

## Quality of Life in Mothers of Food-Allergic Children did not Improve After Children Became Asymptomatic: A Prospective Cohort Study

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### Abstract

**Introduction and Aims:** Evaluate the Quality of Life (QoL) in mothers of Food-Allergic (FA) children and explore the relationship between scores of QoL domains and The CoMiSS™.

**Methods:** An observational, prospective cohort study of children referred for initial evaluation of FA. Inclusion criteria: mothers capable of answering the WHOQOLBREF; not receive any psychological intervention; children ≤ 36 months and diagnosis of FA. Exclusion criteria: children with chronic co-morbidities. The WHOQOL-BREF and The CoMiSS™ were administered at the diagnosis (T0), and The WHOQOLBREF was reapplied at least eight weeks after children were asymptomatic (T1).

**Results:** 86 mothers/children were evaluated. Children's median (months) age was 5,3, and the duration of symptoms was 4.0. Children are adequate in birth weight/length and nutritional conditions. There were positive, highly significant Spearman intercorrelations between the different QoL domains of the WHOQOL-BREF. Also, a negative correlation between the children's Total CoMiSS™ score and the WHOQOLBREF scores domains. The questionnaire was reapplied to 34 mothers at T1, and the median interval between the two questionnaires was nine months. There was no statistically significant difference between T0 and T1 for four WHOQOL-BREF domains, Overall QoL and Satisfaction with Health. A small Effect Size was observed for the Facets of the Physical domain (Mobility, Sleep, and Rest), the Psychological domain (Positive Feelings, Body Image, and Appearance, Negative Feelings), and the Environment domain (Participation and Support of Leisure Activities).

**Conclusion:** The WHOQOL-BREF was appropriate for evaluating the QoL. Mothers demonstrated no improvement in QoL after the child had adequate milk formula and was asymptomatic.

**Keywords:** Quality of Life; Food Allergy; Cow's Milk Protein Allergy; Children; Parents; Mothers

### Abbreviations

FA: Food allergy; QoL: Quality of Life; WHOQOL-BREF: World Health Organization Quality of Life Brief; CoMiSS™: Cow's Milk-related Symptom Score; IQR: Interquartile Range

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### Background

Food allergy (FA) is a chronic and global health condition that disproportionately affects children in industrialized countries [1]. The epidemiology of FA has changed during the last two decades, with an increased number of people diagnosed, medical visits, and high, rising healthcare costs [2]. The prevalence was up to 10%, most notably among younger children [3]. Indeed, cow's milk and egg allergy are the most common FA diagnosed in the first two years of life [4].

Given the increased prevalence of FA among infants, a greater awareness of the impact on families' emotional, social, and financial issues can significantly impact the quality of life [5]. Children's FA negatively impacts family activities at younger ages and may cause stress, fear, anxiety, and a heavy burden on parents [6], significantly impacting physical and psychological health [7]. These manifestations often peak at certain stages in their children's lives, such as when they join nursery or school. A systematic review of ninety-eight studies documented that mothers were the most participants, and anxiety was the most burdensome form of FA-specific emotional distress [8].

Additionally, Proctor., *et al.* [9] highlight a need to assess the psychosocial impacts that parents and families may experience from children with FA. Thus, parents, particularly mothers carrying this burden, may have impaired Quality of Life (QoL) [10,11]. Therefore, further studies evaluating mothers' QoL will be valuable and serve to develop an effective treatment, expanding and ameliorating health care.

### Aim of the Study

Evaluate the QoL of mothers of food-allergic children in two moments: at the diagnosis (symptomatic) and when the child was asymptomatic. In addition, it explores the relationship between the mother's QoL questionnaire domains and scores of a tool for food allergy-related symptoms in children.

### Methods

#### Study design, setting, and selection of participants

The study was a single-center, observational, prospective cohort study including consecutive cases of children referred from the Brazilian Public Health System to a Paediatric Food Allergy Clinic for initial evaluation of FA between December 2017 to December 2019. The available infrastructure includes an outpatient clinic with weekly practice, care standardization, and technical diagnosis capacity. Diagnosing and treating children with FA are regularly clinically followed. Inclusion criteria: mothers who responded to the QoL assessment of the instrument should be adults (over 18 years of age), be able to understand the instructions, and answer the questions formulated in the WHOQOL-BREF; be aware of the patient's clinical condition; live in the same household as the patient; no receiving any form of psychological intervention and accept to participate of the study. Inclusion criteria for children: aged  $\leq 36$  months with a diagnosis of FA. Exclusion criteria for children: dubious diagnosis of FA; chronic co-morbidities, such as genetic, neurological, cardiological, endocrinological, and nephrological diseases. Clinical Research Ethics Committees (protocol CAAE: 81999317.7.0000.5411) approved the study, and informed consent was obtained from mothers.

#### Data collection and diagnosis of food allergy

The WHOQOL-BREF instrument was administered in a private room in a standardized semi-structured form. Blood cell count, C-reactive protein, serum immunoglobulins, urinalysis, stool for ova and parasites, and Prick tests were performed in all children.

Additional tests were completed at the researcher's discretion. Experienced pediatric nurses obtained anthropometric data at the first visit according to World Health Organization guidelines [12]. AnthroPlus evaluated z-scores, and growth deficit adjusted for sex and age was defined when the weight-for-age, length/height-for-age, and weight Length z-score were below -2.0 standard deviations [13].

The diagnosis was based on: 1) a recent suspected history of reproducible signs/symptoms of repeated exposure, 2) a skin prick test using commercial food extract if a wheal diameter of 3 mm was seen at 15 min in the presence of a 3 mm wheal to histamine, 3) Food-

specific serum IgE tests for cow's milk, soy, egg, and other food antigens according to a specific indication of each case, 4) laboratory data, 5) allergen elimination from infant's diet or mother's diet in breastfeeding (FA excluded if no symptoms elicited within 2 - 4 weeks), 6) a controlled open or blind oral food challenge under medical supervision. Two experienced pediatricians (MAC, NCM) determined the final diagnosis based on a combination of the above criteria. Before starting treatment, physicians and nutritionists provided educational material about the avoidance of sensitizing food proteins.

### The WHOQOL-BREF instrument

The WHOQOL-BREF is a self-explanatory, self-assessed, 5-point scale for each answer scored positively, with higher values meaning a higher QoL. This instrument comprises four domains: Physical health (07 facets), Psychological (06 facets), Social relationships (03 facets), and Environmental (08 facets). Two additional items measure Overall Quality of Life and Health Satisfaction with Health. The instrument does not admit a total QoL score, considering that QoL is a multidimensional construct. Domain scores were determined by multiplying the average of all items within a domain by four. Thus, the score can range from zero to 100, and the higher the value, the better the domain of QoL assessed. Correspondingly, the higher the facet scores, the higher the QoL [14]. The instrument was translated, cross-culturally adapted, and validated into the Brazilian Portuguese version [15].

The WHOQOL-BREF was applied at two moments: at the diagnosis (symptomatic = T0) and when the child was asymptomatic (T1). The answers refer to the condition of the last two weeks, and the absence of listed symptoms during the T0 characterize the asymptomatic children. The questionnaire was delivered in print to the children's mothers for completion. If the mother did not understand the meaning of a question, the researcher read the question slowly (assisted application) without using synonyms or giving explanations, avoiding modifying the original meaning of the question. After receiving the questionnaire already answered, the researcher checked that there was at most one answer per question.

### Application of the CoMiSSTM instrument

The CoMiSSTM, "Cow's Milk-related Symptom Score," is a simple, quick, and easy-to-use tool for food allergy-related symptoms that quantify the number and severity of a combination of general, gastrointestinal, respiratory, and dermatological symptoms. Each symptom has a maximum score of six, except for respiratory symptoms (maximum of three). The tool was applied on the same day as the first QoL assessment. The CoMiSSTM score ranges from 0 to 33, with  $\geq 9$  being more associated with FA [16].

### Statistical analysis

Sociodemographic, clinical, and laboratory data and responses to the WHOQOL-BREF questionnaires were compiled into an Excel database and analyzed with GraphPad Prism version 8.4.0 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com). Normality data was assessed using the Kolmogorov-Smirnov test and expressed as simple frequency, relative frequency, median, interquartile range (IQR), and 95% Confidence Interval of the median. Continuous variables were analyzed by the Mann-Whitney test and paired data using the Wilcoxon test. Fisher's exact test examined categorical variables. Spearman's rank correlation calculates inter-correlations of the WHOQOL-BREF and WHOQOL-BREF domains with the CoMiSSTM total score. The correlation coefficient qualifies as small (0.10 - 0.29), medium (0.30 - 0.49), and large ( $> 0.50$ ). Reliability analysis was measured using Cronbach's alpha coefficient, and the accepted reference value (excellent reliability) must be equal to or greater than 0.70 and at a maximum of 0.90. The differences in scores were analyzed using the Effect Sizes, calculated by dividing the mean score change (i.e. follow-up minus baseline) by the standard deviation of the change and classified as Small ( $\geq 0.20$ ), Average ( $\geq 0.50$ ), and Large ( $\geq 0.80$ ) [17]. All tests were two-sided, and  $p < 0.05$  were statistically significant.

## Results

Ninety-nine outpatients were referrals for investigation (13 were excluded: they did not agree to participate or had incomplete data). So, the study involved 86 mother/child dyads. The WHOQOL-BREF was self-administered by 78 mothers (91%), and 08 (9%) needed help

from the interviewer. The median time to complete the questionnaire was 5 minutes. The number and percentage of the final diagnosis subtypes of FA were: Non-IgE-mediated 47 (55%), IgE-mediated 21 (25%), and 18 (20%) mixed or undefined.

**Results at diagnosis**

Table 1 describes the baseline characteristics of parents and children. The median age of the children was 5,3 months, and the time between the onset of symptoms and the presentation was four months. Children were term, adequate in birth weight and length, and with good nutritional conditions. Mothers were unemployed at 48%. The crowding index represented small families that lived in houses with few rooms.

No. of subjects = 86	
<b>Children Characteristics, Median (IQR) or n (%)</b>	
Sex Female, n (% Female)	38 (44)
Age at presentation (months)	5,3 (2,5 - 8,8)
Age at onset of symptoms (months)	1,3 (0,5 - 3,0)
Delivery Vaginal/Caesarean section, n (% vaginal)	39/47 (45,3)
Term/premature, n (% Term)	72/14 (83,7)
First child, n (%)	42 (48,8)
Birth weight (grams)	3200 (2700- 3500)
Birth length (cm)	48,5 (47,0 - 50,0)
<b>At first visit</b>	
Weight for age z- score	-0,19 (-1,14 - 0,52)
Length-for-age z-score	-0,56 (-1,48 - 0,23)
Weight for Length z-score	0,18 (-0,76 - 1,01)
<b>Parental characteristics</b>	
Questionnaire answerer: mother, n (%)	86 (100)
Age of mothers (y)	26,5 (22,7 - 31)
Age of fathers (y)	30 (25 - 35)
Mother’s schooling (12 y of education), n (%)	24/68 (35)
Father’s schooling (12 y of education), n (%)	24/64 (37)
Mother’s unemployment, n (%)	36 (48)
Father’s unemployment, n (%)	5 (6,8)
Crowding Index	0,8 (0,6 - 1)

**Table 1:** Baseline characteristics of 86 parents and children at diagnosis (symptomatic).

Table 2 presents a set of 15 prevalent allergic symptoms in decreasing order of frequency divided into three categories: gastrointestinal, respiratory, and dermatological. The CoMiSS™\* score ≥ 9 was present in 55,8% of the children. The median and IQR for feeding history in days were: exclusively breastfed (90, 35 -120); introduction of cow’s milk (60, 16-120); breastfed + formula fed (30, 0-127); complimentary food (135, 90-180). The family history of allergy was: parents and siblings (45%), one of the parents (37%), and both parents (4%). Laboratory evaluation confirmed mild anemia (Hb < 11) in 33% of children; without eosinophilia, all Immunoglobulins were within average values. There was low positivity for the Prick test (28%).

<b>Gastrointestinal symptoms, n (%)</b>	83	(96,5)
Vomiting/regurgitation	45	(52,3)
Diarrhea	44	(51,1)
Colic	37	(43,0)
Blood in stools	29	(33,7)
Constipation	19	(22,0)
Poor weight gain	19	(22,0)
Cry during defecation	8	(9,3)
Refusal to feed	2	(2,3)
<b>Respiratory symptoms, n (%)</b>	43	(50,0)
Cough	38	(44,1)
Wheezing	30	(34,8)
Rhinoconjunctivitis	16	(18,6)
Recurrent infections	5	(5,8)
<b>Dermatological symptoms, n (%)</b>	49	(56,9)
Atopic eczema	41	(47,6)
Morbilliform erythema	19	(22,1)
Urticaria	11	(12,7)
CoMiSS™ score ≥ 9, n (%)	48	(55,8)

**Table 2:** Chief gastrointestinal, respiratory, and dermatological complaints at diagnosis (symptomatic) in 86 children with food allergy.

Table 3 presents positive, highly significant Spearman intercorrelations between the different QoL domains of the WHOQOL-BREF. Table 4 presents a negative correlation between the children’s Total CoMiSS™ score and the WHOQOL-BREF domains, i.e., the higher the values of the total CoMiSS™ (more symptomatic), the lower the values of the domains, except for Physical health. The psychometric properties for the overall QoL instrument showed good consistency with Cronbach’s alpha of 0.84.

Spearman Correlation, $r$ e $p <$						
	Overall QOL	Satisfaction with health	Physical health	Psychological	Social relationships	Environmental
Overall QOL	-	0,39 $p < 0,0002$	0,33 $p < 0,002$	0,35 $p < 0,0007$	0,44 $p < 0,0001$	0,38 $p < 0,0002$
Satisfaction with health	-	-	0,52 $p < 0,0001$	0,45 $p < 0,0001$	0,37 $p < 0,0004$	0,47 $p < 0,0001$
Physical health	-	-	-	0,55 $p < 0,0001$	0,54 $p < 0,0001$	0,58 $p < 0,0001$
Psychological	-	-	-	-	0,53 $p < 0,0001$	0,66 $p < 0,0001$
Social relationships	-	-	-	-	-	0,54 $p < 0,0001$

**Table 3:** Intercorrelations between domains of mother’s WHOQOL-BREF questionnaire at diagnosis (symptomatic).

Physical health	-0,19 (-0,39 - 0,02); p = 0,07
Psychological	-0,23 (-0,42 - -0,01); p = 0,03
Social relationships	-0,23 (-0,42 - -0,01); p = 0,03
Environmental	-0,21 (-0,41 - 0,0009); p = 0,04

**Table 4:** Correlation between mother’s WHOQOL-BREF questionnaire domains with the children’s CoMiSS™ total score at diagnosis (symptomatic).

**Results comparing variables at T0 and T1**

The questionnaire was reapplied to 34 mothers at T1, and the median (IQR) interval between the two questionnaires was 9 (6 - 15) months. Table 5 presents no statistically significant difference between T0 and T1 for four WHOQOL-BREF domains and Overall QoL and Satisfaction with Health. Table 6 presents a small Effect Size for the Facets of the Physical domain (Mobility, Sleep, and Rest), the Psychological domain (Positive Feelings, Body Image, and Appearance, Negative Feelings), and the Environment domain (Participation and Support of Leisure Activities).

	Symptomatic (Time 0)	Asymptomatic (Time 1)	p<
	Median (IQR)		
Physical health	63 (50 - 81)	66 (54 - 81)	0,8292
Psychological	69 (56 - 75)	69 (56 - 81)	0,4782
Social relationships	69 (50 - 75)	69 (50 - 75)	0,3007
Environmental	63 (50 - 75)	63 (54 - 75)	0,9871
Overall QOL	75 (75 - 75)	75 (69 - 75)	0,9999
Satisfaction with health	75 (50 - 75)	75 (50 - 75)	0,9999

**Table 5:** Mother’s WHOQOL-BREF questionnaire: comparisons between domains at the diagnosis (symptomatic) and asymptomatic.

**Discussion**

The current study evaluated the impact on QoL of 86 mothers of food-allergic children in two moments: at the diagnosis (symptomatic) and when the child was asymptomatic. The study assessed whether the mother’s QOL would improve with adequate treatment and the asymptomatic child. The questionnaire was easily managed with no missing answers for any psychometric scales. Internal consistency confirms the excellent psychometric properties of the WHOQOL-BREF questionnaire [14]. So, WHOQOL-BREF is a generic, short, quick-to-apply instrument used in adults, with the advantage of being applied in healthy individuals and different diseases.

The main results demonstrate children with adequate birth weight and length, good nutritional conditions, and living in small families and houses with few rooms. This study showed mothers with a high percentage of unemployment, and this study did not evaluate the maternal need to give up work. This situation could mean impairment of the financial condition associated with recreation and leisure stood out as two facets with significant commitment both at the time of diagnosis and when the child was asymptomatic. These findings mean no change in the mothers’ QoL after diagnosis.

There was no difference for the four domains between T0 and T1. Also, there was a positive, moderate, and highly significant correlation between different domains of the WHOQOL-BREF. The good associations between the physical health, psychological health, social relationships, and environment domains confirm agreement but not redundancy of these QoL-specific domains. Concerning a small Effect

	Domains and facets	Score Change			Classification
		Mean of differences (T1 -T0)*	Standard deviation	Effect size	
F1	Overall quality of life	0,029	0,797	0,037	
F2	Overall health satisfaction with health	0,059	1,099	0,054	
	<b>Physical health</b>				
F3	Pain and discomfort	0,118	1,149	0,102	
F4	Dependence on medication or treatment	0,029	1,507	-0,02	
F10	Energy and fatigue	0,235	0,987	0,239	
F15	Mobility	0,265	1,189	0,223	**
F16	Sleep and rest	0,353	1,631	0,216	**
F17	Activities of daily living	0,176	1,267	0,139	
F18	Working capacity	0,235	1,281	0,184	
	<b>Psychological health</b>				
F5	Positive feelings	0,265	1,024	0,258	**
F6	Spirituality, religion, and personal beliefs	0,029	0,937	0,031	
F7	Thinking, learning, memory, and concentration	0	1,128	0	
F11	Body image and appearance	0,294	1,219	0,241	**
F19	Self-satisfaction	0,029	1,141	0,026	
F26	Negative feelings	0,265	1,053	0,251	**
	<b>Social relationships</b>				
F20	Personal relationships	0,118	1,094	0,107	
F21	Sexual activity	0,147	1,209	0,122	
F22	Friend's support	0,029	1,193	0,025	
	<b>Environment</b>				
F8	Physical safety and security	0,088	0,965	0,091	
F9	Physical environments	0,059	1,205	0,049	
F12	Financial resources	0,029	1,243	0,024	
F13	Opportunities for new information and skills	0,147	1,209	0,122	
F14	Participation and support of leisure activities	0,265	1,263	0,21	**
F23	Home environment	0,294	1,001	0,294	
F24	Health and social care: availability and quality	0	1,015	0	
F25	Transportation	0,206	1,008	0,204	

**Table 6:** Classification of the Effect Size of WHOQOL-BREF in different facets.

Size between T0 and T1, medicine generally focuses on QoL as an essential outcome measure in health and disease [18,19]. Nevertheless, Effect Size, proposed as the best responsiveness index, was observed in only two Facets of the Physical domain, three Psychological domains, and one Environment domain. No Effect size was observed in the Social relationships domain.

A Belgian group introduced the acronym “CoMiSS™” as a clinical score that aims to distinguish infants with the possibility of having Cow’s Milk Allergy. So, it can be considered a diagnostic approach, and a cut-off score of  $\geq 9$  was proposed. In the current study, a score  $\geq 9$  was present in 55,8% of the children. Interestingly, a negative correlation was observed between the children’s total CoMiSS™ score and the WHOQOL-BREF domains, i.e., the higher the values of the total CoMiSS™ (more symptomatic), the lower the values of the domains (impaired QoL) except for Physical health. This finding supports the possibility of analyzing the association between the severity of the child’s clinical symptoms and the mother’s emotional components evaluated with a QoL questionnaire.

Several studies have documented the QoL of parents of children with FA and significantly impacted health perception, parents’ emotions, and family activities, especially in mothers, with a higher impact on their QoL than other family members [20-22]. The pressure of being primarily responsible for their children’s health often conflicts with their community and family, leading to marital discord [23]. A large cohort study found that 57% of participants outgrew their cow’s milk allergy within 4 - 5 years, and a majority by age 2.5 [24]. Consequently, the mother faces a significant treatment period in the care of FA.

Mothers have a more protective approach to FA children and are more likely to be hypervigilant regarding allergen avoidance. Traditionally has a more significant role in buying and preparing food. Consequently, stress can occur when reading food labels and deciding which foods are safe [25]. Thus, mothers may have an increased fear of exposure to allergens, especially outside their supervision (e.g. at day-care, at home, from a relative or friend), mainly by the fear of accidental reactions and lifestyle restrictions [26,27]. High anxiety levels may occur if the process is sustained long-term [28]. These aspects can compromise QoL, even when children are asymptomatic.

Many studies suggested elevated anxiety among patients and caregivers with FA, and mothers reported more significant anxiety and stress because they usually take more responsibility in FA management. Polloni and Muraro [29] offer a comprehensive overview of the literature data and possible explanations of the association between FA and anxiety. High levels of anxiety were counterproductive and related to maladaptive coping. Pediatricians need to understand their role in recognizing maladaptive anxiety and could help encourage seeking psychological support. Annunziato, *et al.* [30] concluded that 70% of families need mental health services. However, further research is needed to elucidate the association between FA and anxiety.

A recent systematic review highlighted the need for specific interventions to improve self-management for young people with allergic conditions [31]. Maternal anxiety must be considered when assessing treatment plans for food-allergic children, and the intervention may have reduced longer-term anxiety. An assessment with anxiety scores was not performed in this study. Indeed, the simultaneous evaluation of QoL and anxiety would strengthen the study.

This study has some limitations: Firstly, all 86 questionnaires from T0 and 34 from T1 were carried out before the COVID-19 pandemic [32]. Thus, with no impact on the mothers’ QoL assessment. However, due to legal designations by the National Health System regarding hospital routine, we did not assess the mothers’ remnants at T1. Secondly, a formal double-blind placebo-controlled food challenge was not performed to confirm the suspected diagnosis. Such formal challenges are not considered essential in this age group, and due to the study design, children were seen extremely quickly after referral and had typical histories. Thirdly, the study did not perform a specific QoL questionnaire on FA, whereas, at the time of the study, no Brazilian Portuguese language-specific QoL instrument was available. Fourthly, this was a tertiary center study, and the generalizability of the results is not recommended. The strengths: First, specialists recruited and diagnosed patients at a food allergy clinic. Secondly, this is the first Brazilian study evaluating only mothers as respondents to the QoL questionnaire. So, a homogeneous sample of consecutive cases was preserved.

## **Conclusion**

FA contributes to impairment in the QoL of mothers of FA children. As an outcome measure, in 34 mothers reassessed, no improvement in QoL after the child had adequate milk formula and was asymptomatic. The WHOQOL-BREF was appropriate for evaluating the



QoL concerning physical, psychological, social, and environmental factors. Further studies would benefit from addressing some of the methodological limitations of the current study, particularly exploring concomitant maternal anxiety.

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### **Conflict of Interest**

All authors declare that there is no conflict of interest.

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**Volume 12 Issue 4 April 2023**

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