# Anxiety in mothers of infants newly diagnosed with cow's milk protein allergy: A cross-sectional study

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Summary. Introduction and Objectives: Anxiety symptoms are common in mothers of food-allergic children. Although cow's milk protein allergy (CMPA) is the most common food allergy in infants, little is known about whether CMPA has a known effect on anxiety in mothers. The first aim was to assess the anxiety levels in mothers of infants newly diagnosed with CMPA and compare to controls. The second aim was to determine whether there is a difference in anxiety levels of mothers by the symptoms of infants with CMPA. Materials and methods: Mothers of seventy-three infants newly diagnosed with CMPA and 78 mothers of healthy infants were enrolled in this study. The CMPA group were divided into 5 subgroups according to symptoms of infants. The anxiety scores of the mothers were measured with State-Trait Anxiety Inventory (STAI). Results: The median score of the STAI-State (46 vs. 24) and the median score of the STAI-Trait (47 vs. 24) were significantly higher in CMPA group than the control group (p<0.001). The scores of both STAI-State and Trait significantly different between mothers of infants presented hematochezia and respiratory symptoms-anaphylaxis (p=0.002 for STAI-State vs p=0.008 for STAI-Trait). Additionally, there was a statistically significant difference between the educational levels of mothers in CMPA group and STAI State-Trait anxiety median scores (p<0.013, p<0.001 respectively). Conclusion: This study revealed mothers of infants newly diagnosed with CMPA had high anxiety levels. In addition, it was observed having infants suffering from anaphylaxis or hemotochesia and low educational status increased the anxiety in mothers.

Key Words: Anxiety, cow's milk protein allergy, STAI, infants, mothers

# Introduction

Cow's milk protein allergy (CMPA) is the most common cause of food allergies (FA) during infancy and is characterized by an immune response to milk proteins (1). Although the exact global prevalence of CMPA is not known, its prevalence is estimated range from 0.5% to 4.9 (2). CMPA just like other food allergies can be broadly classified into immunoglobulin E (IgE) - mediated (immediate type) reactions, non-IgE-mediated (type 4) mediated and mixed-type reactions (3). Among them, non-IgE- mediated CMPA are common and includes cow's milk protein-induced enterocolitis, cow's milk protein-induced enteropathy and cow's milk protein-induced proctocolitis which often causes rectal bleeding during the infantile period (4). The symptoms of CMPA vary to the underlying mechanism the immune mechanism. IgE-mediated CMPA typically occur within minutes to two hours after ingestion and it is characterized by urticaria and/ or wheezing and/or angioedema whereas symptoms of non-IgE mediated CMPA are delayed 48-72 hours and are predominantly related gastrointestinal tract and/or skin (5). It is often diagnosed based on a detailed medical history and careful physical examination, however, since definitive CMPA's diagnosis remains difficult, diagnostic tests like skin prick tests and specific IgE measurements and elimination diet are useful for evaluating CMPA (6).

Currently, management of CMPA is mainly based on avoidance of milk and milk proteins, which is at least until 9-12 months of age. If the infant is breastfed, mothers should continue to breastfeed by avoiding all milk and dairy products from their diets. If the infant is not breastfed or the mother cannot breastfeed, they should be fed with hypoallergenic formula like amino acid formula (AAF) and foods that do not contain milk and dairy products appropriate for their age (7). The use of a restrictive diet made of milk and dairy products as the main treatment method brings many difficulties for both mother and infant. One of the difficulties encountered is inadequate weight gain in infants who cannot tolerate formulas primarily due to taste problems (8). Other difficulties are that a decrease in health-related quality of life, an increase in stress levels and a misconception of discontinuing breastfeeding for mothers. In addition, strict adherence to the elimination diet in infants with CMPA may negatively impact the nutritional status of the breastfeeding mother (9,10).

Even though the prevalence of CMPA has increased in recent years, surprisingly two studies were conducted to evaluate the psychological status in mothers of children with CMPA. These studies mainly focused on the quality of life on parents of children on an elimination diet (9,11). Given that mothers who have children with chronic illnesses are vulnerable for anxiety, it may be important to determine the anxiety levels of mothers of infants with CMPA. Therefore, the purpose of the present study was threefold: (1) to determine the anxiety scores in mothers of infants newly diagnosed with CMPA compared to healthy controls, (2) to investigate whether there is a difference in anxiety levels of mothers according to the symptoms of infants with CMPA, and (3) to identify possible risk factors associated with anxiety among mothers of infants with CMPA. To our knowledge, to date, this is the first study evaluating anxiety levels in mothers of infants newly diagnosed with CMPA.

#### Materials and Methods

### Study population

This cross-sectional study was carried out on the mothers of infants aged between 4 weeks and 6 months at the Department of Pediatric Gastroenterology and Public Health of Karabuk University Medical Faculty in Karabuk, Turkey, from March 2019 to February 2020. A total of 80 mothers of infants suspected CMPA and 82 mothers of health infants were recruited into the study. The inclusion criteria were mothers of infants who suffered from CMPA. The diagnosis of CMPA was based on the criteria outlined by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (12). In infants with suspected CMPA, an oral food challenge (OFC) test, skin prick tests (SPT), specific IgE measurement and cow milk protein elimination diet are recommended for definitive diagnosis (13,14). In order to discriminate IgE- from non-IgE-mediated allergic reactions in the infants with CMPA, an OFC test, skin SPT and specific IgE measurement were conducted. Exclusion criteria included the mothers with mental disorders, depression and psychiatric diseases; the mothers who had child with chronic disease; the mothers of infants with multiple FA. 7 mothers in the CMPA group and 4 mothers from the control group were excluded from the study. After exclusion of 11 mothers, 73 mothers of infants who were newly diagnosed with CMPA and 78 mothers of healthy infants matched for age were included in the study. All mothers were categorized according to their age groups, education level, marital status, income and place of residence. Economic status was represented by monthly family income and categorized into three groups as low (<250 €), middle (250–750 €), and high (750 € and above). The mothers of infants with CMPA were divided into 5 subgroups according to clinical manifestations of infants. The first subgroup consisted of 25 mothers of infants with eczema. The second subgroup consisted of 19 mothers of infants with hematochezia. The third subgroup consisted of 5 mothers of infants with vomiting. The fourth subgroup consisted of 20 mothers of infants with diarrhea and last subgroup consisted of 4 mothers of infants with respiratory symptoms (an anaphylactic reaction, coughing, dyspnea, hoarness). In addition, the mothers in the CMPA group were categorized according to the type of immune-mediated reaction in their infants (Figure 1). The study was approved by the Ethics Committee for Non-invasive Clinical Research of Karabuk University, under No. 2020/187. All participants provided their written informed consent.

## Measures

For assessment of maternal anxiety, State-Trait Anxiety Inventory (STAI) was used. STAI developed by Spielberger et al. composed of two subscales as the state anxiety scale (STAI-State) and the continuous anxiety scale (STAI-Trait). STAI-State evaluating how the individual feels under certain circumstances, at a particular moment in time consists of 20 items designed on a four-point scale with the following category options: 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so. STAI-Trait consists of 20 items designed on a four-point scale with the following category options: 1) almost never, 2) sometimes, 3) often 4) almost always, and evaluates how the individual generally feels. The score range for both subscales is determined as between 20 and 80 points, and a higher score indicates higher levels of anxiety (15). The test was translated and adapted to the Turkish by LeCompte and Öner et al. It has been shown that the STAI has high internal consistency with Cronbach alpha of 0.83 for the Turkish population (16).

#### Statistical analysis

The data were analyzed with SPSS version 21.0 software for Windows. Results are expressed as median (IQR). Kolmogorov–Smirnov test was carried out to determine the normality of data distribution. The values of STAI-State, STAI-Trait and mother's age had abnormal data distribution, by Kolmogorov–Smirnov test (p<0.05), therefore, median values between groups were determined and compared using Mann-Whitney U test. The sociodemographic characteristics of the mothers were compared with the Pearson's chi-squared test. We carried out intragroup comparisons with the Kruskal–Wallis test, and post hoc comparisons with Tamhane's T2 test. Correlation analyses were evaluated with Spearman's correlation test. We considered p-values of less than 0.05 statistically significant.

# Results

The median age of 73 mothers of infants with CMPA and 78 controls were 30 (23-41) and 29

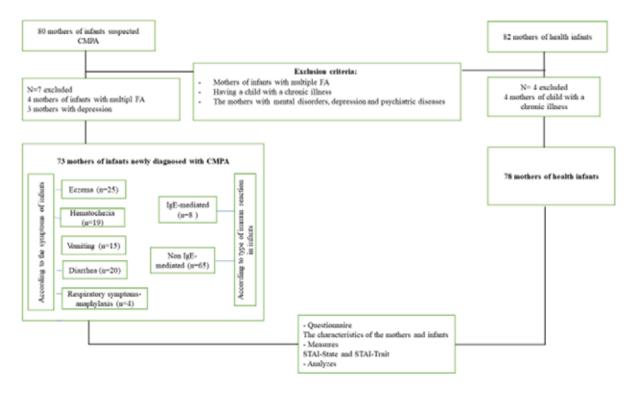


Figure 1. Flow diagram of the study design

	CMPA group (n=73)	Control group (n=78)	p value*
<b>Mothers variables</b> Median age (IQR**), years	30 (23-41)	29 (19-39)	>0.05
Age distribution, (n)			
18-24 years 25-31 years ≥ 32 years	11 (15.1) 32 (43.8) 30 (41.1)	17 (21.8) 31 (39.7) 30 (38.5)	>0.05
Educational status n (%) Secondary school High school University	7 (9.6) 32 (43.8) 34 (46.6)	8 (10.3) 33 (42.3) 37 (47.4)	>0.05
Economic status n(%) High Middle Low	5 (6.8) 48 (65.8) 20 (27.4)	8 (10.3) 52 (66.7) 18 (23.1)	>0.05
Marital status n(%) Married Seperated	69 (94.5) 4 (5.5)	75 (96.2) 3 (3.8)	>0.05
Employment status n(%) Employed Unemployed	36 (49.3) 37 (50.7)	42 (53.8) 36 (46.2)	>0.05
Place of residence Rural Urban	44 (60.3) 29 (39.7)	46 (59.0) 32 (41.0)	>0.05
Infants variables Median age (IQR) months	4 (1-6)	4(1-6)	>0.05
Sex Male n(%) Female n(%)	47 (64.4) 26 (35.6)	51 (65.4) 27 (34.6)	>0.05
Type of feeding Breastfeeding Formula and breastfeeding Formula	28 (38.4) 24 (19.2) 31 (42.5)	41 (52.6) 13 (16.7) 24 (30.8)	>0.05
Clinical presentation n (%) Eczema Vomiting Diarrhea Hematochezia Respiratory symptoms- anaphylaxis	25 (34.2) 5 (6.8) 20 (27.4) 19 (26.0) 4 (5.5)	N/A*** N/A*** N/A*** N/A*** N/A***	
Types of CMPA Non-IgE mediated IgE mediated	65 (89.0) 8 (11.0)	N/A*** N/A***	

Table 1. The characteristics of the mothers and infants in the CMPA and control groups

<sup>•</sup> Pearson's chi square test <sup>••</sup> Interquartile range <sup>•••</sup> Not Available

(19-39) years, respectively. The educational status of the mothers of infants with CMPA and controls were categorized as secondary school graduates (9.6 % vs. 20.5 %), high school graduates (43.8% vs. 56.4%) and university graduates (46.6% vs. 23.1% respectively). 94.5 % of the mothers in the CMPA group and 96.2 % of those in the control group were married. More than half of the mothers in both groups were employed and also all participants had a health insurance. The economic status of 65.8 % of the mothers in the CMPA group and 73.1 of the controls were middle income. Most of the mothers in both groups lived in the city center, 60.3 % of the mothers in the CMPA group and 59.0 % of the controls lived in the rural. No statistically-significant differences were found between the two groups of mothers in terms of sociodemographic characteristics.

The median age of 73 infants with CMPA was 4 months (IQR 1-6) and 64.4% were 47 males. The median age of 78 healthy infants was 4 months (IQR 1-6) and 65.4 % were 51 males. There were no statistically significance differences between the two groups with respect to age or gender (p>0.05). Among the infants with CMPA, there were 25 infants (34.2 %) with eczema, 19 infants (26.0 %) with hematochezia, 5 infants (6.8 %) with vomiting, 20 infants (27.4%) with diarrhea and 4 infants (5.5 %) with respiratory symptoms (an anaphylactic reaction, coughing, dyspnea, hoarness). 89 % infants in the CMPA group were diagnosed with non IgE-mediated CMPA by elimination diet and oral challenge with milk protein. In terms of the feeding practices, infants in the CMPA group were fed with breastfeeding (38.4 %), AAF (19.2 %), both breastfeeding and AAF (42.5 %) while majority (52.6 %) of the controls were fed with breastfeeding. The sociodemographics features of the mothers and characteristics of infants are presented in Table 1.

The median score of the STAI-State in the CMPA group was significantly higher than that in the control group [46 (IQR 35-72) vs 24 (IQR 20-44) respectively; p<0.001]. Similar to the median score of the STAI-State, the median score of the STAI-Trait in the CMPA group was significantly higher than that in the control group [47(IQR 32-70) vs 24(IQR 20-38) respectively; p<0.001] (Figure 2). In the evaluation of anxiety scores according to the type of immune

reaction, the median STAI-State scores (65 vs 45) and STAI-Trait scores (59 vs 47) were significantly higher in the mothers of infants with IgE-mediated reaction than mothers of infants with non IgE-mediated reaction (p<0.001 for both). Compared anxiety levels of mothers of infants with CMPA and socio-demographic characteristics; no statistically significant difference was found between the mothers' ages, marital status, economic situation and state-trait anxiety median scores (p>0.05). On the other hand there was a statistically significant difference between the educational levels of mothers in CMPA group and STAI State-Trait anxiety median scores (p<0.013, p<0.001 respectively) (Table 2).

The mothers' median STAI-State scores for eczema, diarrhea, vomiting, hematochezia and respiratory symptoms-anaphylaxis were 43,45, 40, 53 and 71 respectively. Their median STAI-Trait scores for eczema, diarrhea, vomiting, hematochezia and respiratory symptoms-anaphylaxis were found as 43, 47, 40, 48 and 67 respectively. According to symptoms of infants with CMPA, the mothers' STAI State-Trait anxiety median scores are shown in the figure 3. Anxiety levels of mothers according to the clinical manifestations of their infants with CMPA were evaluated with Kruskal-Wallis and post hoc Tamhane T2 tests. In terms of the scores of STAI-Trait significantly different between mothers of infants presented respiratory symptomsanaphylaxis and mothers of infants with other clinical manifestation (p= 0.04 for eczema, p= 0.01 for diarrhea, p=0.001 for vomiting and p = 0.008 for hematochezia). As for the scores of STAI-State, there were significantly different between mothers of infants with respiratory symptoms-anaphylaxis and mothers of infants with other clinical manifestation (p= 0.001 for eczema, p= 0.001 for diarrhea, p=0.001 for vomiting and p = 0.002 for hematochezia). In addition, the scores of both STAI-State and Trait significantly different between mothers of infants presented hematochezia and respiratory symptoms-anaphylaxis (p= 0.002 for STAI-State vs p=0.008 for STAI-Trait), vomiting (p=0.017 for STAI-State vs p=0.043 for STAI-Trait). In the CMPA group, correlation analysis of maternal age with STAI-State and STAI-Trait revealed no significant relationships (p=0.237 and p=0.661 respectively).

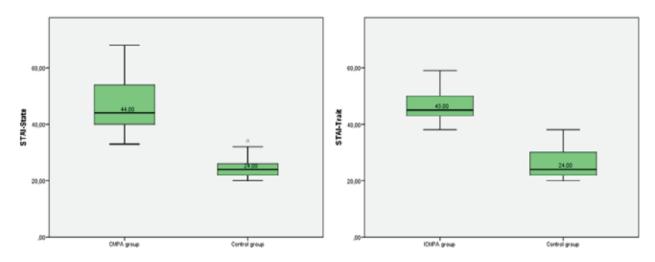


Figure 2. Comparison of median (a) STAI-Trait and (b) STAI-State scores in the CMPA and control groups

# Discussion

In this cross-sectional study, the mothers of infants newly diagnosed with CMPA had higher anxiety scores than controls and we found that the highest anxiety scores were seen in mothers of infants with respiratory problems-anaphylaxis and hematochezia. Moreover, it was detected that low education level increased the anxiety level of mothers of infants with CMPA.

FA, the highest incidence occurs during infantil period, are increasingly common around the world and its clinical spectrum ranges from mild skin involvement to severe, anaphylactic reaction. The most common food allergy in the infantile period is CMPA, and it has been suggested that the symptoms of allergic children significantly affect mothers both socioeconomically and psychologically (17). Despite fact that the frequency of allergic diseases increases and turn into a public health problem, a limited number of studies have been conducted to evaluate the psychological status of mothers of children with allergic diseases and also have mainly focused on multiple food allergies and asthma (18,19). A study conducted by Lau GY et al., they reported mothers of children aged 8- to 16-yearold with FA were more stressed and anxious than their controls (20). Consistently, Boyle RJ et al., found that mothers of children with FA exhibited significantly increased levels of anxiety and also recommended

psychological intervention to reduce anxiety in mothers (21). Recently, Meyer R et al. analysed parents of children aged 4 weeks-16 years with non-IgE mediated allergies, they found parental quality of life and family functions were worse than controls (22). These studies strongly suggest that mothers of children with FA are likely to suffer with stress and anxiety.

Given that mothers anxiety levels and wellbeing were highly influenced by children's health status, it is easily expected that having an infant with milk allergy may cause some changes in the psychological state of mothers. In the present study, we found both the median score of STAI-State and the STAI-Trait in the mothers of infants with CMPA were significantly greater than controls (p>0.05). As a comprehensive study evaluating the anxiety levels in mothers of infants newly diagnosed with CMPA has not been published so far, we could compare our results with similar studies. Protudjer JLP et al. conducted a study in 580 mothers of children aged 0 to 8 years with FA during coronavirus pandemic. They reported mothers of children with FA had high anxiety levels and poor health-related quality of life (23). Interestingly, their study group composed just 32 mothers of allergic children and of whom 26.3 % had infant with CMPA. Likewise, a study carried out in the Chile by Cortes A et al, they measured 206 mother's anxiety levels by using the hospital anxiety and depression scale and found that 42.6% of mothers of infants with FA

45(40-70) 48(39-68) 45(32-61) H*: 4.741 p: 0.093 51(43-70) 48.50(32-66) 44.50(39-68) H*:13.971 p:0.001 51(40-59) 47(39-70) 46(32-51)	24(20-34) 24(20-44) 24(20-40 H*: 0.121 p:0.941 24(22-32) 24(20-34) 24(20-34) 24(20-44) H*: 2.508 p:0.285 25(22-32) 24(20-44)	24(20-34) 26(22-38) 24(20-36) H*: 4.312 p:0.116 24(22-34) 24(22-34) 24(22-36) H*: 6.022 p:0.050 26(22-34)
51(43-70) 48.50(32-66) 44.50(39-68) H*:13.971 p:0.001 51(40-59) 47(39-70)	24(22-32) 24(20-34) 24(20-44) H*: 2.508 p:0.285 25(22-32)	24(22-34) 24(22-34) 24(22-36) H*: 6.022 p:0.050
48.50(32-66) 44.50(39-68) H*:13.971 p:0.001 51(40-59) 47(39-70)	24(20-34) 24(20-44) H*: 2.508 p:0.285 25(22-32)	24(22-34) 24(22-36) H*: 6.022 p:0.050
51(40-59) 47(39-70)	25(22-32)	
47(39-70)		26(22-34)
	24(22-40)	24(20-38) 25(22-36)
H*: 3.334 p:0.189	H*:1.994 p:0.369	H*: 0.995 p:0.608
47(32-70) 49.50(48-51)	24(20-44) 28(24-30)	24(20-38) 28(24-30)
U**: -1.168 p:0.243	U**: -1.354 p:0.176	U**: -,662 p:0.508
45(32-70) 48(39-68)	24(20-44) 24(20-34)	27(20-37) 24(20-38)
U**:-1.573 p:0.116	U**: -,372 p:0.710	U**: -1.957 p:0.050
47(39-70) 48(32-68)	24(20-40) 24(20-44)	24(20-38) 26(22-37)
U**: -1.420 p:0.156	U**: -1.100 p:0.271	U**: -,683 p:0.494
	24(20-31) 24(20-44) 24(22-32)	24(20-38) 26(22-37) 27(22-34)
47.50(39-60) 47(32-70) 44(39-59)	1	H*: 3.917 p:0.141
	44(39-59)	

Table 2. Comparison of the median anxiety score by socio-demographic characteristics of the CMPA and control groups

\* Kruskal Wallis

\*\* Mann-Whitney U test

STAI-State

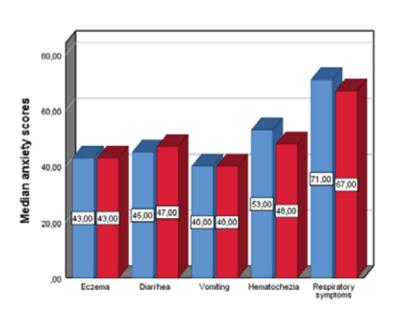


Figure 3. The mothers' STAI State-Trait anxiety median scores according to symptoms of infants with CMPA,

including CMPA had anxiety (17). Both the findings of the present study and all the above support the view that anxiety levels increase in mothers with FA.

It was found that some factors have been linked with the development of anxiety disorders in mother with a sick child (24). These factors such as the age of the mother, education level, income, the number of children living at home, the age of the child, the duration of the symptoms, and the severity of the child's illness may contribute to the new onset of anxiety in mothers of children with illness (25). Seymour et al. conducted a study in 224 Australian mothers of infants (aged 0-12 months), and reported that low education level, low socio-economic status, poor sleep quality and difficult infant behavior elevated level of anxiety in mothers (26). In the present study, we detected mothers' anxiety scores were not influenced by mothers' ages, marital status, the number of children living at home and economic situation during at the stage of diagnosis. On the other hand it was found that low education level increased the anxiety level of mothers in CMPA group. In the light of this result, the low education level might be considered as a factor that increases in the anxiety levels of the mothers.

Anaphylaxis is mainly owing to an IgE-mediated immune reaction in children, and cow milk, egg are the most common triggers of food-induced anaphylaxis in the first years of life. Given that anaphylaxis has a life-threatening nature, it is expected that it provokes anxiety in exposed children and their parents (27,28). In a study of a small number of pediatric patients suffered anaphylaxis by Akeron et al, it was observed the parents felt more anxiety and worry than their children (29). Recently, Fedele DA et al. conducted a study in the 57 families of food allergic children and reported mothers of children who underwent anaphylaxis had suffered post-traumatic stress disorder (30). In the present study the both anxiety scores were found to be highest in mothers of infants suffered from anaphylaxis. Moreover, the median STAI-State and Trait scores were significantly higher in the mothers of allergic infants with IgE-mediated reaction. Even though the previous studies were not conducted on mothers of infants with CMPA, both the results of these studies and our findings have demonstrated that anaphylaxis plays an important role in maternal anxiety.

Hematochezia or rectal bleeding in infants, a relatively uncommon, is mostly a benign and self-limiting. Determining the definitive cause of hematochezia takes time and sometimes invasive testing including colonoscopy is required. If the hematochezia is caused by allergies, it starts when the infants are exposed to the cow's milk protein through breast milk or infant formula. In addition, infants can show this symptom up to two weeks after taking elimination diet (31-33). In this study, the second highest anxiety scores after anaphylaxis were observed in mothers of infants with hematocaesia. Since there is no study measuring the anxiety scores in mothers of infants with hematocaesia caused by CMPA, we could not compare these findings with any study. Thus, we think that comprehensive studies are required to determine whether factors such as prolongation of the diagnostic process and the repetitive nature of the hematocaesia trigger anxiety in mothers of infants with CMPA.

As stated previously, eczema and non-specific gastrointestinal symptoms including, diarrhea, and vomiting can be the manifestation of CMPA. In present study, Twenty-five infants (34.2%) in CMPA group had eczema. This was followed by hematochezia (26%), vomiting (6.8%), diarrhea (27.4%) and respiratory symptoms-an anaphylactic reaction (5.5%). There was no difference among the anxiety scores of mothers whose infants had symptoms of eczema, vomiting, or diarrhea (p>0.05). In the literature, there are several studies determing the anxiety levels of mothers of children with eczema. A study of 33 mothers of children with eczema by Faught et al found that mothers of children with eczema had significantly higher total stress scores than controls (259.6 vs 222.8 p < 0.05 respectively) (34). On the other hand Yamaguchi et al. conducted a study in 216 mothers of children aged 2-6 years old, who had been diagnosed with eczema and reported that eczema and its complications in children were not a determining factor for maternal stress or anxiety (35). Our findings are not compatible with Yamaguchi et al. A reason for this difference might result from their study being carried out in mothers of children aged 2-6 years.

In the treatment of CMPA, it is essential to eliminate cow's milk protein from the infant's or mother's diet. Since eliminating milk and dairy products from the diet of breastfeeding mothers makes them more susceptible to vitamin D deficiency, calcium and vitamin D supplementation is recommended.<sup>12</sup> In present study the all breastfeeding mothers of infants with CMPA were received calcium carbonate of 2500 mg and vitamin D of 880 international units supplementation without measuring theirs Vitamin D levels.

The present study has some limitations. The main limitation, the study was cross-sectional, and there was no prospective follow-up. Therefore, there is no data concerning how the anxiety scores of mothers vary during the elimination diet and challenge period. Second, it has not been reported the determining the anxiety scores in mothers of infants who were newly diagnosed with CMPA so far, thus, we compared our findings to a small number of previous studies.

## Conclusion

Despite limitations, the present study indicated that the mothers of infants with CMPA had higher anxiety levels. Also, it revealed that there were differences in the anxiety levels of mothers according to the clinical manifestations of allergic infants. Based on the results of the study, CMPA seem to create negative effects not only on the infants' health but also on the emotional state of their mothers. Therefore, physicians should be aware that mothers of infants diagnosed with CMPA might experience varying levels of anxiety. To decrease anxiety levels at the diagnosis phase and the early period of the disease, it may be helpful to provide sufficient knowledge on the CMPA and its management to the mothers of infants with CMPA. While informing, the education level of the mothers and the clinical manifestations of the infants should also be taken into consideration. If necessary, professional psychological support might be considered for mothers with high anxiety levels.

Conflicts of interest: We declare that we have no conflicts of interest.

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Author contributions: All authors contributed equally

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