



# Long-term breastfeeding influences disease activity in a low-income juvenile idiopathic arthritis cohort

Francisco Airton Castro Rocha<sup>1,2</sup> · Joaquim Ivo Vasques Dantas Landim<sup>1</sup> · Mariana Lima Nour<sup>1</sup> · Valdenir Freire Peixoto Filho<sup>1</sup> · Leila Nascimento da Rocha<sup>1</sup> · Marco Felipe Castro da Silva<sup>3</sup> · Hermano Alexandre Lima Rocha<sup>4</sup>

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## Abstract

To determine the influence of breastfeeding duration in the clinical activity of low-income juvenile idiopathic arthritis (JIA). Ninety-one JIA patients followed in Fortaleza-CE, Brazil, were cross-sectionally evaluated from May 2015 to April 2016. Breastfeeding duration was obtained by interviewing mothers. Mean age was  $14.6 \pm 5.2$  years with  $10.31 \pm 3.7$  years of disease duration. Polyarticular category predominated, with 39 (42.8%) patients, followed by 23 (25.3%) oligoarticular and 17 (18.7%) enthesitis-related. Forty-seven (61.8%) were receiving methotrexate isolated or combined to leflunomide, which was used by 12 (15.4%); 30 (32.9%) were on biologic DMARD with 16 (53.3%) etanercept, 8 (26.7%) adalimumab, 3 (10%) tocilizumab, and 1 (3.3%) each on infliximab, abatacept, and canakinumab. Mean(SD) CHAQ and JADAS27 were  $0.37 \pm 0.36$  and  $5.03 \pm 6.1$ , respectively and 22 (24%) had permanent joint deformities. No family declared monthly income over US\$900.00 and 32 (37.2%) earned less than US\$300.00. Eighty-three (91%) were ever breastfed; over two-thirds were breastfed for more than 3 months. Those breastfed for more than 6 months had less joint deformities and a tendency to lower JADAS27 and CHAQ scores using minimally adjusted general linear or logistic models, as appropriate. Parental smoking or literacy and family income did not differ regarding breastfeeding time. This is a low-income JIA cohort with the highest breastfeeding prevalence ever reported. Breastfeeding over 6 months was associated with less disease activity.

## Key Point

• Long-term breastfeeding benefits juvenile idiopathic arthritis.

**Keywords** Breastfeeding · Environment · Epidemiology · Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) ranks first as the most prevalent of rheumatic diseases in childhood. Prevalence and/or

severity of JIA has been linked to environmental factors that include breastfeeding and parental smoking [1, 2]. Breastfeeding, particularly in low-income populations, is heavily advised so that the World Health Organization recommends exclusive breastfeeding until the child reaches 6 months of age and maintenance at least until the age of 2 years [3]. Social inequities may unfavorably affect any disease outcome and JIA should not be an exception to this rule [4]. However, our recent data in a low-income JIA population revealed a better than expected evolution with a relatively low median Childhood Health Assessment Questionnaire (CHAQ) score vis-à-vis data from wealthy JIA cohorts [5]. Few studies have proposed that short-term, an ill-defined period, or no breastfeeding increase the risk of developing JIA whereas one study has found otherwise, indicating that breastfeeding did not protect from developing JIA [2, 6, 7]. A single study

✉ Francisco Airton Castro Rocha  
arocha@ufc.br

<sup>1</sup> Departamento de Medicina Clínica, Liga de Reumatologia e Doenças Autoimunes, Faculdade de Medicina, Fortaleza, CE 60430-160, Brazil

<sup>2</sup> Laboratório de Investigação em Osteoartropatias, Instituto de Biomedicina, Rua Cel. Nunes de Melo, 1315-1. Andar, Rodolfo Teófilo, Fortaleza, CE 60430-270, Brazil

<sup>3</sup> Serviço de Reumatologia, Reumatologia Pediátrica, Hospital Geral de Fortaleza, Fortaleza, CE, Brazil

<sup>4</sup> Departamento de Saúde Comunitária, Faculdade de Medicina, Fortaleza, CE 60430-160, Brazil

reported that being ever breastfed was associated with a lower CHAQ score in JIA patients arguing for a potential protective effect [8]. Notwithstanding, there are no data on the influence of breastfeeding duration in JIA activity in patients from underdeveloped regions.

There is a lack of information on JIA populations living in low latitudes, which are also commonly of very low income. Swedish children with JIA breastfed for more than 4 months were shown to be protected from developing the disease. In that study, smoking women of older maternal age and body mass index (BMI) over 30 were less prone to breastfeed their babies [6]. Breastfeeding prevalence in Brazil is very high, particularly in the poorest northeast region of the country [3]. Our objective was to determine the influence of breastfeeding duration in JIA disease activity in our low-income cohort, followed in Fortaleza-CE, located in the northeast of Brazil.

## Methods

Clinical and demographic data from 91 out of our original cohort of 164 patients with a diagnosis of JIA were collected. JIA was diagnosed according to the International League of Associations for Rheumatology (ILAR) [9]. Patients were seen at the rheumatology outpatient clinics of the Hospital Universitário Walter Cantídio (HUWC) and Hospital Geral de Fortaleza (HGF), in Fortaleza, CE, Brazil, between May 2015 and April 2016. The clinical protocol was approved by local Ethics Regulatory Committees (CAAE-72,914,316.4.3001.5045). All patients or their responsible relatives signed an informed consent before any intervention. A clinical chart was filled for each patient registering demographic data, clinical evaluation with a complete physical examination, and current treatment. Parents or relatives were asked about mean monthly family income using October 2017 as reference for conversion of Brazilian R\$ to US\$ currency, as follows: less than US\$300.00, between US\$300.00 and US\$900.00, and above US\$900.00.

BMI was calculated as weight/squared height ( $\text{kg}/\text{m}^2$ ). Cross-sectional disease activity measurement was done using the Juvenile Arthritis Disease Activity Score (JADAS) 27 [10]. A Portuguese version of the CHAQ was used for evaluation of functional status [11]. Low disease activity (LDA), moderate disease activity (MDA), and high disease activity (HDA) were determined as defined previously for oligoarthritis and polyarthritis category patients, considering clinical JADAS (cJADAS) [12]. The number of children with joint deformities, defined as irreversible damage to the anatomic structure and/or function that interfered with joint range of motion that could be attributed to JIA [13], was also recorded.

When directly interviewed, mothers were usually unsure of recalling the precise duration of exclusive breastfeeding. Thus, we categorized whether it occurred both for more or

less than 3 months and also for more or less than 6 months, without specifying exclusive breastfeeding. Smoking data from the mother or other relatives living in the same house were also collected.

Statistics used descriptive analysis for demographics and outcomes using means  $\pm$  S.D. or medians, as appropriate. Dichotomous variables were expressed as absolute and percent values. Differences between means were evaluated using Student's *t* test; dichotomous data were assessed using chi-square or Fisher's exact (when needed) tests. Following descriptive and bivariate analysis, we performed a modeling of minimally adjusted general linear models with robust errors estimators (numeric outcome) or logistic (categorical) models (adjusted for age, gender, parental education, family monthly income, and parental smoking), depending on the theoretical model underlying the tested outcome. The level of significance was set at 0.05. Entering of data and data analysis were done using SPSS v17, SPSS Inc.

## Results

Table 1 illustrates the demographic and clinical data of 91 JIA patients from our original cohort of 164 patients, with  $10.31 \pm 3.7$  (mean  $\pm$  SD) years of disease duration. Reasons to exclude 73 (44.5%) patients were refusal to answer the questionnaire, patients did not have access to their mothers or mothers did not feel able to provide the requested information. All but eight patients were never breastfed meaning more than 90% were ever breastfed; over two-thirds were breastfed for more than 3 months.

Most patients were female and eutrophic. Although no family declared yearly earnings over US\$12,000.00, as we have recently reported [5], we were surprised by having more than one-third classified as overweight/obese. Indeed, no family declared monthly family earnings over US\$900.00. Groups were then divided among those earning more or less than US\$300.00 monthly. Since there were no parents with university grade we categorized as with more or less than 8 years literacy. Polyarticular category predominated, followed by oligoarticular; the cohort displays a relatively low median CHAQ score despite roughly 30% receiving biologics. Those with a CHAQ score  $> 0.75$  used as a cut-off for moderate/high severity [8], represented only 11 (12%) patients of the cohort. Given the low number of patients classified in other JIA categories, we restricted the analysis concerning HDA to those of the oligo and polyarticular categories. Analysis performed using a minimally adjusted general linear model showed that JADAS27 and CHAQ scores as well as the prevalence of permanent deformities were similar in oligo and polyarticular category patients breastfed for more or less than 3 months. However, those breastfed for more than 6 months exhibited less permanent joint deformities and a tendency to

**Table 1** Clinical characteristics of 91 low-income JIA patients

Demographics	
Female [ <i>n</i> (%)]	55 (60)
Age, mean (SD)	14.6 (5.20)
BMI, mean (SD)	21.4 (5.34)
Eutrophic [ <i>n</i> (%)]	26 (56.5)
Low-Weight [ <i>n</i> (%)]	4 (8.7)
Overweight [ <i>n</i> (%)]	8 (17.4)
Obese [ <i>n</i> (%)]	8 (17.4)
Monthly family income	
<US\$300.00	32 (37.2)
US\$(300.00–900.00)	54 (67.8)
Monthly family income	
JIA category [ <i>n</i> (%)]	
Polyarthritis, RF–	24 (26.3)
Polyarthritis, RF+	15 (16.5)
Oligoarthritis	23 (25.3)
ERA	17 (18.7)
Systemic	8 (8.8)
Undifferentiated	3 (3.3)
Psoriatic	1 (1.1)
JADAS27, mean (SD)	5.03 (6.1)
JADAS27, median (IQR)	2.97 (1.5–6.1)
Disease activity [ <i>n</i> (%)]	
Low disease activity	23 (39.6)
Moderate disease activity	23 (39.6)
High disease activity	12 (20.6)
CHAQ, mean (SD)	0.37 (0.56)
CHAQ, median (IQR)	0 (0–0.625)
Non-biologic DMARD	
Methotrexate	47 (61.8)
Leflunomide	12 (15.4)
Biologic DMARD	
Etanercept	16 (53.3)
Adalimumab	8 (26.7)
Tocilizumab	3 (10)
Abatacept	1 (3.3)
Canakinumab	1 (3.3)
Infliximab	1 (3.3)

Data represent mean (%) or median (IQR) of 91 patients

lower JADAS27 and CHAQ scores though not reaching statistical significance. The majority (83%) of the mothers informed being never smokers but 67% of the patients were considered exposed to secondhand smoking. Patients exposed or not to secondhand smoking did not differ regarding breastfeeding time, and there was also no difference regarding family income or parental literacy and breastfeeding duration (Table 2). There were also no significant differences concerning demographics and disease activity among the 73 excluded and the 91 evaluated patients (data not shown).

## Discussion

This is the first study on the influence of breastfeeding duration in JIA activity of patients from low-income families. Breastfeeding for more than 6 months was associated with a lower prevalence of permanent deformities and a tendency to have less disease activity. Breastfeeding prevalence in our cohort was very high, even when compared to data from Scandinavia that reported 85% breastfeeding prevalence in JIA patients [6]. Ever breastfeeding prevalence among Brazilians has been reported to be as high as 90%, particularly in low-income populations of the northern regions, where this study was conducted [14]. Family income and literacy were not different among patients regardless of breastfeeding duration. Surprisingly, at least to our expectations, access to parents and/or relatives was not an easy task. Indeed, some of our patients over 14 years of age did not have contact with their parents leading us to exclude an apparently large number of patients from our original cohort. However, our percentage of exclusion was similar to the 36% that declined to participate in a similar survey conducted in Seattle, WA [2]. The fact that clinical and demographic data of the 73 excluded patients were similar to those of the 91 evaluated JIA patients makes it unlikely that the former could alter our present results.

A British study in JIA patients reported that those never breastfed had a higher prevalence of >0.75 CHAQ scores indicating a protective breastfeeding effect. In that study, the duration of breastfeeding was not considered [6]. There were very few patients (12%) in our cohort with >0.75 CHAQ score precluding a similar analysis with our data. However, bearing in mind that more than 90% of our patients were ever breastfed we may speculate that our data add to a direct positive association pointing to less severe outcome in ever breastfed JIA patients. We should also mention that our patients have access to treatment, including any medication, once they reach a tertiary service. However, delayed access to the first visit with a specialist represents an issue to be improved [4]. Similar to what was described in other cohorts, medications to treat JIA represent a major cost to our health care system [15].

Breast milk influence to the infant immune status seems undisputable, but there is no definition of how much breastfeeding is both necessary to the infant and feasible for modern mothers [7]. Establishing an ideal period would be valuable to help women decide whether or not and for how long to breastfeed without the fear of jeopardizing the infant's health. Human milk composition is not uniform throughout prenatal, delivery, and postnatal periods. Indeed, immune stimuli may be present in higher concentrations in breast milk in the first 2 weeks postpartum. On the other hand, prolonged hyperprolactinemia associated with breastfeeding may impact mother's health. Some diseases including type I diabetes and celiac disease are considered more severe in never breastfed

**Table 2** Clinical features of JIA patients according to the breastfeeding time

	Breastfeeding time cut-off			aP value	Breastfeeding time cut-off			aP value
	> 3 months	< 3 months	ORa (95% CI) ESa (95% CI)		> 6 months	< 6 months	ORa (95% CI) ESa (95% CI)	
JIA category [ <i>n</i> (%)]				0.96				0.31
Oligoarticular	15 (37.5)	7 (36.8)	–		9 (42.8)	12 (35.3)	–	
Polyarticular	25 (62.5)	12 (63.2)	–		12 (57.2)	22 (64.7)	–	
Deformity [ <i>n</i> (%)]				0.17				0.04**
Yes	12 (21)	10(34.5)	Reference		4 (14.3)	16 (33.3)	0.27 (0.7–0.97)	
No	45 (79)	19 (65.5)	0.63 (0.23–1.74)		24 (85.7)	32 (66.7)	Reference	
<sup>1</sup> JADAS27, mean (SD)	5.21 (6.44)	4.86 (5.57)		0.80	3.73 (3.02)	5.99 (7.12)	2.29 (–0.45–5.03)	0.051
<sup>2</sup> CHAQ, median (IQR)	0.33 (0–0.625)	0.46 (0–0.75)		0.33	0 (0–0.375)	0.125 (0–0.75)	0.19 (–0.06–0.46)	0.056
Family income [ <i>n</i> ]				1.00				0.46
>US\$300	36(64)	18 (64)	0.94 (0.36–2.45)		21 (70)	29 (64.4)	0.66 (0.22–1.98)	
<US\$300	20(36)	10 (36)	Reference		9 (30)	16 (35.6)	Reference	
Literacy [ <i>n</i> ]				0.22				0.47
> 8 years	23(39.6)	15 (53.5)	1.36 (0.65–4.11)		15 (50.0)	20 (42.5)	0.68 (0.24–1.98)	
< 8 years	35 (60.4)	13 (46.5)	Reference		15 (50.0)	27 (57.5)	Reference	

Influence of breastfeeding time in JIA disease activity. Modeling of minimally adjusted general linear or logistic models with robust errors estimators (adjusted for age, gender, parental education, family monthly income, and parental smoking)

Data represent *n*(%) of patients. <sup>1</sup>JADAS, Juvenile Arthritis Disease Activity Score; <sup>2</sup>CHAQ, Childhood Health Assessment Questionnaire (median; IQR) and JADAS27 analyzed with general linear model after normalization of variables with logarithms

ORa, adjusted odds ratio (literacy, income); ESa, adjusted effect size; aP, adjusted P

children but it is not clear whether ever breastfeeding affects JIA prevalence and/or outcome [7].

From an immunological standpoint, although the amount and duration of stimulation impact the immune response, persistent repetitive exposure may turn out to be irrelevant either to harm or to heal. The child's immune system is largely influenced by prenatal contact with the mother's circulation. Birth means sensitization of the child with the mother skin, extra-uterine environment and human saliva, to mention a few stimuli. Let us not forget contact with relatives, nurses, and physicians aiming to provide childcare. Defining the relevance of each stimulus to the newborn health status is not an easy task and it is yet to be determined. For instance, one may argue that diverse stimulation, e.g., not being breastfed, but being well-nourished with access to non-human milk, on an immunological or evolutionary standpoint represents different immune triggering, not necessarily "bad" or absence of stimulation. Contact with non-human milk and other exogenous proteins may drive the infant's microbiota into a more varied phenotype which relevance to the development of the infant's immune system can only be speculative [7].

Low parental literacy and family income have been suggested to impact breastfeeding but neither was of significant influence in our cohort. A study conducted in Sweden found that short-term exclusive breastfeeding was less frequent when one of the parents had a university degree [6].

Strengths of this study include that those are the first data collected by directly interviewing mothers from very low-

income families, living in low latitude, with very high breastfeeding prevalence. Our whole cohort can also unfortunately be considered as of low literacy, as compared to data from a Swedish study [6].

A previous study conducted in Turkey suggested a protective effect of breastfeeding in oligoarticular JIA [16]. We are not aware of other JIA studies focusing on how long breastfeeding is needed to impact JIA outcome. If it impacts at all is yet to be determined and our very high breastfeeding prevalence precluded such an analysis.

Limitations of our study include the low number of patients classified in categories other than polyarticular and oligoarticular JIA. Indeed, it has been proposed that JIA patients of the enthesitis-related and psoriatic arthritis categories are more prevalent in never breastfed patients [8]. Other limitations include that we did not collect data on exclusive breastfeeding and exact number of months was not collected because mothers were unsure about this information thus precluding a continuous analysis of the data. Finally, the cross-sectional design of this study does not allow a conclusion about direct causality.

Our cohort represents the highest breastfeeding prevalence among low-income JIA patients ever reported. Breastfeeding for more than 6 months had a tendency to be associated with lower disease activity. Replicating this information in other cohorts may help establish a comfortable minimum breastfeeding period.

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## Compliance with ethical standards

**Disclosures** None.

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