatol*. 2007;34(6):1336-1340.
32. Weissbrich B, Süss-Fröhlich Y, Girschick HJ. Seroprevalence of parvovirus B19 IgG in children affected by juvenile idiopathic arthritis. *Arthritis Res Ther*. 2007;9(4):R82.
33. Aghighi Y, Gilani SM, Razavi M, et al. Juvenile rheumatoid arthritis in children with Ebstein Barr virus infection. *Pak J Biol Sci*. 2007;10(20):3638-3643.
34. Aslan M, Kasapcopur O, Yasar H, et al. Do infections trigger juvenile idiopathic arthritis? *Rheumatol Int*. 2011;31(2):215-220.
35. Cooke A. Review series on helminths, immune modulation and the hygiene hypothesis: how might infection modulate the onset of type 1 diabetes? *Immunology*. 2009;126(1):12-17.
36. Klement E, Lysy J, Hoshen M, Avitan M, Goldin E, Israeli E. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. *Am J Gastroenterol*. 2008;103(7):1775-1782.
37. Carlens C, Jacobsson L, Brandt L, Cnattingius S, Stephansson O, Askling J. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. *Ann Rheum Dis*. 2009;68(7):1159-1164.
38. Murdaca G, Greco M, Borro M, Gangemi S. Hygiene hypothesis and autoimmune diseases: a narrative review of clinical evidences and mechanisms. *Autoimmun Rev*. 2021;20(7):102845.
39. Miller J, Ponsonby AL, Pezic A, et al. Sibling exposure and risk of juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2015;67(7):1951-1958.
40. 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(1):36.
41. Radon K, Windstetter D, Poluda D, et al. Exposure to animals and risk of oligoarticular juvenile idiopathic arthritis: a multicenter case-control study. *BMC Musculoskelet Disord*. 2010;11:73.
42. Clarke SLN, Mageean KS, Maccora I, et al. Moving from nature to nurture: a systematic review and meta-analysis of environmental factors associated with juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2022;61(2):514-530.
43. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. *Int J Epidemiol*. 2005;34(3):664-671.
44. Shenoi S, Bell S, Wallace CA, Mueller BA. Juvenile idiopathic arthritis in relation to maternal prenatal smoking. *Arthritis Care Res (Hoboken)*. 2015;67(5):725-730.
45. Klein K, Gay S. Epigenetics in rheumatoid arthritis. *Curr Opin Rheumatol*. 2015;27(1):76-82.
46. Klareskog L, Padyukov L, Alfredsson L. Smoking as a trigger for inflammatory rheumatic diseases. *Curr Opin Rheumatol*. 2007;19(1):49-54.
47. Lewis KA, Brown SA, Tiziani S, Carrasco R. Sociocultural considerations in juvenile arthritis: a review. *J Pediatr Nurs*. 2017;37:13-21.

How to cite this article: Koker O, Aliyeva A, Sahin S, et al. An overview of the relationship between juvenile idiopathic arthritis and potential environmental risk factors: Do early childhood habits or habitat play a role in the affair? *Int J Rheum Dis*. 2022;00:1-10. doi: 10.1111/1756-185X.14431