Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

ORIGINAL ARTICLE

OPEN ACCESS

Effects of the affinity to the Mediterranean diet pattern together with breastfeeding on the incidence of childhood asthma and other inflammatory and recurrent diseases

Fernando M. Calatayud-Sáez[a]*, Blanca Calatayud[b], Monica Luque[b], Ana Calatayud[c], JG Gallego[d], Francisco Rivas-Ruiz[e]

[a]*Pediatrician at the Child and Adolescent Clinic "La Palma", Ciudad Real, Spain*
[b]*Nutritionist at the Child and Adolescent Clinic "La Palma", Ciudad Real, Spain*
[c]*Nurse and nutritionist trainee at Child and Adolescent Clinic "La Palma", Ciudad Real, Spain*
[d]*Family doctor at Health Center No. 1 of Ciudad Real, Spain*
[e]*Research unit, Costa del Sol Health Agency, Marbella, Málaga, Spain*
The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

Received 11 March 2021; Accepted 7 September 2021
Available online 1 November 2021

KEYWORDS
childhood asthma;
dietary awareness;
dietary intervention;
inflammatory disease;
the Mediterranean diet

Abstract
Introduction: There is an increasing amount of data relating the dietetic pattern to health variables, although data concerning the child population are scarce. The aim of the study was to assess the effects of affinity to the Traditional Mediterranean Diet (TMD) pattern, together with breastfeeding, on the incidence of childhood asthma and other inflammatory and recurrent diseases (IRD) in children under 2 years of age.
Methods: Single-group intervention study evaluating differences in results according to degree of adherence to TMD recommendations. According to their adhesion to the TMD-Breastfed Test, patients were classified into two groups: Group 1 (with greater adherence) and Group 2 (with less adherence). The incidence of childhood asthma and IRD was evaluated and compared with both groups.
Results: The score of the TMD-Breastfed Test was optimal in Group 1 and good in Group 2. It shows a marked reduction in both consultation groups "on request" compared with "planned," with low morbidity and low use of antibiotics. The incidence of infectious diseases and recurrent bacterial complications shows a clinically relevant difference between both groups. The incidence of childhood asthma was greater and statistically significant in Group 2, with less adherence to breastfeeding.

*Corresponding author: Fernando M. Calatayud-Sáez, Child and Adolescent Clinic "La Palma". C/Palma 17 Bajo A, 13001 Ciudad Real, Spain. *Email address*: altayud@gmail.com

https://doi.org/10.15586/aei.v49i6.338

Conclusions: In these cohorts of breastfed patients with good adherence to TMD patterns, there was evidence of a low incidence of childhood asthma and the IRD, more pronounced in the highest adherence Group 1. Some non-TMD foods have been linked to the occurrence of childhood asthma and IRD, as their dietary limitations have contributed to decreasing morbidity.

Introduction

The dietary composition in the diet of breastfed patients is a fundamental factor in the state of health and well-being. In recent years, conventional diets have been gradually withdrawn, and an excess of animal-based foods, as well as processed and ultra-processed foods, have been introduced, which could be the source or one of the most important factors in the development of inflammatory and recurrent diseases (IRDs) in childhood. There are several studies on the effects of the Mediterranean Diet on the inflammatory and degenerative processes of the adult population, and their influence on the prevention and the subsequent control of cardiovascular, respiratory, inflammatory, neurological, and degenerative diseases.[1-4] In addition, they have been able to show the pro-inflammatory effects of some foods introduced by Western Civilization; in one international study with European funding, it was confirmed that children who eat refined and processed foods have higher inflammatory markers in their blood, compared with children who eat fruits and vegetables in abundance.[5,6] We also wish to highlight that illnesses caused by food hypersensitivity, like non-IgE-mediated food intolerances, are increasing, which lead to inflammatory disease in several zones of the organism.[7-11] The current treatment of these entities (proctocolitis, enterocolitis, enteropathy, eosinophilic esophagitis, noncoeliac wheat sensibility, etc.) involves the elimination of the proteins concerned. In accordance with these studies, it can be considered that many IRDs which we attend to in pediatric consultations can be avoided and even improved by promoting breastfeeding and the traditional diet. When an inflammatory disease becomes severe, becoming recurrent in patients, we have considered it convenient to carry out a nutritional report on the family, with the aim of detecting and correcting diet changes, and adjusting them to the diet pattern, which in our environment corresponds to the traditional Mediterranean Diet (TMD). Until now, our studies have been quasi-experimental, without a control group, leading to apprehensions about the observed improvement, which could be due to the natural evolution of these diseases, which habitually disappear from 5 to 6 years of age.[12-14] In accordance with these previous studies, as a preventative measure, we can expect breastfed patients with a healthy diet from birth to have low morbidity and not develop recurrent conditions. In Accordance to these previous studies, we can expect that infants with a healthy diet from birth to have low morbidity and not develop recurrent conditions.

With the objective of evaluating the result of diet quality on childhood health, we designed a study whose objective was to link the degree of adhesion to the TMD with breastfeeding, and contrast it with the incidence of childhood asthma and other inflammatory recurrent diseases in the first 2 years of life.

Equipment and methods

Prospective observational cohort study, where the two cohorts of study are identified based on their affinity to the TMD pattern, was employed. All infants who attended a primary care pediatric consultation in Castila la Mancha, between January 2015 and March 2018, were included in the study. The majority of the children were recruited shortly after being born. Breastfeeding was promoted, and all were offered the chance to follow a TMD plan (Figure 1). Parental consent was required to be included in the study. In the consultation, the diet recommendations and the intention to evaluate the possible relationship which breastfeeding and the degree of completion of the TMD have with the onset of childhood asthma and other IRDs were explained.

Study variables

1. **Adherence to breastfeeding and TMD:** To evaluate the adhesion, we used the TMD-Breastfeeding Test (TMD-L), which was carried out by a nutritionist on an individual basis, at 6, 12, 18, and 24 months of age. The TMD-L test involves responding to a questionnaire with 12 items (Table 1). The satisfactory answers represent a positive connotation in connection with the TMD and carry 2 points, except for the first item concerning breastfeeding which carries 6 points (one point for each month of exclusive breastfeeding). The mixed responses are worth between 0 and 1 points (in the case of mixed breastfeeding, 0.5 points for each month). Insufficient answers are worth 0 to −2 points. The total sum of the answers to items will give us the result of affinity to the TMD. The highest mark is 28 points and the minimum can be negative (up to −16). In the 6th month control, only the type of breastfeeding is scored. When the TMD-L test is carried out, the difficulties involved and how diet can be changed to obtain better results are analyzed. This questionnaire has allowed us to calculate the TMD-L index. According to the obtained results, three scales of the TMD quality are obtained: (1) optimal, when the score is higher than 15; (2) good or with room for improvement, when the score is between 8 and 15, both inclusive, and (3) low quality, when the score is lower than 8.

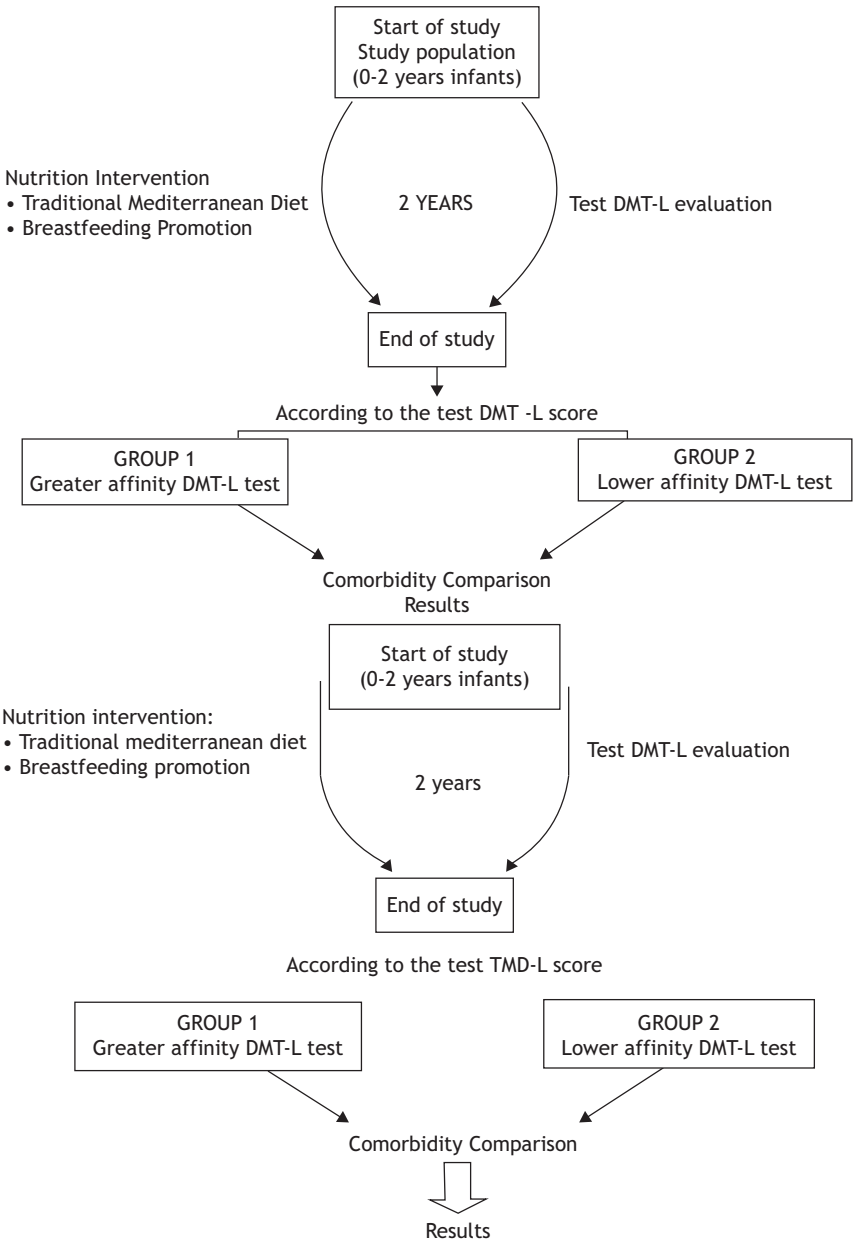

Figure 1 Study design diagram.

2. **Morbidity assessment:** The effect of morbidity is evaluated and all the visits to a pediatric consultation are noted, distinguishing between an "on request" consultation due to illness and a "programmed" consultation for a check-up. Bureaucratic consultations were not taken into account. Details of all the incidents and illnesses arising in the study period were gathered. The incidents requiring attendance at the emergency unit were recorded. All prescribed medicines were noted.
   Independent variables: In studies previously carried out by our group, independent variables were defined in accordance with the international consensus,[12-14] such as upper respiratory tract infection (ITRS), acute otitis media (OMA), acute rhinosinusitis, and asthma attack or bronchospasm. We have defined IRD as the repetition of three episodes of one inflammatory disease in a 6-month period or four episodes within a year. Thus, we would have recurring acute otitis media, relapsing rhinosinusitis, otitis media with effusion, persistent nasal obstruction, and recurrent wheezing or childhood asthma. In addition, we have applied the nutritional program "Learn to eat the Mediterranean way," which we use in this study, with the aim of monitoring adherence to the TMD with a nutritionist. In Table 2, the main differences between the TMD and the diet which has been structuring itself in "Western civilization" are shown.
3. **Variables dependent on the results:** Depending on the score achieved when ending the study, in the TMD-L Test, the breastfed patients were distributed into two groups, and were correlated with the incidence of

Table 1 TMD-breastfed TEST (traditional Mediterranean diet).

				6th month	12th month	18th month	24th month
Breastfeeding*	Exclusive 6	Mixed 3	Adapted −2				
Drinks	Water 2	Natural juice 0	Manufactured drink −2				
Fruit**	More than 2 pieces 2	1-2 pieces 1	<1 piece −2				
Vegetables, leafy vegetables, and root vegetables**	More than 200g/day 2	100-200 g/day 1	<100 g/day 0				
Whole grains	Between 50 and 100 g/day 2	More than 100 g/day 1	None −2				
Refined grains and potato	Less than 50 g/day 2	50-100 g/day 0	More than 100 g/day −2				
Pulses, seeds, and ground nuts	2 or >times/week 2	1-2 times/ week 1	None −2				
Fish, white meat, and eggs	Less than 30 g/day 2	Between 30 and 50 g/day 1	More than 50 g/day 0				
Red and processed meat	None 2	Occasionally 1	Often −2				
Fermented dairy	1 or <1 piece 2	1-2 pieces 1	>2 pieces 0				
Cow's milk	None 2	Occasionally 1	Yes- drunk −2				
Family diet: shows self-control	Considerable autonomy 2	Limited autonomy 1	Lack of autonomy 0				
Total							

*Exclusive breastfeeding: 1 point for each month. Mixed breastfeeding: 0.5 points for each month. In the 6th month control, only the type of breastfeeding is scored. **Fresh, natural, unprocessed, and perishable foods.

Table 2 Differences between the traditional Mediterranean diet and the "Western civilization" diet.

Traditional Mediterranean Diet	Western Civilization Diet
• Breastfeeding	• Adapted milk
• Varied, seasonal fruits	• Baby food jars and canned fruits
• Vegetables and leafy vegetables	• Baby food jars, and canned vegetables and leafy vegetables
• Pulses and nonprocessed nuts	• Canned pulses and dried, fried, or salted nuts
• Minimally processed and fermented whole grains	• Refined, processed cereals with industrial fermenting agents
• Fermented milk, principally goat's and sheep's	• Whole processed milk, mainly from cows
• Occasional lean meat, in small quantities	• High consumption of red, processed meats
• Minimally processed, perishable, fresh, and local foods	• Nonperishable processed and ultra-processed foods
• Limits on products with added chemicals	• Presence of chemical agents and enzyme disrupters

childhood asthma and IRD. The cutoff point to classify the two groups was made by calculating the sample average. **Group 1, with greater adherence to the TMD**: with a test score above the average cutoff point. **Group 2, with lesser adherence to the TMD**: with a test score below the average cutoff point.

4. **Laboratory evaluation:** This was carried out exclusively with children who had some type of IRD: general biochemistry, along with immunoglobulins, total IgE and specific to respiratory and food allergens, inflammatory markers (PCR-hs, TNF-alpha, IL-1, IL-6, C-3 y C-4), and test for histamine response to food antigens or the HANA Test.[15]

In the files of those who prematurely withdrew from the study, the reasons leading to the suspension of the study (moving home, conflict with the limits on foods, social difficulties to carry out the diet) are noted. This study adapted itself at all times to the rules of Good Clinical Practice and the ethical regulations agreed upon in the Helsinki declaration and its subsequent modifications, along with the Organic Law 15/1999, of 13 December, for Personal Data Protection. The study's protocol was approved by the Ethics Committee for Clinical Research of Ciudad Real's Integrated Care Management. (Internal code: C-95, Act 03/2017).

Sample size: To achieve an output of 80%, which detects differences in the hypothesis test for independent samples, taking into account a 5% significance level, assuming a proportion of recurring diseases at 90% in the group of least affinity to the TMD, and 70% in the group of greater affinity to the TMD, a minimum of 50 patients were included in each of the branches of the study.

Statistical plan: A descriptive analysis was carried out for all the samples, using measures of central tendency, dispersion, and position for quantitative variables, and frequency distribution for the qualitative variables. Taking adherence to the TMD with the average score over 2 years as a segmentation variable (cutoff point 67), a comparative variable was carried out with respect to the variables, using the general lineal model for repeated measures in the case of variables with four evaluations, the Student *t*-test for independent samples for quantitative variables, and the chi-square test for dichotomous qualitative variables. In the different analyses, the level of statistical significance was established at $p<0.05$.

Results

Families of 122 patients were invited to participate in the study. A total of 103 patients completed the study, of whom 48 were women and 55 were men; 19 did not complete the study. The obtained results were similar for both sexes, which is why they are given below. There were also no significant differences in the pondero-statural development in both groups, as both developed properly. At the age of two, none of the patients was overweight or obese. We collected data on the family history of allergy in both groups, without significant differences.

The average of the four controls was established at 67 ± 14.60 points. Group 1 obtained an optimal response in their TMD-L test scoring (Percentile- 75: 74) and Group 2 obtained a response which was classified as good (Percentile- 25: 56). Breastfeeding became the most prominent item for belonging to one group or the other. Many families from Group 2 were not able to keep up breastfeeding for several reasons, despite being made aware of it. In the rest of the items on supplementary feeding, there was no significant difference. There were small, insignificant differences in the age of starting nursery education and in the number of siblings in both groups (Table 3). With regard to attendance rates, the results were similar. There were more planned consultations than on request consultations in both groups (average of 11.71 ± 2.91 compared to 7.17 ± 2.4).

Table 3 Nursery, no. of siblings, and form of consultation per patient in 2 years.

	Group 1	Group 2	P
Age upon starting nursery (months)	11.62 ± 5.48	13.86 ± 6.09	0.55
Number of siblings	0.69 ± 0.75	0.80 ± 0.69	0.43
On request consultations (2 years)	6.83 ± 2.28	7.51 ± 2.48	0.14
Planned consultations (2 years)	12.52 ± 2.92	10.88 ± 2.68	0.04
Attendance at emergency unit (2 years)	0.63 ± 0.84	1.25 ± 1.30	0.05
Hospitalization (2 years)	0.06 ± 0.23	0.22 ± 0.50	0.04

The incidence of IRD was low in both groups, although more notable in Group 1. The number of bronchospasm attacks was lower and clinically relevant in Group 1, the incidence in this group being almost half of that of Group 2. The number of medicines used in the patients with bronchospasm attacks was lower in Group 1, less than half of that of Group 2 (Table 4).

During the age period studied, we had a total of 38 IRD episodes, the majority being childhood asthma (61%). Of these, 10 were in Group 1 and 28 in Group 2. The difference in the incidence of childhood asthma in Group 1 compared with Group 2 was close to the level of significance (P: 0.09). The patients with IRD (in both groups) developed elevated inflammatory markers, especially TNF-alpha, and in a smaller proportion PCRhs, IL-1, IL-6, C-3, and C-4. The HANA test[15] marked foods suspected of promoting an inflammatory response not mediated by IgE (Table 5).

Discussion

The hypothesis that we had postulated, i.e., a quality diet based on DMT together with breastfeeding should reduce IRD, has been confirmed. In view of the results, we wanted

Table 4 Incidence of average number of episodes of and treatment in 2 years for infectious diseases and childhood asthma in the two groups.

Incidence by patient in 2 years	Group1	Group 2	P
Acute otitis media	0.37 ± 0.68	0.51 ± 1.04	0.4
Rhinosinusitis	0.13 ± 0.34	0.20 ± 0.56	0.5
Infection of the upper respiratory tract with bacterial complications	0.69 ± 0.96	1.22 ± 1.13	0.01
Antibiotic cycle treatment	0.44 ± 0.80	0.61 ± 0.77	0.29
Bronchospasm attack or childhood asthma attack	1.15 ± 2.11	1.94 ± 2.14	0.06
Inhaled corticosteroids	0.75 ± 1.31	1.65 ± 1.95	0.17
Oral corticosteroids	0.08 ± 0.33	0.25 ± 0.65	0.08
Inhaled bronchodilators	1.06 ± 1.93	1.92 ± 2.17	0.03

Table 5 Analytical results in the children who developed inflammatory and recurrent diseases (IRD).

Analytic results	Group 1	Group 2
IgA low	1	3
IgG low	2	2
IgE high	3	0
TNF-high	7	17
IL-1	0	1
IL-6	0	1
PCR hs (high sensitivity)	0	2
C-3 and C-4	2	2
Histamine response test to food antigens Or HANA test	**Group 1**	**Group 2**
• Cow's milk	8	14
• Veal	6	9
• Pork	4	7
• Chicken	3	4
• White fish	2	4
• Blue fish	6	3
• Wheat	6	7
• Rice	1	2
• Soya	1	2

to highlight the low incidence of infectious diseases, recurrent bacterial complications, childhood asthma, and other IRDs in the sample group, but above all in the group with greater affinity to the TMD. This holds well to such an extent that the "upon request" consultations for illness were lower than the planned consultations, something uncommon for primary care pediatric consultations. Childhood asthma was the IRD with the most incidences in the total sample, with a significant difference between the two groups, and 40% lower in Group 1.

The majority of the families achieved marks ranging between good and optimal in the DMT-L test. Breastfeeding was key for differentiating both groups.[16] The ponderostatural development was appropriate in all those studied, highlighting the lack of overweight and obese children, which compared to the figures which the WHO gives us for these ages – above 20% – can be considered to be very satisfactory.[17] We have developed the DMT-L test, faced with a lack of instruments providing an appropriate assessment of the dietary pattern; in a recent publication, we refer to these matters.[14] After starting schooling, we have not found significant differences in the incidence of morbidity between the two groups. The scarce impact which attending nursery had on our study is noteworthy. Attending nursery has been associated with a greater frequency of recurring infections and wheezing, as well as consumption of antibiotics, bronchodilators, and anti-inflammatories.[18,19] The low incidence of infectious diseases in both groups does not seem to be noteworthy. The age at which they began to attend nursery was similar; however, "upon request" consultations due to illness was relatively low in both groups (three to four visits/year) compared to a national morbidity study for the same age group during the same time period (nine to ten visits/year).[20] The incidence of acute otitis media, rhinosinusitis, and other bacterial complications[21,22] strikingly decreased in Group 1 with greater affinity to TMD (only one in three patients/year), and with acceptable figures in Group 2 (one in every two), if we compare it with the usual figures in the national database (almost two episodes per patient/year).[20] The necessity of applying drug therapy, and in particular antibiotics, notably reduced in Group 1 (only one in five to six patients took a course of antibiotics per year) and we could also catalogue Group 2 as satisfactory (one in every three to four), compared with the bibliographic data shown (four courses of antibiotics per child and year).[20]

Recurring otitis media is common at this age, although in our study its incidence was low in both groups (2% and 7% respectively); and in a post-vaccination study, a prevalence of 24% in those young than 3 years was shown, the peak incidence being between 6 and 12 months.[23] The protective effect of breastfeeding for at least 6 months has been suggested, although from this age, other risk factors have an influence.[24] Among them, the early introduction of adapted milk has been highlighted.[25] It should be noted that we hardly had patients with IRD – except childhood asthma – if we compare it with the national data.[20] Asthma and bronchospasm attacks, as is seen in Table 4, were a lot higher in Group 2, in which adapted milk prevailed. The average of both groups is similar to these national figures, for which reason we postulate the hypothesis that "adapted cow's milk is very much involved in this inflammatory disorder." The use of inhaled corticosteroids and bronchodilators was twice as high in Group 2, with similar figures to the national database.[20] Childhood asthma (recurrent wheezing) is generally triggered by viral infections, which stimulate a previously pro-inflamed mucus. For this reason, inhaled corticosteroids are used over prolonged periods of time to stop or control this incorrect inflammatory response.[26] Likewise, the food industry has placed hypoallergenic milks on the market, with a high level of vaccinated protein hydrolysis, based on evidence from studies which try to prevent childhood asthma.[27] In our study, patients from Group 1 who were breastfed were those who had a lower level of childhood asthma (nine patients); also, it seems to us that the figure could further reduce if we were to limit mothers' consumption of some pro-inflammatory foods – among these foods cow's milk – whose metabolites and immune responses could pass to the mother's milk. We did not conduct nutritional reports and analytical studies on the mothers, and we now think that it would have been interesting to have them evaluated. Group 2 had a higher incidence of childhood asthma (15%), for which reason the suspicion that adapted milks could be linked to the appearance of childhood asthma increases, and the idea that breastfeeding is an important protective factor is strengthened.[28] Cow's milk was the food antigen most frequently shown by the Hana test, but not the only one; frequently beef and pork followed, and among foods of plant origin, wheat sensibility stood out. The majority of patients who had IRD had positive inflammatory markers, above all TNF-alfa and to a lesser extent PCRhs, IL-1, IL-6, C-3, and C-4. The introduction of additional foods is associated with changes in the gut microbiota composition, with the possibility of these changes altering the immune and metabolic mechanisms.[29] Recent studies have revealed that foods consumed affect the immune response. The

components of these foods act on several immune cells and their effects are mediated by the intestinal immune system and, in some cases, by the gut microbiota. The improvement of the immune response provides defenses to the host against infection and inhibits immune responses, suppressing allergies and inflammation.[30-37] All of this makes us suspicious that there are factors related to the introduction of infant foods, which are altering inflammatory and immune mechanisms, favoring the onset of IRD.[38,39] We consider that it would be interesting to expand these studies, to assess the impact of the elimination of suspicious foods, for the treatment of IRD. The lack of a control group is one of the limitations of our study. The lack of nutritionists in the public health system is also an important limitation for the reproduction of this study, as it would not have been possible without their collaboration.

In view of the results, we think that not all food offered in childhood can be given with the confidence that it will be well tolerated, above all foods which have a greater antigenic capacity and which have not been common in child nutrition in the Mediterranean region. Foods that have been more connected to IRD have been proteins of animal origin: cow's milk, beef, pork, and fish. We can conclude by saying that adapted milk and other foods of animal origin could be involved in the appearance and development of childhood asthma, and IRDs, given that limiting them in the diet has contributed to lowering related morbidity. A diet based on the TMD along with breastfeeding notably reduces the incidence of childhood asthma and IRDs, even when attending nursery.

Conflicts of interest

We have had financial and institutional support, with a grant from the Fundación de la Mutua Madrileña, and also another grant from the Spanish Association of Primary Care Pediatrics, for the development of this study. There is no potential conflict of interest that may introduce any bias in the content of the presentation, or has a business relationship that participants may perceive as such a conflict.

References

1. Galilea-Zabalza I, Buil-Cosiales P, Salas-Salvadó J, Toledo E, Ortega-Azorín C, Díez-Espino J, et al. Mediterranean diet and quality of life: baseline cross-sectional analysis of the PREDIMED-PLUS trial. PLoS One. 2018;13(6):e0198974. https://doi.org/10.1371/journal.pone.0198974
2. Trichopoulou A, Martínez-González MA, Tong TY, Forouhi NG, Khandelwal S, Prabhakaran D, et al. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Med. 2014;12:112. https://doi.org/10.1186/1741-7015-12-112
3. Sexton P, Negro P, Metcalf P, Wall CR, Ley S, Wu L, et al. Influence of Mediterranean diet on asthma symptoms, lung function, and systemic inflammation: a randomised controlled trial. J Asthma. 2014;50(1):75–81. https://doi.org/10.3109/02770903.2012.740120
4. García-Marcos L, Castro Rodríguez JA, Weinmayr G, Panagiotakos DB, Priftis KN, Nagel G. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. Pediatr Allergy Immunol. 2013;24:330–338. https://doi.org/10.1111/pai.12071
5. González-Gil EM, Tognon G, Lissner L, Intemann T, Pala V, Galli C, et al. IDEFICS Consortium. Prospective associations between dietary patterns and high sensitivity C-reactive protein in European children: the IDEFICS study. Eur J Nutr. 2017 Mar 18. https://doi.org/10.1007/s00394-017-1419-x
6. González-Gil EM, Santabárbara J, Russo P, Ahrens W, Claessens M, Lissner L,et al. Food intake and inflammation in European children: the IDEFICS study. Eur J Nutr. 2016 Dec;55(8):2459–2468. https://doi.org/10.1007/s00394-015-1054-3
7. Espín-Jaime B, Díaz J, Blesa L, Claver A, Hernández A, García JI, et al. Allergy to cow's milk proteins not mediated by IgE: consensus document of the Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition (SEGHNP). An Pediatr (Engl Ed). 2019 Mar;90(3):193.e1–193.e11. https://doi.org/10.1016/j.anpedi.2018.11.007
8. García-Mérida MJ, Espín-Jaime B. Allergy to cow's milk proteins not mediated by IgE. In: AEPap (ed.), 2020 Pediatrics Update Congress. Madrid: Lúa Ediciones 3.0; 2020. p. 239–245. https://www.aepap.org/sites/default/files/documento/archivos-adjuntos/congreso2020/239-246_Alergia%20a%20las%20prote%C3%ADnas%20de%20la%20leche.pdf
9. Fox A, Brown T, Walsh J, Venter C, Meyer R, Nowak-Wegrzyn A, et al. An update to the milk allergy in primary care guideline. Clin Transl Allergy. 2019;9:40. https://doi.org/10.1186/s13601-019-0281-8
10. Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. Unit Eur Gastroenterol J. 2017;5:335–358. https://doi.org/10.1177/2050640616689525
11. Catassi C, Alaedini A, Bojarski C, Bonaz B, Bouma G, Carroccio A, et al. The overlapping area of non-celiac gluten sensitivity (NCGS) and wheat-sensitive irritable bowel syndrome (IBS): an update. Nutrients. 2017;9:pii: E1268. https://doi.org/10.3390/nu9111268
12. Calatayud-Sáez FM, Calatayud B, Gallego JG, González-Martín C, Alguacil Merino LF. Mediterranean diet and childhood asthma. Allergol Immunopathol. 2016;44(2):99–105. https://doi.org/10.1016/j.aller.2015.04.007
13. Calatayud-Sáez FM, Calatayud B, Gallego JG, González-Martín C, Alguacil Merino LF. Effects of Mediterranean diet in patients with recurring colds and frequent complications. Allergol Immunpathol. Sep-Oct 2017;45(5):427–424. https://doi.org/10.1016/j.aller.2016.08.006
14. Calatayud-Sáez FM, Calatayud B, Calatayud A. Effects of the traditional Mediterranean diet in patients with otitis media with effusion. Nutrients. 2021;13:2181. https://doi.org/10.3390/nu13072181
15. Elorza FL, Rubio N, Lizaso M, Malagón F, Dorado ME. Standardization of the histamina liberation test. Allergol Immunopathol. 1982;10:221–228. https://pubmed.ncbi.nlm.nih.gov/6183962/
16. Gimeno-Navarro A. Breastfeeding Committee of the AEP. Breastfeeding in figures: rates of initiation and duration of breastfeeding in Spain and in other countries. Year of edition. 2017. http://www.aeped.es/sites/default/files/documentos/201602-lactancia-materna-cifras.pdf
17. WHO. Childhood overweight and obesity. Commission to end childhood obesity. Facts and figures on childhood obesity. https://www.who.int/end-childhood-obesity/facts/es/
18. Del Castillo-Aguas A, Gallego-Iborra A, Gutiérrez-Olid M, Pérez-González O, Moreno-Muñoz G, Ledesma-Albarrán JM. Infectious morbidity and resource use in children under 2 years old at childcare centres. J Paediatr Child Health. 2017;53(2):116–122. https://doi.org/10.1111/jpc.13372

19. Domínguez-Aurrecoechea B, Fernández M, Ordóñez MÁ, López P, Pérez JL, Merino L, et al. Infectious diseases and use of health care resources in children less than 2 years-old who attend kindergarten. An Pediatr (Barc). 2015;83(3):149–159. https://doi.org/10.1016/j.anpedi.2014.10.008
20. Ordoñez-Alonso MA, Domínguez-Aurrecoechea B, Pérez-Candás JL, López-Villar P, Fernández-Francés M, Coto-Fuente M, et al. Influence of daycare attendance on attendance at Emergency and Primary Care. Rev Pediatr Aten Primaria. 2016;18:243–252. http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1139-76322016000300005
21. Chonmaitree T, Trujillo R, Jennings K, Alvárez-Fernández P, Patel JA, Loeffelholz MJ, et al. Acute otitis media and other complications of viral respiratory infection. Pediatrics. 2016;137(4):e20153555. htts://doi.org/10.1542/peds.2015-3555. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4811317/
22. Toivonen L, Schuez-Havupalo L, Karppinen S, Teros-Jaakkola T, Rulli M, Mertsola J, et al. Rhinovirus infections in the first 2 years of life. Pediatrics. 2016;138(3):e20161309. https://doi.org/10.1542/peds.2016-1309
23. Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the post pneumococcal conjugate vaccine era. Pediatrics. 2017;140(3):e20170181. https://doi.org/10.1542/peds.2017-0181
24. Brennan-Jones CG, Eikelboom RH, Jacques A, Swanepoel D, Atlas MD, Whitehouse AJ, et al. Protective benefit of predominant breastfeeding against otitis media may be limited to early childhood: results from a prospective birth cohort study. Clin Otolaryngol. 2017;42(1):29–37. https://doi.org/10.1111/coa.12652
25. Brennan-Jones CG, Whitehouse A, Park J, Hegarty M, Jacques A, Eikelboom RH, et al. Prevalence and risk factors for parent-reported recurrent otitis media during early childhood in the Western Australian Pregnancy Cohort (Raine) study. J Paediatr Child Health. 2015;51(4):403–409. https://doi.org/10.1111/jpc.12741
26. Working group of the Clinical Practice Guide on Childhood Asthma. Clinical practice guide on childhood asthma. Clinical Practice Guidelines in the SNS. Ministry of Health, Social Services and Equality; 2015. http://www.guiasalud.es/GPC/GPC_548_Asma_infantil_Osteba_compl.pdf [access 16 April 2020].
27. Von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, et al. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol. 2013;131:1565–1573. https://doi.org/10.1016/j.jaci.2013.01.006
28. Alwarith J, Kahleova H, Crosby L, et al. The role of nutrition in asthma prevention and treatment. Nutr Rev. 2020:nuaa005. https://doi.org/10.1093/nutrit/nuaa005
29. Differding MK, Benjamin-Neelon SE, Hoyo C, Østbye T, Mueller NT. Timing of complementary feeding is associated with gut microbiota diversity and composition and short chain fatty acid concentrations over the first year of life. BMC Microbiol. 2020;20(1):56. https://doi.org/10.1186/s12866-020-01723-9
30. Layhadi JA, Samji MH. Uncovering the immunological properties of isolated lymphoid follicles. Allergy. 2020;00:1–2. https://doi.org/10.1111/all.14598
31. Rezende RM, Weiner HL. History and mechanisms of oral tolerance. Semin Immunol. 2017;30:3–11. https://doi.org/10.1016/j.smim.2017.07.004
32. Hachimura S, Totsuka M, Hosono A. Immunomodulation by food: impact on gut immunity and immune cell function. Biosci Biotechnol Biochem. 2018;82(4):584–599. https://doi.org/10.1080/09168451.2018.1433017
33. Meslier V, Laiola M, Roager HM, De Filippis F, Roume H, Quinquis B, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. Gut. 2020 Feb 19. Pii: gutjnl-2019-320438. https://doi.org/10.1136/gutjnl-2019-320438
34. Domínguez-Andrés J, Netea MG. Impact of historic migrations and evolutionary processes on human immunity. Trends Immunol. 2019. https://doi.org/10.1016/j.it.2019.10.001
35. Salas-Salvadó J, García P, Sánchez JM. Food and nutrition through history. Editorial Glosa S.L.; 2005. ISBN 84-7429-257-3. www.editorialglosa.es https://www.iberlibro.com/servlet/BookDetailsPL?bi=30100048293&cm_sp=plp-_-9788474292572-_-used
36. Campbell TC, Campbell TM. The China study. Cap. 11–12. BenBella Books, Inc. 10300 N. Central Expressway; 2012. https://www.socakajak-klub.si/mma/The+China+Study.pdf/20111116065942/
37. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients. 2020;12:1181. https://doi.org/10.3390/nu12041181
38. Calatayud-Sáez FM, Calatayud B, Calatayud A. Persistent nasal obstruction: an expression of the pro-inflammatory state? Sinusitis. 2021;5:90–100. https://doi.org/10.3390/sinusitis5010010
39. Calatayud-Sáez FM, Calatayud B, Calatayud A. Effects of the traditional Mediterranean diet in childhood recurrent acute Rhinosinusitis. Sinusitis. 2021;5(2):101–115. https://doi.org/10.3390/sinusitis5020011