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## Evaluation of the frequency of food intake and the maintenance of the effect of glutamine supplementation on the attenuation of symptoms of moderate asthma in children, post wash out

*Avaliação da frequência do consumo alimentar e da manutenção do efeito da suplementação com glutamina na atenuação dos sintomas de asma moderada em crianças, pós wash out*

#### Abstract

The objective of the study was to compare the frequency of food intake of children with moderate asthma with that of children without respiratory diseases and to evaluate the maintenance of the effect of the immunomodulator glutamine on the attenuation of asthma symptoms after the washout period. Longitudinal intervention study with children from 2 to 7 years of age. The study consisted of three groups: glutamine case group, control group with asthma and control group without respiratory disease, with 15 children each. The clinical evaluation was performed by means of the ISAAC Questionnaire – Asthma Module before the beginning of the supplementation and in monthly visits during the 4 months of the study, and repeated after the 6-month washout

period. Children in the control group without respiratory disease were evaluated (food intake frequency) at a single point in time. The food intake was assessed by means of the adapted FFQ. There was a significant decrease in the ISAAC score in the glutamine group after 4 months of supplementation [8.0 (1.46) x 4.0 (1.96),  $p < 0.001$ ], as well as in the control group with asthma [8.67 (1.79) x 5.93 (2.28),  $p < 0.001$ ]. After the washout period there was a significant increase in the score and return of asthma symptoms in the glutamine case group [4.0 (1.96) x 7.27 (2.02),  $p < 0.001$ ]. The food intake was similar among children with asthma and without asthma, characterized by daily consumption of milk and low consumption of vegetables, fruits and meat. The beneficial effect of glutamine was not maintained after the washout period.

**Keywords:** Food intake. Children. Respiratory diseases. Immunomodulators.

### Resumo

O objetivo do estudo foi comparar a frequência do consumo alimentar de crianças com asma moderada com a de crianças sem doenças respiratórias e avaliar a manutenção do efeito do imunomodulador glutamina na atenuação dos sintomas de asma, pós-período *wash-out*. Estudo de intervenção, longitudinal, realizado com crianças 2 a 7 anos de idade, constituído por três grupos: grupo caso glutamina, grupo controle com asma e grupo controle sem doença respiratória, com 15 crianças em cada. A avaliação clínica foi realizada por meio do Questionário ISAAC – Módulo Asma, antes do início da suplementação e em visitas mensais durante os quatro meses do estudo, e repetida após o período *wash-out* de seis meses. As crianças do grupo controle sem doença respiratória foram avaliadas (frequência alimentar) em um único momento. O consumo alimentar foi avaliado por meio do QFA adaptado. Houve diminuição significativa da pontuação ISAAC no grupo glutamina após quatro meses de suplementação [8,0 (1,46) x 4,0 (1,96),  $p < 0,001$ ], bem como no grupo controle com asma [8,67 (1,79) x 5,93 (2,28),  $p < 0,001$ ]. Após período *wash-out*, houve aumento significativo da pontuação e retorno dos sintomas da asma no grupo caso glutamina [4,0 (1,96) x 7,27 (2,02),  $p < 0,001$ ].

O consumo alimentar foi semelhante entre crianças com e sem asma, caracterizado por consumo diário de leite e baixo consumo de hortaliças, frutas e carne. O efeito benéfico da glutamina não foi mantido após o período *wash-out*.

**Palavras-chave:** Consumo alimentar. Crianças. Doenças respiratórias. Imunomoduladores.

## INTRODUCTION

Asthma is the most common chronic respiratory disease in the world, and its prevalence has increased significantly in recent years. It is characterized by chronic inflammation of the lower airways and leads to episodes of wheezing in the chest, shortness of breath, tightness in the chest and cough.<sup>1</sup>

Some factors influencing the occurrence of asthma are climate changes such as decreasing temperatures, excessive humidity and/or very dry weather. Exposure to atmospheric pollutants aggravates the increase in episodes of respiratory infections in the colder seasons of the year, due to poor air quality that irritates the airways.<sup>2</sup>

In addition, children are more susceptible to respiratory diseases due to the stage of maturation of the respiratory and immune system, feeding in the first years of life and frequency of infections, which occur in children from 6 to 8 times per year while in adults only 2 to 4 times per year.<sup>3</sup>

In the same context of respiratory diseases in children, the International Study of Asthma and Allergies in Childhood (ISAAC) was created in the 1990s to investigate respiratory diseases through standardized questionnaires, making valid comparisons of the prevalence and severity of asthma in children. Each response corresponds to a score and a diagnosis of asthma and allergy is considered when the final score is equal to or greater than five.<sup>4,5</sup>

It is also noteworthy that diet is a form of treatment in the control of asthma attacks. Healthy eating in childhood is important, as it is the stage of development, growth and shaping of the eating habits of the child.<sup>6</sup> A balanced diet high in fruits and vegetables that contain antioxidants, vitamins and minerals, provides protective action on the respiratory system and reduces the occurrence of asthma.<sup>7</sup> However, studies evaluating the diet of children with respiratory diseases are scarce compared to the diet of children without respiratory problems.

Glutamine, the object of this study, is a fundamental amino acid for the immune system, and can be used as a complementary therapy for children. When considering the benefits of the immunomodulator glutamine, such as decreased infections, reduced length of hospitalization, improved inflammatory response, integrity of the intestinal mucosa and immune system in children with severe diseases, the use of this immunomodulator in health promotion is relevant.<sup>8</sup> The effectiveness of glutamine supplementation in children with gastrointestinal disorders, malnutrition, chronic diseases and trauma, due to antioxidant competence, in the regulation of the immunological and metabolic function, and synthesis of proteins that this immunomodulator causes in the body<sup>9</sup> has been reported in literature. However, in relation to their use in children with asthma, articles are scarce.

Thus, the objective of the study was to evaluate the frequency of food intake of children with moderate asthma compared to children without respiratory diseases and to evaluate the maintenance of the effect of the glutamine immunomodulator supplementation on the attenuation of the symptoms of moderate asthma after the wash-out period.

## METHODS

### Study design

This was a longitudinal intervention study, with quantitative characteristics, conducted in Guarapuava - Paraná, with children in the age range of two to seven years old, of both sexes, with prior medical diagnosis of moderate asthma, whose parents voluntarily agreed that the child would participate in the study by signing the Free and Informed Consent Form. This research was approved by the Committee for Ethics in Research with Human Beings (COMEP) of Universidade Estadual do Centro-Oeste - UNICENTRO, under number 1,142,314/2015.

### Sample study

A convenience sample was used in order to form 3 study groups. Initially, the telephone number of the guardians of the children was obtained from the pediatrician who accompanied them, and after an explanatory conversation about the study, a home visit was made to collect the data only for the parents of the children who agreed to participate in the study, until the number of 15 children in each group was obtained.

The total study sample consisted of 45 children with moderate respiratory disease and no respiratory disease, who were under periodic medical follow-up from August 2015 to June 2016. The glutamine case group was composed of 15 children with moderate respiratory disease who received the immunomodulator glutamine, in the amount of 0.3 g/

kg of weight/day,<sup>9</sup> during the 4-month period. The asthma control group was composed of 15 children with moderate asthma, who did not receive the immunomodulator. A control group without respiratory disease was also included, with 15 children without respiratory diseases, to evaluate and compare the diet.

### Evaluation periods

The evaluations of the children in the three groups, throughout the study, occurred through home visits in the following periods: initial evaluation before starting the supplementation in the group that received glutamine and also an initial visit in the control group with moderate asthma in the same period; 4 monthly evaluations in the glutamine group and in the control group with moderate asthma, during the 4 months in which the supplementation occurred in the group that received the immunomodulator; and 1 final visit in all the groups that occurred 6 months after the end of the supplementation of the group that received the immunomodulator. The children in the control group without respiratory disease were evaluated at a single point in time in the study.

In all visits, a clinical and food intake evaluation was performed in the glutamine group and moderate asthma control group. Food intake was evaluated in the control group without respiratory disease at the final visit.

### Clinical evaluation

The clinical evaluation and evaluation of the respiratory disease symptoms were performed in the glutamine case group and asthma control group using the nutritional history and the ISAAC Questionnaire – Asthma Module of the International Standard Questionnaire (International Study of Asthma and Allergies in Childhood – ISAAC).<sup>4</sup> This questionnaire is a tool for the diagnosis of respiratory diseases, containing simple questions about respiratory disease. Each answer corresponds to a score, and an ISAAC overall score equal to or greater than five points indicates a diagnosis of asthma and respiratory allergies in children.

In addition, the parents or guardians of children with asthma (glutamine case group and control case control) were asked about the hospitalization episodes, the frequency of hospitalization per year, symptoms (cough, fever, dyspnea, wheezing), year of diagnosis of the respiratory disease, duration of the attacks, medications administered to the child, and adherence to drug treatment in each home visit.

### Food intake evaluation

To evaluate food intake, a Food Frequency Questionnaire (FFQ) adapted for the study<sup>10</sup> was used, which contained 18 foods and inquired whether the food intake frequency was daily, weekly, monthly or never consumed. In the initial evaluation, the parents or guardians of the

child were asked about the dietary changes that occurred during periods of asthma attacks in the case group and the control group with asthma.

**Adherence to the use of the glutamine immunomodulator**

At each visit, the children of the glutamine case group were also evaluated for symptoms related to the intake of the immunomodulator and adherence to daily use. The adherence to the use of glutamine was performed through the return of empty packages (sachets). At the end of the 4-month period, the children of the glutamine case group were instructed to stop the supplementation. After a 6-month washout period, they were evaluated again using the ISAAC questionnaire.

**Data analysis**

The data tabulation was initially performed with the help of Excel® software and analyzed by descriptive statistics, with means, standard deviation, relative and absolute frequencies. The distribution of numerical variables was verified through the *Shapiro-Wilk* and *Kolmogorov-Sminorv* tests. To compare the quantitative variables between the case and control groups, the *T-Test* for independent samples was used. For comparison of the quantitative variables relative to the initial and final periods of the study, for both groups, the *T-Test* for paired samples was used. The *Chi-square* Test was used to compare categorical variables. Statistical analyses were performed with a significance level of 5%.

**RESULTS**

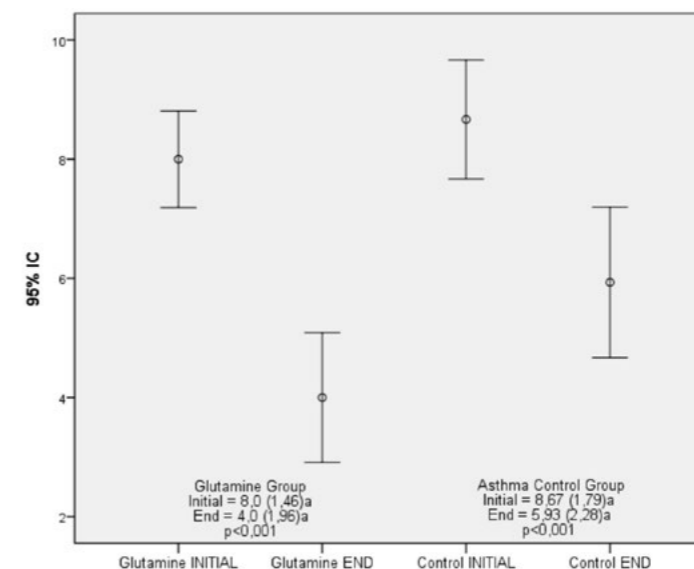
A total of 45 children participated in the study, 30 of them with previous medical diagnosis of respiratory disease and the remaining 15 without respiratory disease, with a mean age of 4.13 (1.59) years. Of these, 41.7% (n=25) were girls and 58.3% (n=35) were boys.

Figure 1 shows the average score obtained in the ISAAC questionnaire in the initial and final periods of supplementation for the glutamine case and asthma control groups. For the glutamine case group, the initial ISAAC score was 8.0 (1.46) decreasing to 4.0 (1.96) at the end of the study (p<0.001). For the control group with asthma, the initial ISAAC score was 8.67 (1.79) decreasing to 5.93 (2.28) at the end of the study (p<0.001).

After the suspension of glutamine supplementation (6-month washout), it was observed that the score increased from 4.0 (1.96) to 7.27 (2.02), with (p<0.001). These data are shown in Figure 2.

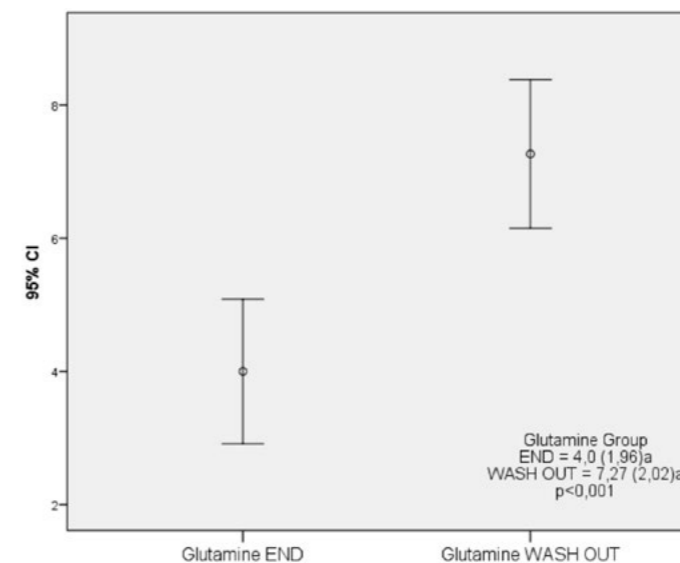
It was found that 60% (n=9) of the children in the control group with asthma and 80% (n=12) of the children in the glutamine case group have their food intake decreased during

**Figure 1.** Comparison of ISAAC score by groups in the initial and final periods



Notes: p = T-test for independent samples statistical value  
<sup>a</sup>Values expressed as mean and standard deviation (SD)

**Figure 2.** ISAAC score comparison of the glutamine case group in the final and wash-out periods



Notes: p = T-test for independent samples statistical value  
<sup>a</sup>Values expressed as mean and standard deviation (SD)

the disease episodes. In addition, 86.7% (n=13) of the children in the control group with asthma and 100% (n=15) in the glutamine case group had no appetite during the respiratory disease attacks.

The food intake frequency questionnaire showed that the general diet of children in all groups was similar (most consume milk daily and vegetables, fruits and meat less frequently), and without significant difference between groups (p>0.05). It was observed that children in the control group without respiratory disease consume ice cream more frequently each week than children in the other groups (53.3%, n=8, p=0.034). These data can be observed in chart 1.

**Chart 1.** Comparison of food intake frequency of children in the glutamine case group, control group with asthma and control group without respiratory diseases

Foods	Glutamine Case Group (n=15) <sup>a</sup>				Asthma Control Group (n=15) <sup>a</sup>				Control Group without Respiratory Disease (n=15) <sup>a</sup>				p <sup>b</sup>
	D	W	M	N	D	W	M	N	D	W	M	N	
Stuffed cookie	13,3 (2)	20 (3)	26,7 (4)	40 (6)	6,7 (1)	20 (3)	0 (0)	73,3 (11)	6,7 (1)	33,3 (5)	20 (3)	40 (6)	0,256
Rice	80 (12)	20 (3)	0 (0)	0 (0)	93,3 (14)	6,7 (1)	0 (0)	(0)	80 (12)	13,3 (2)	6,7 (1)	0 (0)	0,380
Bakery bread	6,7 (1)	66,7 (10)	0 (0)	26,7 (4)	40 (6)	26,7 (4)	6,7 (1)	26,7 (4)	26,7 (4)	40 (6)	20 (3)	13,3 (2)	0,058
French fries	0 (0)	40 (6)	40 (6)	20 (3)	0 (0)	33,3 (5)	40 (6)	26,7 (4)	0 (0)	20 (3)	53,3 (8)	26,7 (4)	0,686
Ice cream	0 (0)	20 (3)	40 (6)	40 (6)	0 (0)	33,3 (5)	40 (6)	26,7 (4)	0 (0)	53,3 (8)	46,7 (7)	0 (0)	0,034
Milk	66,7 (10)	13,3 (2)	6,7 (1)	13,3 (2)	93,3 (14)	0 (0)	6,7 (1)	0 (0)	63,3 (11)	13,3 (2)	13,3 (2)	0 (0)	0,378
Yogurt	6,7 (1)	46,7 (7)	20 (3)	26,7 (4)	6,7 (1)	73,3 (11)	6,7 (1)	13,3 (2)	13,3 (2)	80 (12)	6,7 (1)	0 (0)	0,267
Beef	13,3 (2)	80 (12)	0 (0)	6,7 (1)	13,3 (2)	86,7 (13)	0 (0)	0 (0)	33,3 (5)	66,7 (10)	0 (0)	0 (0)	0,212
Chicken	0 (0)	80 (12)	6,7 (1)	13,3 (2)	0 (0)	86,7 (13)	0 (0)	13,3 (2)	6,7 (1)	86,7 (13)	6,7 (1)	0 (0)	0,519
Boiled eggs	0 (0)	26,7 (4)	13,3 (2)	60 (9)	13,3 (2)	60 (9)	13,3 (2)	13,3 (2)	0 (0)	80 (12)	6,7 (1)	13,3 (2)	0,037
Lettuce	13,3 (2)	20 (3)	13,3 (2)	53,3 (8)	13,3 (2)	26,7 (4)	13,3 (2)	46,7 (7)	6,7 (1)	26,7 (4)	20 (3)	46,7 (7)	0,961
Carrot	13,3 (2)	40 (6)	13,3 (2)	33,3 (5)	13,3 (2)	60 (9)	6,7 (1)	20 (3)	6,7 (1)	53,3 (8)	20 (3)	20 (3)	0,721
Banana	40 (6)	46,7 (7)	0 (0)	13,3 (2)	40 (6)	46,7 (7)	6,7 (1)	6,7 (1)	6,7 (1)	66,7 (10)	13,3 (2)	13,3 (2)	0,336
Orange	13,3 (2)	66,7 (10)	13,3 (2)	6,7 (1)	13,3 (2)	53,3 (8)	20 (3)	13,3 (2)	6,7 (1)	66,7 (10)	0 (0)	26,7 (4)	0,690
Apple	13,3 (2)	66,7 (10)	6,7 (1)	13,3 (2)	33,3 (5)	53,3 (8)	6,7 (1)	6,7 (1)	26,7 (4)	60 (9)	0 (0)	13,3 (2)	0,673
Bean	66,7 (10)	26,7 (4)	0 (0)	6,7 (1)	60 (9)	26,7 (4)	13,3 (2)	0 (0)	80 (12)	13,3 (2)	6,7 (1)	0 (0)	0,638
Caramels	26,7 (4)	46,7 (7)	6,7 (1)	20 (3)	0 (0)	53,3 (8)	33,3 (5)	13,3 (2)	13,3 (2)	46,7 (7)	26,7 (4)	13,3 (2)	0,530
Soda	6,7 (1)	66,7 (10)	20 (3)	6,7 (1)	0 (0)	66,7 (10)	6,7 (1)	26,7 (4)	6,7 (1)	80 (12)	0 (0)	13,3 (2)	0,440

Notes: D = daily consumption frequency; W = weekly consumption frequency; M = monthly consumption frequency; N = never

**DISCUSSION**

Recent studies on asthma show that most people have had repercussions of asthma since the first years of life,<sup>11</sup> thus requiring constant treatment, since there is no complete prevention of the disease or a cure.<sup>12</sup> However, treating asthma goes beyond medication. The symptoms of this disease are due to several factors, such as the environment, emotional state, infectious processes and diet. Thus, preventing the factors that trigger asthma is as important as using medication, so it is essential to investigate the effect of immunomodulators in this clinical condition.

In this study, the mean age of the children evaluated was 4.13 years, most of whom were boys, as in the study by Cunha et al.,<sup>13</sup> who reported that during childhood the dis-

a: data are expressed as percentage and sample number - % (n)

b: comparison using the Chi-square Test, significance of 5%

ease is more prevalent in boys, while during the adolescence, the prevalence is higher in females. Ferrari et al.<sup>14</sup> found, analyzing two age groups, that asthma is more prevalent in younger children.

When evaluating the effect of glutamine supplementation, although the decrease in the ISAAC score was significant in both groups (glutamine and asthma control), the glutamine group had a lower score, which may be associated with the beneficial effect of this immunomodulator. According to studies, this benefit can be influenced by the mechanism of action of the amino acid glutamine in increasing the production of anti-inflammatory cytokines and type 1 T lymphocytes, which play a role in the regulation of the immune system, since in vitro they were able to inhibit the cytokines with pro-inflammatory action.<sup>15,16</sup>

Therefore, it was decided to suspend the supplementation and reassess the symptoms of these children after 6 months. It was observed that the ISAAC score returns to values very close to the initial phase of the study before starting the supplementation. This fact tends to indicate the need for continuous supplementation of this immunomodulator so that the beneficial effect on the attenuation of asthma symptoms is maintained. Boligon and Ruth<sup>17</sup> aimed to verify the impact of the use of glutamine in patients with head and neck neoplasia and in concomitant chemotherapy and radiotherapy. They were divided into a control group (without the use of glutamine) and a test group (which used glutamine), and finally it was observed that the use of glutamine helped during treatment to maintain their nutritional status and prevent mucositis.<sup>18</sup> This study shows that glutamine helps in modulating the immune system. However, studies on glutamine supplementation in children with asthma and with washout were not found.

Glutamine is the most abundant free amino acid in plasma and muscle tissue and is involved in different functions. These functions can be seen in clinical trials in rats with asthma, with improved survival, increased immune barrier, increased bowel function, and decreased bacteria.<sup>15</sup> Clinical trials in humans show that treatment with glutamine decreases infections and length of hospital stay. And the increased oral availability of glutamine promotes an immediate immune response mediated by T cells.<sup>16</sup>

When evaluating children with moderate asthma, it was observed that there was a decrease in diet and appetite during periods of respiratory disease crisis. It is noteworthy that these changes may in the long run lead to changes in nutritional status. However, this study did not focus on the assessment of the nutritional status. Some authors report that there are determinants in the choice of foods that lead to changes in appetite and food intake such as biological, social, and especially psychological determinants.<sup>19,20</sup> Another point that may limit food intake is the excessive consumption of high-calorie foods, because they quickly satisfy children, preventing them from eating other foods.<sup>19</sup>



Although no significant difference was observed in the food intake of children, it is important to discuss the quality of the intake frequency of some foods. It was observed that in the three study groups, milk is not consumed daily by all children. Frizão et al.<sup>21</sup> show that low milk consumption is an aggravating factor, since calcium is essential for the bone health of children. Similarly, it was observed that the daily consumption of beef and chicken is low in all groups, as well as the daily consumption of beans in children with asthma, foods that are important protein sources. According to Cunha,<sup>22</sup> the main function of proteins is growth, exchanges of tissues in different parts of the body, and therefore they are important nutrients for the development of children. Regarding beans, in addition to being a source of protein, their low consumption can reduce iron consumption and cause future problems such as anemia.<sup>23</sup>

All groups also presented low daily intake of fruits and vegetables, foods that are important for the presence of micronutrients that are essential for the growth and healthy development of the child. Their low intake may anticipate diseases that could only arise in adulthood. National food intake studies indicate that most children do not meet the nutritional recommendations for food groups, including fruit and vegetables, in their diets.<sup>24,25</sup>

Regarding the most frequent weekly consumption of ice cream in the group of children without respiratory disease, no studies were found regarding this information. However, this can be only a statistical data found, which may be related to the maternal care that mothers have with their children, mainly due to the existence of asthma, as these are cold foods that can precipitate symptoms of the disease.

In this study, because no significant difference was found in the frequency of food consumption among children with asthma and without respiratory disease, it is wondered if the presence of asthma affects food consumption. It should also be noted that other factors may interfere with food choice. According to Moura,<sup>26</sup> children are not mature enough to control their choices and end up preferring sweets, which are poor in nutritional substances, leading to future problems. Parents are largely responsible for the construction of children's eating habits, since it is during childhood that they are formed. Thus, it is noticed that asthma may not influence the food choices, but other external factors that interfere with the findings of this study, such as the increasing consumption of foods with higher energy concentration, which are promoted by the industry through the production of tasty foods, with high energy density and relatively low cost. Another factor is that the diet of the parents usually has a decisive influence on the diet of the child, affecting the food preferences of the child. Television is one of the potential factors that stimulate eating, which has the power to promote appropriate behaviors to achieve such ends.<sup>26</sup>

The limitations of the study included the difficulty of the mothers in helping the children to adhere to the supplementation in the long term. The costs of glutamine and the fact that

the study was conducted in a region with a peculiar climate for asthma symptoms are also factors to be highlighted. The scarcity of studies similar to this one limited the discussion. Thus, it is important to develop studies that compare the effect of glutamine supplementation with the seasonal period. However, the relevance of this study is shown as a clinical investigation of the effect of this immunomodulator as an auxiliary tool in the monitoring and treatment of children with chronic asthma.

## CONCLUSION

Most children with respiratory disease change their eating habits during an asthma attack, which can affect their nutritional status. The food frequency questionnaire showed that the general diet of children of all groups was similar, characterized as standard diet in childhood. It is noteworthy that healthy eating is extremely important in childhood, because this is the phase in which the child creates their eating habits and develops. In addition, parents need to remember the importance of a balanced diet to ensure adequate nutrition and nutritional status, and consequently, good health of the children.

Glutamine proved to be beneficial throughout the study in attenuating clinical symptoms of asthma. However, the suspension of its long-term use brings loss of effect, with recurrence of clinical symptoms in children. Thus, it is proposed that the supplementation of this immunomodulator be continuous.

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### Contributors

Pietrobon C, Honicky M and Melhem ARF worked in all stages from the conception of the study to the revision of the final version of the article; Zattar JP and Nodari C participated in the data collection; Zattar JP, Saciloto M and Cavagnari MAV participated in the writing, revision and correction of the manuscript.

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